SUPPORTING
HEALTHCARE
RESEARCH

ST VINCENT'S
CENTRE FOR APPLIED
MEDICAL RESEARCH

2012 ANNUAL
RESEARCH REPORT

CONTENTS

WELCOME

Welcome to the latest edition of the St Vincent's Centre for Applied Medical Research Annual Report. We have a long and proud tradition in teaching and research that contributes to the delivery of improved health outcomes for people with, or at risk of, disease.

This year we feature some interesting case studies which demonstrate our commitment to supporting healthcare research.

These stories strengthen St Vincent's Public Health Services as centres of excellence and innovation in clinical care, holistic care, research and education.

ABOUT US

St Vincent's Centre for Applied Medical Research (AMR) conducts world class applied medical research and is located in Darlinghurst in Sydney, New South Wales. We are located in close proximity to Sydney's central business district and collocated with other major medical research institutes, together forming the St Vincent's Research Precinct, also known as the Darlinghurst Research Hub.

We have a rich and proud history, drawing inspiration from the Sisters of Charity and who established St Vincent's Hospital on the Darlinghurst site more than 150 years ago.

Committed to the mission and values of the Sisters of Charity and the Sisters of Mercy, these values - compassion, justice, human dignity, excellence, unity, mercy, hospitality and respect - drive our daily activities and vision to continue the tradition of teaching and connecting world class medical research with healthcare across the broader hospital campus and beyond.

AMR's roots began back in 1983 when the Centre for Immunology was formed in agreement with the University of New South Wales, providing the community with a clinical and diagnostic service of the highest standard in the area of immunology and also undertaking biomedical research, education and training responsibilities.

The Centre for Immunology was instrumental in addressing the rapidly increased workload of the immunology departments of St Vincent's Hospital when the HIV epidemic affected the community. After two decades of immense activity, CFI was vacated and all of St Vincent's laboratory research programs were re-located to the new and purpose built laboratory based medical research Lowy Packer Building in October 2008. This world-class facility has dramatically enhanced the quality and productivity of our research programs on the Darlinghurst campus, providing our researchers with a 20% larger facility but more importantly, bringing all our groups together under one roof. With the move to the new building, a new governance structure was born to reflect the intimate collaborative work with other campus partners, particularly the Kirby Institute, UNSW, leading to the formation of St Vincent's Centre for Applied Medical Research. Our rebadging reflected the growth and evolution of our research programs, no longer focussing on immunology but branching out into areas such as virology, neurobiology, structural biology, adult stem cell research, cancer and applied clinical research in the form of well-run clinical trials. •

DIRECTOR'S REPORT

The year 2012 was another outstanding yet critical year in developing a future vision for AMR and reflecting on our successes of recent times. AMR had considerable success in obtaining competitive grants funding and published in prestigious international scientific journals. Research publication success is a key performance indicator of success for the St Vincent's Hospital Darlinghurst campus and the number of publications produced by AMR is the most prolific on the healthcare campus and a testament to the excellence and commitment of our researchers. AMR published more than 80 peer reviewed papers in leading international medical and life sciences journals and secured close to $8 million in competitive research grants.

A number of our research programs are joint programs with the Kirby Institute for Infection and Immunity of the University of New South Wales. The joint venture brings together high profile researchers working in immunology and infectious diseases, clinical trials, biostatistics, epidemiology, public health and prevention with the clinician researchers at St Vincent's Hospital who serve these affected and often vulnerable communities. This work exemplifies St Vincent's commitment to clinical care and research and the core mission and values of the Mary Aikenhead Ministries.

AMR welcomed the opportunity to further expand our research portfolio in the field vascular dermatology, fluid mechanics and phlebology led by Associate Professor Kurosh Parsi. A/Professor Parsi also heads the Dermatology clinical service at St Vincent's Hospital. The new program complements our existing research programs in haematology, immunology and cancer and further complements the theme that underpins all of the research programs at AMR in that they are directly focussed on improved health outcomes for the patients we serve.

We were very fortunate to receive a major gift of $2 million in 2012 to establish the Peter Duncan Neurosciences Research Unit which will be primarily concerned with research into regeneration of brain tissue in a variety of disorders. The unit will bring together laboratory basic discovery research scientists and neurosurgical teams focused on the use of adult stem cells as therapy, deep brain stimulation and advanced neurosurgical procedures such as transplantation and research focussed on biochemical pathways that modulate stem cell growth and differentiation. This program is headed by Professor Bruce Brew.

Professor Samuel Breit leads the Inflammation and Cytokine Biology Research Program and continues his internationally recognised research into chronic inflammatory diseases which has led to the successful commercialisation of years of basic discovery laboratory research into clinically relevant biomarkers that directly impact on patient clinical management of obesity and cancer.

Professor Anthony Kelleher heads the HIV Immunovirology Program providing insights into HIV immunology, natural history and support of a growing number of clinical trials. Close links with the NSW State Reference Laboratory for HIV at St Vincent's pathology has enabled the transfer of new biomarkers from the research bench into diagnostic service delivery.

Professor Andrew Carr heads the Clinical Research Program (CRP), providing high quality clinical trials services across the St Vincent's Campus for the clinical implementation of more than eighty academic, pharmaceutical, and investigator-initiated clinical studies.

Gastro-oesophageal Cancer Program led by surgeon researcher Associate Professor Reginald V Lord has identified a biomarker which confirms the presence of a precursor to a type of cancer known as adenocarcinoma. This new biomarker seems to predict the survival for patients with this type of cancer, again another example of where our research makes a difference to patient's lives.

The HIV Gene Therapy Program led by Professor Geoff Symonds is evidence of AMR's partnership with biotechnology industry. With our growing portfolio of translational research industry and hospital based research programs, we can collaborate together and leverage ideas and infrastructure for a common goal.

Associate Professor Richard Harvey heads the Rhinology and Skull Base Research program. As our second surgical researcher led program A/Professor Harvey brings together a collective group of clinicians and researchers working on inflammatory and neoplastic diseases of the upper airways.

Professor Paul Curmi heads the Structural Biology Research Program and is located on the University of New South Wales campus in Kensington associated with the School of Physics. The program continued to develop complex molecular imaging equipment to understand the way specific proteins behave which give insights into drug development and new treatments. The Structural Biology program provides highly specialised support to a range of AMR laboratory research programs.

Professor David Ma is a clinician researcher specialising in haemopoetic stem cell transplantation and haematological conditions. His research program focusses on advancing our knowledge of the genetics of normal and blood cancer stem cells aiming at improving the benefits and stem cell transplantation and survival of patients with blood related cancers. Another prime example of our expanding translational research portfolio directly impacting on the health of current and future generations.

AMR achievements can in part be measured by the achievements of our staff in the lists of publications and collaborations and other measures of professional recognition noted in this annual report. I thank all of them for their contribution, and I also thank St Vincent's, our collaborators, our funders, our Precinct Partners and the University for their continued support for our work.

PROFESSOR DAVID A COOPER FAA AO
Director •

OPERATIONS REPORT

In the last decade, St Vincent's through the direct research activity of its flagship research enterprise - St Vincent's Centre of Applied Medical Research (AMR) and our research partners like the Kirby Institute of the University of New South Wales, the Garvan Institute of Medical Research, and the Victor Chang Cardiac Research Institute, have created the St Vincent's Research Precinct which is the greatest concentration of medical researchers on a hospital campus in New South Wales, if not Australia.

Transforming healthcare is what St Vincent's is all about and we believe that we're well placed to take the leadership role in clinical research to accelerate the translation of new knowledge into leading edge practices, devices, therapies and techniques.

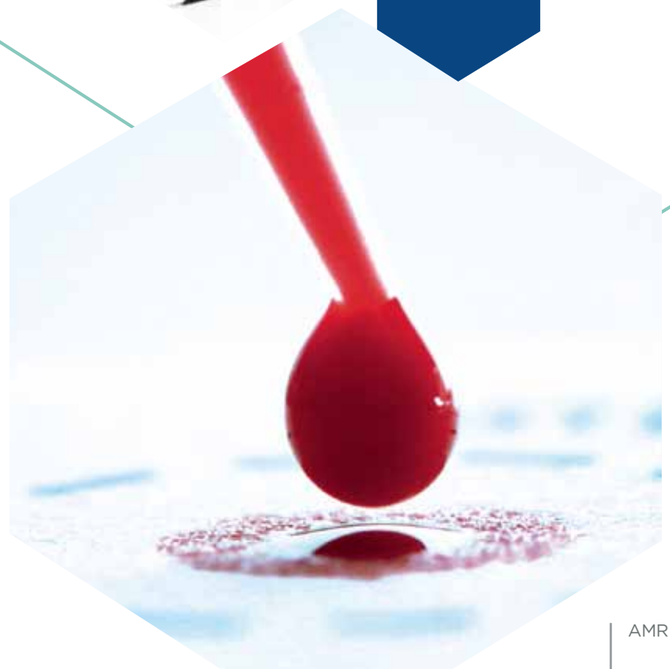
There is a new urgency to make sure that scientific discoveries generated through basic discovery and clinical research will make real world differences particularly those vulnerable communities and the disadvantaged, putting pressure on processes that can apply – or 'translate' breakthroughs as quickly as possible in to practical results.

AMR and the St Vincent's Research Precinct continues to grow. Our own research capacity continues to grow with the continued and valued support of the Hospital, University and the Ministry of Health. Linking basic discovery researchers together with healthcare and clinical researchers has been an ongoing strategic vision of AMR. The concept that research leads to improved health outcomes is evidenced by the numerous examples of laboratory tests, new drugs, health service improvement and devices being transferred into the clinical services sector and being routinely used to manage patients in the community often in very remote and resource poor settings.

Our strategic investment in state-of-the-art core research facilities and equipment means we are well placed into the future. This approach encourages sharing of valuable facilities and equipment and promotes interaction of our talented people creating an efficient environment that stimulates collaboration and creativity.

AMR PROVIDES STATE OF THE ART FACILITIES

Our next challenge will be to explore the feasibility of developing a Translational Research Centre on the remaining site on the St Vincents Research Precinct that will provide an interface for our clinician researchers with the people and communities who we serve. This next chapter in the St Vincent's Research journey will aim to bring together and harmonise our efforts in wet laboratory facilities, biobanking and tissue banking facilities, research ethics and governance management, clinical trials conduct and support, identify and nurture our aspirational research programs while continuing to support and grow our established programs.



While the St Vincent's Research agenda continues to evolve, AMR will continue to adapt and respond to the changing needs of the campus and continue to produce high quality work. Our family of staff, students, visiting scholars and collaborators will continue to work closely together to contribute to the success of the vision. I would like to thank every member of our organisation for their contribution, particularly those who ensure our environment operates safely, smoothly and is a gratifying place to work.

PHILIP CUNNINGHAM
Chief Operating Officer •

IN 2012, AMR PUBLISHED MORE THAN 80 PEER REVIEWED PAPERS IN LEADING INTERNATIONAL MEDICAL AND LIFE SCIENCES JOURNALS AND SECURED CLOSE TO $8 MILLION IN COMPETITIVE RESEARCH GRANTS

ORGANISATIONAL STRUCTURE

INSTITUTE OF VIROLOGY BOARD OF MANAGEMENT

DIRECTOR OF RESEARCH
Professor David Cooper FAA AO

CHIEF OPERATING OFFICER
Philip Cunningham

HIV PATHOGENESIS
Dr Kazuo Suzuki, Dr Kersten Koelsch

HIV IMMUNOVIROLOGY AND INFECTIOUS DISEASE CLINICAL RESEARCH
Professor Anthony Kelleher

HIV BIOLOGY
Dr Stuart Turville

CELLULAR IMMUNOLOGY
Dr John Zaunders

AMR/KIRBY JOINT PROGRAM IMMUNOVIROLOGY
Professor Anthony Kelleher

VIRAL HEPATITIS LABORATORY PROGRAM
Dr Tanya Applegate

VIRAL HEPATITIS CLINICAL RESEARCH
Professor Gregory Dore

AMR/KIRBY INSTITUTE JOINT PROGRAM VIRAL HEPATITIS
Professor Gregory Dore

STROKE
Dr Ramesh Markus

PARKINSON AND MOVEMENT DISORDERS
Dr Stephen Tisch, Dr Paul Darveniza

NEUROVIROLOGY AND NEUROIMMUNOLOGY
Dr Gilles Guillemin

NEUROPSYCHOLOGY
Dr Lucette Cysique

NEUROVIROLOGY CLINICAL RESEARCH
Professor Bruce Brew

ADULT STEM CELLS
Dr Juliana Lamoury

APPLIED NEUROSCIENCES PROGRAM
Professor Bruce Brew

STEM CELL TRANSPLANTATION
Dr Helen Tao

POST TRANSPLANT IMMUNE RECONSTITUTION
Dr John Moore

MALIGNANT HAEMATOLOGY
Dr Catalina Palma

HAEMOSTASIS AND THROMBOSIS
Dr Joanne Joseph

BLOOD, STEM CELL AND CANCER PROGRAM
Professor David Ma

REHABILITATION MEDICINE
A/Prof Steven Faux

HIV METABOLIC RESEARCH
Professor Andrew Carr

HIV IMMUNOLOGY AND INFECTIOUS DISEASES
Prof Andrew Carr, Professor Anthony Kelleher

ANAL CANCER
A/Prof Richard Hilman

CLINICAL RESEARCH PROGRAM
Professor Andrew Carr

NEURO-INFLAMMATION
Dr David Brown

CYTOKINE BIOLOGY
Professor Samuel Breit

CYTOKINE AND INFLAMMATION PROGRAM
Professor Samuel Breit

GASTRO-OESOPHAGEAL CANCER PROGRAM
A/Professor Reginald Lord

RHINOLOGY AND SKULL BASE RESEARCH PROGRAM
A/Professor Richard Harvey

STRUCTURAL BIOLOGY PROGRAM
Professor Paul Curmi

DERMATOLOGY, PHLEBOLOGY AND FLUID MECHANICS PROGRAM
A/Professor Kurosh Parsi

HIV GENE THERAPY PROGRAM
Professor Geoff Symonds

GOVERNANCE

The Institute of Virology builds upon a long standing relationship between St Vincent's Centre for Applied Medical Research and the Kirby Institute for infection and immunity in society, with a joint commitment to excellence in teaching, research and healthcare.
The Institute of Virology Board of Management is a Standing Committee appointed through the Trustees of Mary Aikenhead Ministries (TMAM) and St Vincent's Health Australia (SVHA) convened in accordance with the powers granted under the Constitutions of St Vincents & Mater Health. Sydney and St Vincent's Hospital Sydney. The Board of SVHA has a majority of independent Directors as defined by established best practice corporate governance guidelines. The Board of Management provides overview in respect of the operations and strategic development of AMR. The Board is comprised of an independent Chairman, and all members are free from any interest and any business or other relationship which could be perceived to materially interfere with their ability to act in the best interests of AMR.

MR PAUL MCCLINTOCK AO (CHAIRMAN)

Paul McClintock is Chairman of Medibank Private Limited, Thales Australia, Myer Holdings Limited, I-MED Network and the Institute of Virology.
From July 2000 to March 2003 Mr McClintock served as the Secretary to Cabinet and Head of the Cabinet Policy Unit reporting directly to the Prime Minister as Chairman of Cabinet with responsibility for supervising Cabinet processes and acting as the Prime Minister's most senior personal adviser on strategic directions in policy formulation. Mr McClintock's former positions include Chairman of the COAG Reform Council, the Expert Panel of the Low Emissions Technology Demonstration Fund, Intoll Management Limited, Symbion Health, Affinity Health, Ashton Mining, Plutonic Resources and the Woolcock Institute of Medical Research.
Mr McClintock was also a Director of the Australian Strategic Policy Institute and Perpetual Limited, a Commissioner of the Health Insurance Commission and a member of the Australia-Malaysia Institute Executive Committee.
Mr McClintock graduated in Arts and Law from the University of Sydney and is an honorary fellow of the Faculty of Medicine of that University, and a Life Governor of the Woolcock Institute of Medical Research.

MR PAUL ROBERSTON AM (MEMBER)

Mr Robertson has over forty years of experience in finance, including both commercial and investment banking, with extensive experience in risk management. A former Executive Director of Macquarie Bank, Mr Robertson has extensive experience in banking, finance and risk management. Mr Robertson holds board and committee positions with a variety of organisations including St Ignatius College Riverview, the Jesuit Province of Australia, Ursuline Sisters Province, Social Ventures Australia, Cheviot Bridge Limited and the Financial Markets Foundation for Children. Mr Robertson has previously served as Director and Chair of St Vincents & Mater Health Sydney.

MR JONATHAN ANDERSON (MEMBER)

Mr Anderson is the Chief Executive Officer of St Vincent's Health Network, Sydney. He brings to the role an extensive and successful career in public health care 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, subacute and aged care facilities. In 1997 he joined St Joseph's Hospital as Executive Director and prior to this was the Executive Director of Lottie Stewart Hospital. He has held other senior positions including General Manager Rachel Forster Hospital; Director of Finance and Administration at Rozelle Hospital; Director St Vincent's Hospital Toowoomba; and other senior positions at Central Sydney Area Health Service. Jonathan has also had responsibility for specialised corporate roles such as the Sisters of Charity Health Service National Risk Manager and National Aged Care Coordinator. Jonathan has a Bachelor of Economics from Sydney University and a Masters of Management from MGSM.

PROFESSOR PETER SMITH RFD (MEMBER)

Prof Smith is Dean of Medicine at The University of New South Wales. He specialised in cancer medicine and research. Prof Smith has held senior hospital management posts in Brisbane and Melbourne and senior academic appointments at the Universities of Queensland, Melbourne and Auckland. He has served in a consulting role to government, including as Chair of the recent inquiry into Vietnam Veterans Cancer Incidence and Mortality. Prof Smith is currently a Director of the Garvan Institute of Medical Research, NewSouth Innovations, Arts and Health Foundation and a number of research centres and institutes. Prof Smith was appointed as Director of St Vincent's Health Australia on 1 October 2010.

PROFESSOR DAVID COOPER AO (MEMBER)

Professor Cooper is Director of St Vincent's Centre for Applied Medical Research. In addition to the Centre for Applied Medical Research, Professor Cooper is also Director of the Kirby Institute for infection and immunity in society. The Kirby Institute is funded by the Australian Government Department of Health and Ageing, to conduct research into the HIV/AIDS epidemic in Australia, with the ultimate aim of reducing the burden of the HIV/AIDS epidemic for the affected community. He is a Director of HIV-NAT, a clinical research and trials collaboration based at the Thai Red Cross AIDS Research Centre at the Chulalongkorn University Hospital in Bangkok, Thailand and is a past President of the International AIDS Society (IAS) and Chairman of the World Health Organisation-UNAIDS HIV Vaccine Advisory Committee (VAC).

MS RHONDA TOPP (SECRETARY)

BOARD ATTENDEES

Professor Terry Campbell AM – Director of Research, St Vincents and Mater Health Sydney and Senior Associate Dean, Faculty of Medicine, University of New South Wales

Mr Philip Cunningham – Chief Operating Officer, St Vincent's Centre for Applied Medical Research

Mr Daren Draganic – Operations Manager, Kirby Institute for infection and immunity in society

Scientific Management Committee

The focus of the AMR Scientific Management Committee is to improve the effectiveness and efficiency of research activities. This Committee provides a forum for individual research programs to update the Director about activity and output. The Committee identifies opportunities and manages risks for improving research productivity with emphasis upon effective networking between research programs, medical research sector, hospitals, universities and the biomedical and pharmaceutical industry.

Professor David Cooper AO (Chair)
Professor Samuel Breit
Professor Bruce Brew
Professor Terry Campbell AM
Professor Andrew Carr
Mr Philip Cunningham
Professor Paul Curmi
Associate Professor Richard Harvey
Professor Anthony Kelleher
Associate Professor Reginald VN Lord
Professor David Ma
Associate Professor Kurosh Parsi
Professor Geoff Symonds
Mr Karl Nguyen (Secretary)

OUR IN-HOUSE DEVELOPED TEST HELPS NOT ONLY WITH THE CONDUCT OF CLINICAL TRIALS BUT ALLOWS ST VINCENT'S TO BE ONE OF ONLY TWO LABORATORIES IN AUSTRALIA TO OFFER THIS TEST, WHICH DIRECTLY IMPACTS UPON PATIENT MANAGEMENT

HIV IMMUNOVIROLOGY PROGRAM

The activities of the HIV Immunovirology Program during 2012 can be divided into three categories. There is substantial, daily interaction with the Immunovirology and Pathogenesis Program at the Kirby Institute of the University of NSW, which is also collocated with the NSW HIV State Reference laboratory (NSW Reference laboratory) at AMR.

A substantial proportion of laboratory based activity involved provision of routine or semi-routine laboratory support, essential for the successful conduct of clinical trials and epidemiological studies conducted by the AMR Clinical Research Program and several programs within the Kirby Institute. This section of the laboratory led by Kate Merlin and assisted by Bertha Fsadni, Maria Piperias, Melanie Lograsso and Julie Yeung continued to perform well in external quality assurance programs and received renewal of its NATA accreditation. During 2012, the results of the Spartac trial were published in the New England Journal of Medicine. The laboratory had acted as the central Australian laboratory for this critical trial looking at the effect of antiretroviral therapy commenced at primary infection. This trial has taken over seven years to complete and the sustained performance of the laboratory throughout this period was one of the reasons for the trial's successful completion. The laboratory acted as the central global laboratory for flagship Kirby studies such as SECOND-LINE, Encore, MARCH, and ATAHC II. It has additionally acted as the central laboratory for the Long term non-progressor cohort and the Opposites Attract Study. For Encore and SECOND-LINE, this included not only storage of samples from sites all over the world within the St Vincent's Biobank, but the laboratory acted as the central laboratory for the determination of plasma viral loads, the primary endpoint of both studies and performed all the sequencing and determination of drug resistance profiles. This represents a successful collaborative effort with the NSW Reference laboratory, particularly with the input from Philip Cunningham and Alex Carrera.

Collaborative strategies and sophisticated databases were developed to aid efficient data transfer and to ensure data quality. This has allowed the conduct of the laboratory aspects of these large complex trials to be streamlined, allowing the laboratory to meet very stringent and tight deadlines. The laboratory also completed extensive optimisation and verification studies of DNA-based viral tropism assays which were then successfully transferred to the NSW Reference laboratory. The laboratory played a substantial role in the development of an external quality assurance program for viral tropism that was used to qualify laboratories both in Australia and overseas for the conduct of assays for the MARCH study. This work was driven by Kazuo Suzuki and Katherine Marks. This transfer has been successful with the Reference laboratory performing well in the external quality assurance program. The development of this test helps not only with the conduct of these trials but allows St Vincent's to be one of only two laboratories in Australia to offer this test, which directly impacts on patient management, allowing the tailoring of optimal antiretroviral regimens routinely to HIV infected patients across Australia.

During 2012, the laboratory also commenced the development of a quantitative viral load test for HIV-2 which is a relatively rare infection compared to HIV-1. Plasma viral load measurements are critical to the optimal management of HIV-infection but no commercial assay is available for measuring HIV-1 viral loads. In response to requests from physicians across Australasia, Kazuo Suzuki and Leon McNally from the NSW Reference laboratory initiated the development of a quantitative viral load test for HIV-2, which was validated during 2012. It will be offered by the NSW Reference laboratory as a special test from early 2013, another example of research outcomes influencing the delivery of quality healthcare at St Vincent's.

The St Vincent's Biobank at AMR serves as a repository of extraordinarily valuable samples with samples from seminal clinical trials and from natural history studies in pathogenically informative populations of patients with HIV-infection such as those with primary infection and long term non-progressors. This repository with its linked clinical databases continued to provide valuable material for productive collaborations particularly with Stephen Kent's group at Melbourne University and Martyn French's group at Royal Perth. Each of these collaborations resulted in several peer reviewed publications in 2012. In addition, these cohorts were used for a range of studies conducted within the laboratory including studies providing insight into new regulatory pathways of T cell function involving micro-RNAs which in turn appear to impact on rates of progression of HIV-infection. Several papers on this work were accepted for publication during 2012 and one attracted editorial commentary in the European Journal of Immunology.

Senior scientists within the program were responsible for their own research projects on pathogenesis and development of therapeutics. In 2012, the utility of a patented, simple T cell assay developed and patented by John Zaunders, in assisting the diagnosis of latent TB was demonstrated by publication of data based on two separate clinical studies conducted in parallel at St Vincent's and at Chulalongkorn University, Bangkok. Several other clinical studies in a variety of populations demonstrating the utility of this advanced in 2012. This included: studies of immune restoration in HIV infected patients in collaboration with investigators at HIV-NAT driven by PhD student, Denise Hsu, studies of CMV responses in paediatric bone marrow transplant patients at both Sydney and Westmead Children's hospitals in collaboration with John Ziegler and Mahila Mamasivayam, and studies of HPV responses in gay men driven by Winnie Tong (PhD student), Andrew Carr, Richard Hillman from St Vincent's and Andrew Grulich from the Kirby Institute. This latter study was supported by a grant from the St Vincent's Curran Foundation.

A computationally efficient clustering algorithm applicable to the analysis of complex multiparameter flow cytometry data, called SOPHE developed by Dr Inge Koch from UNSW working with John Zaunders, was successfully patented and is being developed for commercialisation. During 2012 web based software was produced and beta testing of the algorithm was commenced.

The initial analyses of the first year of the PINT study, which provided new insights into dynamics of establishment and maintenance of the viral reservoir, were published in two separate manuscripts. Samples from this trial were a major focus of on-going work in the laboratory in 2012. Further insights into the mechanisms underlying the maintenance of the viral reservoir were sought from the elucidation of the relative infection rates of various T cell subsets and their turnover rates. This complex work represents effective collaboration between members of the Immunovirology laboratory (John Zaunders), several programs at the Kirby Institute (Kristin McBride (PhD Student), Kersten Koelsch, Sean Emery, David Cooper and Janaki Amin), The School of Mathematics and Statistics at the University of NSW (John Murray), as well as the local General Practitioners and the clinical trials unit at St Vincent's who recruited the patients. Developmental work for the characterisation of viral DNA load and phylogenetic profiles of virus-infected, antigen-specific CD4+ T cells was carried out by William Hey Cunningham (PhD Student working with John Zaunders and Kersten Koelsch). Further, the infection of Follicular T helper cells was demonstrated by Yin Xu (PhD student) working with John Zaunders, Kazuo Suzuki and Tony Kelleher. This work, which resulted from a successful collaboration with Stephen Kent from the University of Melbourne, has implications for HIV vaccine design. These sophisticated work plans are only possible using a combination of molecular and cellular assays developed within the laboratory. These and other studies involving identification of lymphocyte subsets was aided by an upgrade of our flow cytometer to a 3 laser machine capable to analysing 15 parameters simultaneously. This was achieved through the award of an equipment grant to Tony Kelleher and John Zaunders, allowing a machine purchased in 2003 to remain state of the art. Other work in the laboratory driven by Laura Cook (PhD student) working closely with Mee Ling Munier and David van Bockel, and Chan Phetsouphanh (PhD student) looks to further develop the sophistication of these assays in determining immune responses from small but important subsets of T cells.

During 2012 the first in vivo testing of our unique siRNAs that induce prolonged transcriptional gene silencing of HIV-1 in a Hu-SCID mouse model were completed with our Japanese collaborators. These constructs were developed by Kazuo Suzuki who drove these experiments which provided very encouraging data regarding the ability of these constructs to suppress viral replication when delivered by retroviral constructs. The results of elegant molecular and confocal microscopy demonstrating that these constructs work in the nucleus in concert with Ago1 were published. The proposed development of these constructs was supported through the award of an NHMRC Project grant to Kazuo Suzuki, Stuart Turville and Geoff Symonds and Tony Kelleher to commence in 2013.

At the end of 2012 the laboratory took delivery of a sophisticated confocal endo-microscope from Optiscan. It will be used with collaborators Tri Phan and Daniel Christ at the Garvan Institute of Medical Research and Mark Danta at St Vincent's Hospital to visualise dynamic changes in the integrity of mucosal surfaces and for the monitoring real time of mucosal immune responses in vivo.

The overall quality of the work generated by the program and its ability to collaborate effectively to produce high quality clinically important results was recognised through the awarding of a highly prestigious NHMRC program grant to commence in 2014 to a group of investigators that included Program Head Tony Kelleher. •

GASTRO-OESOPHAGEAL CANCER PROGRAM

The Gastro-oesophageal Cancer Program primarily studies the genetic basis of adenocarcinomas of the oesophagus and gastro-oesophageal junction, and the precursor disease for these cancers, Barrett's oesophagus. In Barrett's oesophagus, the normal lining of the lower oesophagus (the tube connecting the mouth with the stomach in the abdomen) is replaced by cells resembling those of the intestine.

The Program is headed by Associate Professor Reginald V Lord, a dedicated clinician researcher on the St Vincent's campus. Not only does he run a this laboratory program at AMR, but has clinical duties in both the public and private arms of St Vincent's and also see patients in his private rooms at St Vincent's Clinic. He is an upper gastro-intestinal specialist.

The laboratory's major interest is in identifying biological markers (biomarkers) which indicate the presence of Barrett's oesophagus, an increased risk of cancer development in Barrett's oesophagus, or better or worse survival after treatment by the operation oesophagectomy for patients with oesophageal cancer.

Our researchers have identified a biomarker which seems to predict survival for patients with oesophageal adenocarcinoma. This biomarker is not suitable for routine use in pathology laboratories (mRNA expression marker in FFPE tissue) but we are testing whether a simple immunohistochemistry test can provide the same information regarding whether people with this cancer are likely to survive, and for how long.

In collaboration with Dr Marcel Dinger at the Kinghorn Cancer Centre, we are undertaking in depth sequencing of the transcriptome of oesophageal adenocarcinoma. In collaboration with the Australian Proteome Analysis Facility we are studying secreted proteins in the blood of patients with Barrett's oesophagus or adenocarcinoma.

Patients with cancer limited to the most superficial layer of the oesophagus are now being treated by endoscopic therapies rather than having surgery as the first treatment. In collaboration with investigators at Westmead Hospital Sydney, Flinders Medical Centre Adelaide, and the St Vincent's and Royal Melbourne Hospitals in Melbourne we have been studying the benefit of this endoscopic approach by comparing the genetic profile of the oesophageal lining after treatment by the main three treatments: radiofrequency ablation, endoscopic mucosal resection, and argon plasma coagulation. A cost effectiveness study on the radiofrequency ablation treatment has also been undertaken with the Health Economics Department of the University of Technology, Sydney.

The other major projects investigated by the laboratory are:

- immune regulation and stem cells in Barrett's oesophagus and adenocarcinoma,
- the effect of surgical weight loss on diseases associated with obesity and the mechanism of these beneficial effects
- the association between obesity and cancer

The research activities of the laboratory are funded through a Centre for Research Excellence and Project Grant from NHMRC, the St Vincent's Curran Foundation and the Notre Dame University School of Medicine. •

OUR RESEARCH HAS LED TO THE SUCCESSFUL COMMERCIALISATION OF YEARS OF BASIC DISCOVERY LABORATORY RESEARCH INTO CLINICALLY RELEVANT BIOMARKERS THAT DIRECTLY IMPACT ON PATIENT CLINICAL MANAGEMENT OF OBESITY AND CANCER

CYTOKINE BIOLOGY AND INFLAMMATION RESEARCH PROGRAM

The Cytokine Biology and Inflammation Research Program, formed two decades ago at the Centre for Immunology, is largely laboratory based but with a strong clinical focus. The Program is directed at gaining a better understanding of chronic inflammatory diseases and then utilising this knowledge to improve diagnosis, management and therapy of such conditions. Chronic inflammatory responses underlie the pathogenesis of many human diseases such as rheumatoid arthritis, multiple sclerosis and cardiovascular disease. They also play a major role in the initiation, progression and spread of cancers. More recently, it has been discovered that they are important in mediating many of the adverse consequences of obesity. Some major mediators of chronic inflammatory responses are cytokines, macrophages and dendritic cells.

This program is headed by Professor Samuel Breit whose major research focus, over many years, has largely revolved around two areas: i) biology, therapeutic and diagnostic applications of MIC-1/GDF15 and ii) the biology and mechanism of action of CLIC1. Associate Professor David Brown, the deputy director of the Program, is not only a key collaborator in the MIC-1/GDF15 research area, but also oversees a sub-program directed at regulation of central nervous system immunity, with a major focus on dendritic cells.

The cytokine MIC-1/GDF15 is a divergent member of the TGF-b superfamily first cloned and characterised by this program. Its expression is markedly increased in response to injury, inflammation or malignancy. As a result, it is frequently overexpressed in many patients with cancer such as those of prostate, breast, colon and pancreas. This overexpression starts early in cancer and can be detected by changes in its serum levels. At least early in the course of cancer, MIC-1/GDF15 probably helps to limit cancer growth and spread. However, MIC-1/GDF15 expression increases as tumours progress, it may aid in dissemination. Furthermore, in advanced cancer the very high serum MIC-1/GDF15 serum levels can lead to anorexia/cachexia, because of its actions on appetite regulatory centres in the brain.

MACROPHAGE INHIBITORY CYTOKINE-1 (MIC-1/GDF15)

Whilst studied less extensively, MIC-1/GDF15 also plays a role in chronic inflammatory diseases such as rheumatoid arthritis and cardiovascular disease. MIC-1/GDF15 is expressed at sites of injury and inflammation such as the atherosclerotic vessel wall and rheumatoid arthritis joint and mice engineered to overexpress it are protected from disease development. Local expression of MIC-1/GDF15 is reflected by changes in its serum levels, which tend to predict disease course or treatment outcome. Because of disease associated changes is serum levels of MIC-1/GDF15, these levels are a powerful predictor of all cause mortality.

MIC-1/GDF15 has several potential clinical applications that require pharmaceutical industry involvement to progress. To this end St Vincent's Hospital have licensed its MIC-1/GDF15 technology:

- To develop MIC-1/GDF15 as an appetite suppressant and anti-inflammatory substance has been licensed to Novo Nordisk, a Denmark based multinational pharmaceutical company specialising in protein therapeutics.
- To develop humanised monoclonal antibodies to MIC-1/GDF15 for therapy of anorexia/cachexia of cancer and other diseases has been licensed to Aveo Oncology, a large US based biotechnology company.
- To develop and market an assay for blood measurement of MIC-1/GDF15 for the diagnosis and management of vascular diseases has been licensed to Roche Diagnostics, one of the world's largest diagnostics companies.

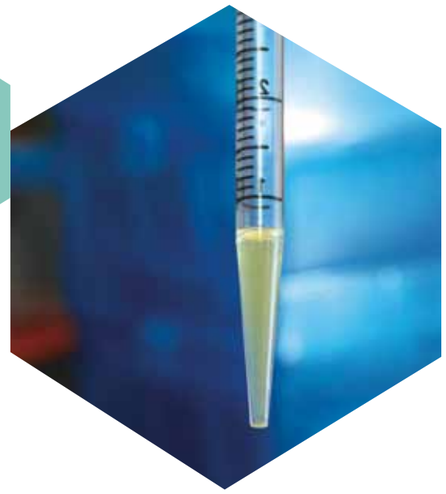
As world leaders in the study of MIC-1/GDF15, the laboratory continues to investigate and publish extensively on the role of MIC-1/GDF15 in the biology of cancer, appetite regulation and inflammation. We believe the development of clinical applications though the exploitation of our technology will help improve disease diagnosis and therapy.

CHLORIDE INTRACELLULAR CHANNEL 1 (CLIC1)

CLIC1 is the first cloned human member of the highly conserved CLIC family of intracellular chloride ion channel proteins. Proteins of this family are unusual for ion channels, because they are structurally related to the GST omega proteins, are small in size, are readily soluble and have the capacity to move on and off membranes. CLIC1 has been extensively studied and characterised, and while electrophysiology and high-resolution structures of CLIC1 in its soluble form have been obtained, its biology is poorly understood. However, gene knockout mice have mildly impaired platelet function and are protected from inflammatory disease. The mechanisms underlying these actions are the main focus of the laboratory.

CENTRAL NERVOUS SYSTEM IMMUNITY

The normal nervous system was previously thought to be exempt from the effects of the immune system. Recently, the work of several researchers, including A/Prof Brown, have demonstrated that there is a constant dialog between the nervous and immune systems, with two key cells of the immune system, dendritic cells and T-cells, playing an important part in regulating nervous system health. Abnormalities in the conversation between these two cells leads to a wide range of nervous system abnormalities, which extend from psychiatric to neurodegenerative disease. Neurodegeneration, the loss of nerve cells, is the core abnormality underlying Alzheimer's disease. Other common diseases that are impacted upon include stroke in the elderly, as well as spinal cord injury and multiple sclerosis in younger patients. Also, seriously affecting young patients are the psychiatric consequences of autoimmune brain diseases. This leads to treatment resistant depression or psychosis that requires immunotherapy. Because of these findings, A/Prof Brown is examining ways to ensure the nervous system interacts appropriately with the immune system to promote the maintenance of neuron health and function. The examination of immunoregulation in this diverse set of neurological diseases, and consequent development of therapeutic interventions, holds the promise of reducing the significant economic and social burden of many of these neurological and psychiatric diseases. •



case study

GOOD TO GET BACK TO NORMAL...

Over the past 5 years it has become increasingly clear that there are immune causes for psychiatric disease and this can be missed when people have their first episode of mental illness. Because mental illness completely changes someone's life and often leads to significant life-long disability, stigma and significant cost for the community to care for sufferers, it is very important for any reversible cause to be found and treated. To facilitate these aims, Associate Professor David Brown is conducting basic research in how the brain communicates with the immune system and is supervising the implementation of testing to detect immune causes of psychiatric and neurological disease. Additionally, he has started the Neuroimmunology Clinic at St Vincent's Hospital to diagnose and treat sufferers of these diverse neuroinflammatory diseases. An example of the importance of this amalgamation of basic research, provision of adequate pathological testing and clinical diagnosis on the same campus follows.

Melanie was a happy student studying Medicine until she had her first mental breakdown. The first thing Melanie's family noticed was a marked change in behaviour. Things that had never been a problem became the focus of temper tantrums and Melanie could not sleep well. After several months of upheaval in the family, declining ability at university and sleeplessness, Melanie was taken to the local hospital emergency department. This was the beginning of a 5-year odyssey in the State's mental health system.

After being taken to hospital Melanie was diagnosed with acute psychosis and admitted to the hospital's psychiatric unit. Melanie responded to medications to treat her psychosis and was soon discharged. She was shortly able to make a full recovery and went back to university. However, several months after her return she noticed that her study habits again deteriorated, as did her behaviour. Melanie's father described the night when she had a small fit before being taken back to the hospital.

"We were sitting on the couch watching television and Melanie had her head on my shoulder. The next thing I knew I felt Melanie's head banging against me and she slumped to the floor shaking all over and frothing at the mouth. Seeing my little girl like that made me the most scared that I have ever been"

Again Melanie was taken to the local hospital emergency department and admitted. Again a diagnosis of acute psychosis was made and again Melanie was treated with antipsychotic medication. However, this time when Melanie regained consciousness, she could not speak.

Despite intensive medical therapy, Melanie did not improve and the doctors were unsure of the diagnosis because she was very treatment resistant. Many doctors of different specialities examined Melanie and it was decided that the best course of treatment was electroconvulsive therapy. This led to a gradual improvement in Melanie's condition to the point that after 10 months in the psychiatric ward she could now talk and return home.

Despite ongoing psychiatric medical therapy, after being home for some time, Melanie had a minimal capacity to form new memories and had lost a significant amount of her previous memory. She could not read and spent most of her time in her room. Additionally, her sleep patterns never returned to normal. While she was awake she was drowsy because of the high doses of medication she required. Needless to say she could not return to her medical studies. Melanie's parents described their despair.

"We did not know what to do. We did not think the treatment was working and the doctors could not work out if there was another cause for Melanie's condition. We kept on searching and taking Melanie to other doctors."

A/Prof David Brown saw Melanie at the newly established Neuroimmunology Outpatients' clinic at St Vincent's Hospital. The clinic provides the facilities for comprehensive investigation of neuroimmunological diseases. To do this, Neurologists, Immunologists and Immunopathologists use state of the art equipment, immunological testing and treatments available on the campus. In Melanie's case a diagnosis of a rare autoimmune antibody condition that can lead to all Melanie's symptoms was made. With this diagnosis and with specific immunotherapy, Melanie has ceased all her psychiatric medications and is well on the way to recovery and hopefully recommencement of her studies and a life of fulfilment. A/Prof Brown comments on Melanie's diagnosis and treatment.

" Melanie has benefited from the application of basic research to the clinic. A few months after Melanie got sick the antibody that caused her condition was first described. Similarly we know that there are likely to be many other antibodies that cause similar devastating syndromes that are present, but not yet identified to allow the development of tests to diagnose their presence and facilitate their treatment. The Neuroimmunology Clinic and the associated basic research infrastructure on campus will allow us to investigate these conditions and identify the cause of them to allow their treatment in the future." •

APPLIED NEUROSCIENCES PROGRAM

The Applied Neurosciences Program is translational research dedicated to an improved understanding of chronic neurological and neurodegenerative disorders such as Multiple Sclerosis, HIV-associated neurocognitive disorders, Alzheimer's disease, Parkinson's Disease and stroke. Within this program is the newly established Peter Duncan Neuroscience Unit which overlaps with the latter conditions but with an especial emphasis on adult stem cells and Parkinson's disease with disease treatment applications using neurosurgical techniques such as transplantation and deep brain stimulation. By utilising a multi-disciplinary approach, the research program involves an array of new techniques in field of neurobiology, stem cell biology, neuroimmunology, neurovirology and neuropsychology.

The adult stem cell sub-program involves Dr Simon Jones who has taken over from Dr Juliana Lamoury. Dr Jones conducts in vitro cell culture research focusing on adult stem cells, continuing collaboration with centres in the USA, Germany, Japan, Melbourne and the University of Sydney. The aim is to promote nerve cell repair in multiple sclerosis (MS) by targeting the kynurenine pathway (KP) in brain stem cells. The project has wider implications and likely applications to brain repair more generally. The KP describes the breakdown of the essential amino acid tryptophan. We have recent data showing that activation of the KP in brain stem cells affects their ability to proliferate and mature into functional nerve cells with direct implications for repair. We are now expanding these data and exploring the effects of manipulation of the KP on brain repair in MS models.

The neuroimmunology sub-program involves A/Prof Guillemin with studies of the KP in Alzheimer's disease, amyotrophic lateral sclerosis, brain tumours and MS. The results thus far have established a significant pathogenetic role for the KP in each of the latter diseases via toxicity to brain cells and immune evasion. The data in Alzheimer disease are particularly encouraging. Inhibitors of the KP are now being explored for efficacy in Alzheimer disease. These results will also potentially have a very significant clinical benefit for MS patients. In 2013 A/Prof Guillemin will move to Macquarie University to take up a personal professorial chair. However, he will continue at AMR as a conjoint appointee and will continue active collaboration. The neuroimmunology sub-program also involves Dr Gayathri Sundaram who works with animal models on therapeutic strategies for treating MS using the experimental autoimmune encephalomyelitis (EAE) animal model. The study involves characterization of the kynurenine pathway (KP) in EAE and treatment with KP modulators to decrease the activity of EAE and by extension MS. The data have shown that the KP is activated in EAE correlating with disease progression and severity. These results have been validated in cerebrospinal fluid and blood samples form MS patients at various stages of the disease. As a consequence a new MS blood biomarker of disease activity and prognosis has been discovered. These research projects have been presented in major conferences like Pan-Asian Committee for Treatment and Research in Multiple Sclerosis and Australian Neuroscience Society

The neuropsychology and neuroHIV group involves Dr Lucette Cysique and is spread across the St Vincent's Darlinghurst campus, ranging from AMR through to the UNSW Clinical School and the Neurology, Infectious Diseases and Medical Imaging departments of St Vincent's Hospital. The group conducts cross-disciplinary research into the neurocognitive changes associated with Alzheimer disease, chronic immune disorders most particularly HIV, cancer, cardio-vascular diseases, as well as their underpinnings in brain structural and metabolic changes. Several clinical trials of novel agents for Alzheimer disease have been conducted. Dr Cysique is a research fellow at St Vincent's Hospital Clinical School, Faculty of Medicine UNSW, and an honorary research officer at Neurosciences Research Australia.

The movement disorders sub-program involves Dr Stephen Tisch who is a consultant neurologist at St Vincent's Hospital. His research background and interests are in movement disorders and deep brain stimulation including Parkinson's disease dystonia. He is involved in clinical trials of new medications for Parkinson's disease, a St Vincent's based study of remote access speech therapy for patients with Parkinson's disease and a Melbourne based collaborative study of a new device to measure symptoms in Parkinson's disease. This device will allow us to better evaluate our patients' symptoms over time to optimise therapy. With Paul Darveniza, the group has an ongoing clinical study of patients with spasmodic dysphonia and other rarer forms of laryngeal dystonia who respond well to laryngeal boutlinum toxin injections. The group plans to conduct further studies of novel drug therapy in adult's onset dystonia.

The stroke sub-program is led by Dr Romesh Markus. Numerous clinical trials have been conducted both nationally and internationally. These have recently re-defined the optimal level of blood pressure control in stroke with very significant translational benefits to patients. •

OUR CLINICAL RESEARCH PROGRAM PROVIDES HIGH QUALITY CLINICAL TRIALS SERVICES ACROSS THE ST VINCENT'S CAMPUS FOR THE CLINICAL IMPLEMENTATION OF MORE THAN EIGHTY ACADEMIC, PHARMACEUTICAL, AND INVESTIGATOR-INITIATED CLINICAL STUDIES.

CLINICAL RESEARCH PROGRAM

The Clinical Research Program provides high quality clinical trials services across the St Vincent's Campus for the clinical implementation of academic, pharmaceutical, and investigator-initiated clinical studies. CRP has expertise in multi-centre, investigator-driven, clinical research projects. The major focus and highlight of the CRP in 2012 was the successful implementation of several multi-centered clinical research projects in HIV, anal cancer and rehabilitation medicine. CRP's staffing in 2012 comprised the Head of the Program, 2 PhD candidates, the clinical research manager, 2 clinical project managers, 10 nurse study coordinators, 3 physiotherapist study coordinators, 1 part-time neuropsychologist and an administration officer.

The program currently has 80 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, treatment and observation cohort study in patients with HIV-associated neurocognitive disorders (HAND);
- Viral hepatitis - treatment and observational cohort studies in patients with and without HIV infection, including new oral treatments for hepatitis C;
- Anal cancer - observational cohort studies of the relationship between AIN and human papillomavirus in men;
- Immunology - immunogenicity of a candidate Ross River vaccine in healthy adults;
- Rehabilitation medicine – randomized multi-centered study for treatment in motor vehicle accidents; and
- Neurology - treatment studies of acute stroke, Alzheimer's disease and Parkinson's disease.

Innovation and research leadership continue as central themes for the HIV metabolic unit in 2012. This has been seen with the commencement of clinical studies in health volunteers and in HIV-positive patient adults looking at the metabolic complications of HIV antiretroviral medicine. An exciting HIV non-occupational post-exposure prophylaxis study led by the HIV Clinical Nurse Consultant is studying the safety of a new HIV antiretroviral drug in 125 men at two clinics in Sydney and was completed. There are plans for further projects in this clinical area to commence in early 2013.

In collaboration with the Kirby Institute, the SPAN observational cohort study is evaluating of the relationship between human papillomavirus and anal cancer in 500 HIV-positive and negative men. An educational program training medical staff to undertake high resolution anoscopy is underway to meet the SPAN study recruitment targets.

The program is established as an effective advocate and collaborator with established research networks, encompassing public sector, industry and investigator-initiated research on the St Vincent's Campus and other clinical sites. One of the highlights for 2012 has been the near completion of recruitment for the Acute Rehabilitation Initiative (ARI) project which is a randomized, multi centered study of rehabilitation treatment after motor vehicle accidents that is being conducted across three sites, namely St Vincent's, St George Hospital and Wollongong Hospital.

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 2 (a) (b) and 3 of development. The Viral Hepatitis research group is actively collaborating with pharmaceutical companies in participating in new and interesting compounds in the treatment of Hepatitis C infection.

In 2013, CRP will be central to the proposed development of campus-wide clinical research services, including colocation with the Research Office and gradual integration with other clinical research groups on the campus. •

case study

NURTURING OUR FUTURE CLINICIAN RESEARCHERS

One of the most effective ways to connect research with healthcare at St Vincent's is by enabling our clinicians to spend some of their time conducting research at AMR. Dr Winnie Tong is a PhD candidate and has agreed to share some of her thoughts about life as a clinician researcher at AMR.

Winnie began her PhD at AMR in 2010 and is jointly supervised by two Program Heads, Professor Andrew Carr of the Clinical Research Program and Professor Anthony Kelleher of the Immunovirology Program.

"I worked for both of them as a registrar in my first year as an immunology advanced trainee - I knew them both to be great clinicians first, then came to appreciate their impressive record as researchers. They were always approachable and supportive so I was confident they would make great PhD supervisors. I also spoke to their previous students and they were both highly recommended".

"I enjoy solving problems, and research gives me the opportunity to look at a problem in depth. Research is quite different from clinical work in the sense that you have the latitude to really ask "why?" or "how?" and spend time looking into answering these questions."

Her PhD project looks at measuring immune responses in a patient's blood to human papillomavirus (HPV), and looking to see if their immune responses correlate with precancerous disease caused by HPV. This is important in order to learn more about how to manage HPV-related precancerous disease, and also in understanding how HPV causes cancer, which may lead to new ways of treating HPV. She bounces between the immunology clinic and AMR laboratories at St Vincent's Hospital as the laboratory work for measuring these immune responses needs to be done as soon as possible after the blood is taken from the patient.

"Being at AMR, which is part of St Vincent's Hospital, is key to making translational research projects like this possible".

Students at AMR enjoy a culture which promotes knowledge creation and sharing. AMR is located within the St Vincent's Research Precinct, with other leading bodies such as the Kirby Institute, Victor Chang Cardiac Research Institute and the Garvan Institute. Winnie particularly appreciates

"the friendly and dynamic culture at AMR. No matter what your background (science or medical), you are encouraged in a positive way to learn from everyone within your lab and also on the wider campus. There are a great array of visiting lecturers and a smorgasbord of campus based seminars, journal clubs etc. to choose from every week". •

BLOOD, STEM CELL AND CANCER RESEARCH PROGRAM

The Blood, Stem Cell and Cancer Research Program focuses on the clinical application of translational research into human stem cell therapy and blood diseases. The Program uses the 'state of the art' molecular, biochemical and cell culture techniques combined with bioinformatics and clinical materials to dissect the complex mechanisms controlling normal stem cells and conditions leading to the formation of cancer knowledge gained from these laboratory results is then applied to improve patient outcomes. The Program has three research strands, being cancer stem cells, normal haematopoietic stem cells (HSC) and haemostasis.

The Program is headed by Professor David Ma, who holds the positions of Director of Research at the Department of Haematology at St Vincent's Hospital, and conjoint Professor of Medicine at the University of New South Wales. Professor Ma is internationally recognised for his strength in clinical and translational research, where he has held executive appointments in various national and international research and clinical organisations. He was the first to report the existence of multi-drug resistance, P-glycoprotein in acute leukaemia in humans. Several of his other research projects have led to new diagnostic tests, such as enumeration of stem cells for HSC harvest in blood and marrow transplantation. He has been a key investigator in some of the pioneering clinical studies in Immunotherapy and HSC transplants for leukaemia and lymphoma.

Haematological malignancies such as leukaemia, lymphoma and myeloma, are cancers of the blood and lymphatic tissues (haematopoietic tissues). They can occur in any person, young or old and may, be rapidly fatal for some sufferers. Research has shown that gene mutations lead to the transformation of normal stem cells to become cancerous. Our unit focuses on discovering genes controlling the growth and survival of cancer stem cells in these haematological malignancies and how these genes differ from those in normal haematopoietic stem cells. The practical goal of our research projects is to discover specific diagnostic tests and treatments for these cancers.

The cancer stem cell research strand is comprised of two projects. The first investigates the role of microRNAs, a class of novel regulatory genes, pathogenesis of acute myeloid leukaemia (AML), and clinically challenging and aggressive cancer of the blood. Our experiments have shown that one of these microRNAs enhances the survival of leukaemic cells, while another microRNA induces the death of leukaemic cells. We have also demonstrated that other microRNAs block the maturation of normal HSCs thus contributing to the development of leukaemia. We are now studying the mechanisms through which these microRNAs effect their functions, their epigenetic regulation, and their roles in leukaemogenesis. This project is being performed with national and international

collaborations. Our discoveries to-date have brought us one step closer to our goals identifying new tests for predicting treatment outcome and to identify genes that could be targeted by new anti-leukaemia therapies.

The second cancer stem cell project is to discover the genetic abnormality that leads to childhood leukaemia in Down Syndrome (DS). Leukaemia is a major cancer in children, and those with DS have a twenty times higher risk of developing leukaemia. A blood disorder in DS that starts in utero and presents in neonates, will evolve into an acute leukaemia in some children, particularly acute megarkaryoblastic leukaemia. Although genes on chromosome 21 are implicated as the initial step in pathogenesis, other genetic defects are likely to be involved. Induced pluripotent stem cells (iPSCs) are a promising platform for modelling human diseases. iPSCs are embryonic stem cell-like cells that were first created by reprogramming skin fibroblasts from DS using a cocktail of transcriptional factors. In collaboration with the research team at the University of Queensland, we have generated and shown that HSCs from DS-iPSCs replicate some of the abnormal characteristics of haematopoietic cells seen in DS children. We are in the process of identifying specific genetic events speculated to be involved in the multi-step

development of leukaemia in these children. The clinical goal is for early detection and prevention of disease progression to leukaemia.

The second research strand focuses on investigating ageing-associated defects in HSC function, particularly in immune recovery after HSC transplantation and autoimmune disease development. HSCT is a well-recognised treatment for certain malignant and non-malignant diseases, and adult mobilised peripheral blood (PB) is the main source of HSCs for transplantation. We have observed that T-cell reconstitution is impaired in 'aged' HSCs, which may contribute to limiting the effectiveness of adult HSC transplants. By comparing gene expression profiles of cord blood and adult PB HSCs, we have identified differences in cellular signalling pathways, including the Wnt pathway, which may contribute to the observed T-cell deficits. We have also found differences in gene expression between normal HSCs and HSCs from patients with autoimmune diseases, suggesting that accelerated ageing of HSCs may contribute to the development of autoimmune diseases. Our goal is that the outcomes of this research effort will improve the immune reconstitution of HSC transplant recipients and the treatment of patients with autoimmune diseases, leading to increased patient survival and quality of life.

The third research strand in our Program is on haemostasis. Platelets are small, circulating blood cells that contribute to the maintenance of blood flow by preventing bleeding at the site of vascular injury. Platelets circulate in a resting state and upon activation, react by a number of different mechanisms to instigate clot formation. Abnormalities in platelet number and/or function can result in bleeding or thrombosis. We are conducting a number of projects that investigate the role of platelets in diseases in collaboration with members of the Department of Dermatology/Phlebology and the Department of Cardiology at St Vincent's Hospital. One mechanism by which platelets contribute to clot formation is the release of platelet-derived microparticles. These are small (less than 1ßm) fragments of the platelet membrane that carry proteins from their parent platelet, and also expose phosphatidylserine, a phospholipid essential for the clotting process to occur. As well as investigating their clotting function, our Program also examines the role of these microparticles in disease pathogenesis and the development of novel diagnostic methods. The goal is to improve the care of patients with haemostatic problems, aligning with St Vincent's Hospital aim of continuing the delivery of compassionate holistic care.

The Program supervised numerous undergraduate medicine students undertaking their Independent Learning Project year in 2012. This allows our future doctors to appreciate the importance of research as a tool to improving the delivery of healthcare to patients. It is through this early connection that students are encouraged to consider a career as a clinician researcher at St Vincent's and ensure our Mission is strengthened and we have the capacity and agility to respond to and influence the changing healthcare landscape. •

RESEARCH FOR GLOBAL HEALTHCARE

AMR has a strong tradition of responding to the needs of the community both locally and internationally through our far-reaching research. We are inspired by the journey of the five Pioneer Sisters of Charity, who left their friends, families and religious family in Ireland to sail into Sydney Harbour in 1838, thereafter establishing St Vincent's Hospital in 1857. This inspiration challenges us to go the extra mile in supporting and caring for the poor and marginalised in our communities through connecting research with healthcare.

Professor David Ma has continued this tradition of service to the poor and marginalised through his personal journey to the communities of Myanmar where has was able to share his skills garnered from years of clinical practice and research at St Vincent's Hospital.

"In February, I was privileged to lead a specialist team to conduct a lecture tour as invited guests of the Myanmar Society of Haematology of the Myanmar Medical Association and the Minister of Health. This visit was arranged following an initial meeting with Professor Aye Aye Gyi, Departmental Head of Clinical Haematology North-Okkalapa General Hospital Yangon, at the first WHO/WBMT workshop on HSC transplantation in emerging countries in Hanoi a year earlier.

The primary purposes of the visit were to foster academic and research exchange and to assist our Myanmar colleagues to improve the delivery of healthcare services. This included the establishment of a stem cell transplant program for adults and children suffering haematological cancers and other blood diseases.

During the five day visit, we attended meetings at the Yangon General Hospital, the National Blood Centre, the North Okkalapa General Hospital, and the Universities of Medicine I and Medicine II in Yangon. This was followed by a trip to the capital, Nay-Pyi-Taw to meet Dr Pe Thet Khin, the Minister for Health, to discuss ways to improve haemato-oncology service in Myanmar. We then travelled to Mandalay to meet with the healthcare and academic staff at the Mandalay General Hospital and the University of Medicine, Mandalay.

Myanmar is the one of the largest countries in Southeast Asia with many natural beauties, historical monuments and great potentials. During this tour, we were able to appreciate the strength of their existing health system was the result of a tradition of academic excellence that has led to developing and maintaining a highly skilled medical workforce. The management of malignant and non-malignant haematology is particularly challenging in a setting where resources, including diagnostics, transfusion services, human resources and therapeutics are limited. Modernisation of the health services in Myanmar may reduce the overseas brain drain and provide economic stimuli to their country. Currently, many well-to-do citizens go overseas for their treatment creating an economic loss to their country.

Our team was extremely impressed by the enthusiasm, ingenuity and the dedication of the hospital and university staff. We came away with a keen vision and commitments to offer our supports to our Myanmar colleagues and to explore ways this could be achieved." •

DERMATOLOGY, PHLEBOLOGY AND FLUID MECHANICS RESEARCH PROGRAM

2012 welcomed the Dermatology, Phlebology and Fluid Mechanics Research Laboratory to AMR. The program began as a start-up operation of the Sydney Skin and Vein Clinic, working closely with the Australasian College of Phlebology. Eventually outgrowing its original location at Bondi Junction, A/Prof Kurosh Parsi proceeded to incorporate his research program with AMR, coinciding with his appointment as Director of Dermatology at St Vincent's Hospital. This natural transition saw the increased connection of his research with healthcare and the ability to leverage upon the translational research expertise of other programs at AMR.

The Program conducts translational research projects in the fields of skin cancer, general and vascular dermatology, sclerosant research, venous thromboembolism, vascular malformations and fluid mechanics research. The overall aim is to improve the quality of life and patient care through medical research, contributing to the healthcare community better understanding the causes of skin disease whereby more effective treatments can be developed.

According to the Cancer Council of Australia, Australians have the highest incidences of skin cancer in the world, at nearly four times the rates of Canada, USA and UK. Skin cancer accounts for 80% of all newly diagnosed cancers. The Dermatology Outpatient Clinic is a well-established branch of St Vincent's Hospital, offering skin cancer screening for a large population. An average of one hundred patients present to the clinic each week, of which 80-90% are diagnosed with skin cancer in some form. The Program intends to leverage off the St Vincent's Biobank to establish a tissue bank for the collection and storage of skin cancer biopsies obtained from patients under investigation for suspected skin cancer to facilitate collaborative research projects with the Departments of Oncology, Haematology and Molecular Genetics at St Vincent's Hospital.

A/Prof Kurosh Parsi is the chief investigator of a vascular dermatology research project which examines the incidence of venous disease and platelet dysfunction in Pigmented Purpuric Dermatoses (PPD). PPD's are a group of chronic conditions of unknown aetiology characterised by extravasation of erythrocytes and marked haemosiderin pigmentation of the skin. The project has observed that a high proportion of patients with PPD have venous disease, use antiplatelet agents, or use supplements known to affect platelet function. Furthermore, withdrawal of these agents typically leads to disease resolution. This project will eventually assess the incidence of venous disease and platelet dysfunction in patients with PPD. Another area of interest in vascular dermatology is Steward-Bluefarb Syndrome, which is a rare condition presenting with acroangiodermatitis secondary to an underlying arteriovenous malformation. This is a retrospective study of St Vincent's patients presenting with this condition.

Dr Margot Whitfield leads a number of general dermatology research projects, with findings potentially benefiting the patients of St Vincent's Hospital, in particular those that present themselves to the Dermatology Outpatient Clinic. One current project investigates the contributory role of bacteria into rosacea. Rosacea is a common skin disease, characterised by facial flushing, telangiectasia, papules and pustules. It is generally regarded as inflammatory in nature. Another project looks at the use of antimicrobial peptides in hidradenitis suppurativa. Hidradenitis supperativa is a dermatological condition commonly affecting the sweat glands, the cause of which is controversial. It is hypothesised

that bacterial infection contributes to the disease and that antimicrobial peptides may assist in treating the disease.

The Program works closely with the AMR Blood, Stem Cell and Cancer Research Program in the field of phlebology. A key aim of the Phlebology Research group is to gain a greater understanding of the biological activities of detergent sclerosants in order to improve the efficacy of treatment and to decrease the incidence of adverse events post sclerotherapy. Furthermore, the group aims to investigate new applications of sclerotherapy for the treatment of venous disease and vascular malformations. There are existing collaborations with the Department of Haematology and multiple overseas collaborations.

Sclerotherapy is routinely performed for the treatment of varicose veins and venous malformations. The procedure involves the injection of a detergent sclerosing agent (sclerosant) in order to strip the endothelial lining leading to vessel closure and eventual fibrosis. The procedure is rarely complicated by stroke, deep vein thrombosis (DVT) and pulmonary embolism. A greater knowledge of the biological activities of these sclerosants can improve the safety and efficacy of this procedure.

The project titled “The role of d-dimer in the differential diagnosis of deep vein thrombosis and deep vein sclerosis” investigates the characteristics of the non-thrombotic pathology, deep vein sclerosis (DVS), and to determine the predictive value of the D-dimer assay in differentiating between DVT and DVS. Deep vein occlusion has been observed on ultrasound following sclerotherapy of superficial veins. It is unknown whether such occlusion is thrombotic or fibrotic in nature.

The fluid mechanics stream of the Program is a collaboration with the School of Aerospace, Mechanical and Mechatronic Engineering at the University of Sydney. There are a number of projects under investigation by A/Prof Kurosh Parsi and Professor Masud Behnia.

Sclerotherapy using modern sclerosants has been practiced for at least fifty years. Over this time, a number of technical innovations have been introduced (such as the introduction of sclerosant foam) that have increased the efficiency of the procedure. Foam is typically generated as a combination of liquid sclerosant and a gas (O2, CO2 or room air). A small proportion of patients however develop neurological complications (migraine, transient ischaemic attacks or stroke) and it is presumed that this is due to the migration of gas bubbles into the brain. This study aims to determine the effects of gas type (O2, CO2 or room air), sclerosant concentration and air ratio on the formation and fate of gas bubbles to address complications experienced by patients. •

RHINOLOGY AND SKULL BASE RESEARCH PROGRAM

The Rhinology and Skull Base Research Program brings together a collective group of clinicians and researchers that work on inflammatory and neoplastic disease of the upper airway. The group headed by Associate Professor Richard Harvey, has three main research directions. In collaboration with respiratory (A/Prof Janet Rimmer), immunology (Prof Bill Sewell) and pathology (Dr Peter Earls) researchers, we investigate the origins of chronic rhinosinusitis (CRS) and other eosinophillic airway disorders, such as asthma, in both the pathophysiology but, importantly, novel therapeutic techniques. Secondly, research is undertaken into surgical techniques to manage tumours of the nose, sinus, skull base. Finally, assessment and management of nasal breathing and airflow remains the third focus of our group.

The Rhinology and Skull Base Program have been very fortunate this year to setup Australia's first air-liquid interface (ALI) model from sino-nasal epithelial cells. With sponsors from both industry, Ent Technologies, and the St Vincent's Curran Foundation, special microscope and video equipment was purchased to establish an in-vitro or lab based model that allows our group to not only culture sinus cells but differentiating them under controlled conditions where the apical surface of the cell culture is exposed to air and the cell lining develops functional cilia similar to a 'true' mucosal surface. The ALI model allows assessment of the impact of multiple insults to our respiratory system from cigarette smoke, diesel fumes, environmental pollution, allergens and viruses. The cilia are assessed under a special high speed camera and their mechanical function is analysed. This model puts us at the forefront of research into the origins of inflammatory respiratory conditions and the testing of novel therapeutic agents.

We had our first dedicated skull base PhD student, Leon Lai, complete his thesis on the "The Evolution of Intracranial Aneurysm Surgery through History, Contemporary Practices, and Continuing Innovations". This worked compromised multiple anatomical studies on surgical access to the skull base including systematic reviews and meta-analysis of perioperative outcomes in skull base surgical cases. The secondary research theme was also continued with several Cochrane reviews and a meta-analysis of the surgical outcomes of endoscopic and external dacrocystorhinotomy (tear duct surgery). We are proud to now be part of the Cochrane ENT Disorders group with A/Prof Richard Harvey joining the Cochrane team as an associate editor.

Clinical research continues into the inflammatory changes that occur in chronic rhinosinusitis (CRS). This year we completed several large studies on the bone remodelling and neo-osteogensis that occurs in this condition. Studies focused on the changes observed, their clinical relevance, hisopathological correlation and prognosis to therapy. Three honours students joined us this year to continue investigation into CRS. A joint program was commenced with John Zaunders and his group to investigate the presence of innate lymphoid cells(ILCs) in sino-nasal mucosa. These ILCs are unique non-B non-T lymphoid cells that are only recently described and thought to mediate much of our body's initial immune response to the outside environment.

Finally, a second nasal airflow testing lab was established under our collaboration with George Marcells, rhinoplastic surgeon. A full time honours student is currently investigating airflow obstruction due to collapse of the cartilages of the nose (nasal valve dysfunction) and the surgical interventions that we perform to correct this situation. The additional testing facilities and patient throughput is likely to greatly enhance our research output and includes us as one of the few units in the world to be routinely performing objective assessment for these procedures.

The Rhinology and Skull Base team remains a dynamic multidisciplinary team of researchers and clinicians actively involved in the care of patients with inflammatory and neoplastic disease of the upper airway. We remain dedicated to ensuring that our research remains directly translatable and changes clinical practice. •

OUR CLINICAL RESEARCH PROGRAM PROVIDES HIGH QUALITY CLINICAL TRIALS SERVICES ACROSS THE ST VINCENT'S CAMPUS FOR THE CLINICAL IMPLEMENTATION OF MORE THAN EIGHTY ACADEMIC, PHARMACEUTICAL, AND INVESTIGATOR-INITIATED CLINICAL STUDIES.

THE STRUCTURAL BIOLOGY PROGRAM

The Structural Biology Program is the only research group that is physically located at the Kensington campus of the University of New South Wales due to the availability of state of the art imaging equipment. We use various technologies such as x-ray crystallography, recombinant DNA technology, protein chemistry and biophysics and bioinformatics. X-ray crystallography is used to determine the structures of several proteins including molecular chaperones, ion channels, cell receptors, serpins and light harvesting proteins. Computer methods such as molecular dynamics simulations are being used to determine the mechanical and electrostatic properties of proteins of known structure.

Some of the projects the group is currently working on are:

- The CLIC chloride ion channels
- Ribonucleicproteins (RNPs)
- Light-harvesting proteins

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 proteins 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.

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.

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.

Proteins are the fundamental molecular machines in any living system. Understanding how these machines work requires a knowledge of the three dimensional atomic structure of the protein, with computer methods are being used to attack this problem. The focus of our group is to understand the molecular and cellular function of various protein systems. Our key experimental technique is x-ray crystallography, although we also utilise a battery of other biochemical and biophysical techniques to enhance our understanding. The laboratory has several themes including: membrane proteins, proteins that undergo dramatic structural changes, light harvesting proteins and molecular machines. The program uses the tools of modern molecular biology to prepare proteins of choice. These are then characterised via biophysical and biochemical means prior to structure determination. We use computational and bioinformatic tools to analyse our structures. We are also exploring the physical basis for the structures observed in proteins, structural patterns, their structural transitions and mechanisms of action. This laboratory is part of the Initiative in Biomolecular Structure (IBiS). •

VIRAL HEPATITIS CLINICAL RESEARCH PROGRAM

The Viral Hepatitis Clinical Research Program (VHCRP) focuses on therapeutic research in the field of viral hepatitis. The VHCRP team is one of 11 research programs within the Kirby Institute and was founded in 2003. Within VHCRP, the laboratory group operates at AMR, working closely with a large international network of collaborators from leading academic institutions.

This combined research effort supports studies on host and viral immune interactions, HCV transmission and resistance to therapy. It also supports St Vincent's achievement of connecting research with healthcare, improving excellence in holistic care and being recognised as a leader in research and teaching built on a relationship model that requires collaborating with our staff, research institutions and clinical and education partners. Developing these partnerships will ensure that AMR is equipped to develop new models of health delivery which will be at the forefront of patient centred care.

The Program supports Honours, PhD and MD candidates in the field of HCV research. Current research projects active within the laboratory team include:

Defining Risk And Mechanisms of Permucosal Transmission for acute C HCV infection within high-risk populations (RAMPT C).

This study seeks to characterize further permucosal transmission of HCV in both HIV-positive and negative Men who have Sex With Men (MSM) through three sub studies.

1. Molecular phylogenetic analysis of NS5b and E1/2 regions of the HCV genome for both retrospectively and prospectively recruited patients together with HCV and HIV clinical parameters. This will explore clustering of HCV cases.
2. Semen study of HCV RNA quantification and molecular sequencing in acute and chronic HCV cases both HIV-positive and – negative, together with serum HCV analysis and sexually transmitted infection testing (STI). This is to explore the relationship between serum and semen HCV viral loads and the possible role of STIs in sexually transmitted HCV.
3. Behavioural study of HIV positive MSM with acute HCV: detailed interviews exploring the role of sexual and drug practices in HCV transmission.

Investigating Transmission dynamics of HCV Among injecting drug users in Canada and Australia (ITHACA).

Frequent exposures to HCV due to ongoing high-risk behaviour in IDUs suggest the likelihood of undiagnosed mixed infections remains high. The transmission dynamics and the prevalence and rate of new and mixed HCV infection will also be assessed in samples collected from a number of well-characterised longitudinal studies of either high risk HCV-negative populations in Vancouver Canada, or patients with recently acquired HCV in clinical settings in Australia. These cohort studies have identified a large number of new HCV infections within both older long-term injectors and young people who initiate injecting, and provide an invaluable opportunity to assess transmission networks among these geographically and socially distinct groups.

Development of tools to help diagnose acute HCV infection and predict spontaneous clearance.

Acute HCV is largely asymptomatic at presentation and often remains undiagnosed as a result. It is important to determine whether someone with newly diagnosed HCV is in the acute or chronic phase of infection to improve patient outcome by initiating early therapy and to also help standardise surveillance of HCV incidence. Initiation of treatment is often delayed in patients with acute HCV to determine if they will spontaneously clear the virus without the need for therapy.

Spontaneous clearance naturally occurs in approximately 25% of patients. The laboratory is developing methods in house and working with collaborators from Gartnavel General Hospital (Scotland) and the University of Toronto (Canada) and The University of New South Wales (Australia) to develop these tools to assist management of acute HCV.

Development of Dried Blood Spots (DBS) as a tool to enhance HCV surveillance and clinical research.

It has been clearly demonstrated that DBS can provide a mechanism to better engage people who inject drugs (PWID) in surveillance programs designed to monitor factors associated with spread of infectious disease. DBS assays may improve the feasibility of conducting large multi-national clinical trials and provide a viable alternative to support patient care in resource poor settings. In collaboration with Tony Kelleher (Immunovirology and Pathogenesis Program, The Kirby Institute) and Philip Cunningham (NSW State Reference Laboratory for HIV & Molecular Diagnostic Medicine Lab, St Vincent's Hospital), the VHCRP laboratory is developing virological assays to facilitate an accurate estimate of the true HCV incidence in PWID, characterize HCV genotype distribution, mixed HCV infection and phylogenetic analysis of potential transmission networks. Assays to detect human genetic polymorphisms associated with HCV spontaneous clearance and treatment outcome are also being developed.

The Program is also responsible for management of Hepbank, a comprehensive collection of well characterized samples from HCV positive patients recruited from various clinical trials led or managed by the VHCRP team. These samples are used for VHCRP laboratory research projects, as well as being available to external research institutions for HCV related research. Over 20,000 samples are currently stored in the Hepbank repository. In addition the team supports protocol development, sample collection and processing for current VHCRP HCV clinical trials such as ATAHC II, ACTIVATE, RAMPT-C, ATAHC RECALL, SEARCH-C and DARE C, details of which can be viewed at the Kirby Institute's website. The team has developed a new database (LabKey), which links laboratory data generated from approved substudy research with clinical, demographic and sample data, in now in use to design and analysis of current and future studies. LabKey also allows entry of laboratory sample data remotely for samples processed offsite to assist trial management. •

HIV GENE THERAPY PROGRAM

The HIV Gene Therapy Program is operated by Calimmune, a world-class biotechnology company that is based in the USA. The work of this program at AMR is evidence of our linkages with the biotechnology industry and leveraging the core competencies of both organisations. This type of collaboration ensures that the connections between privately funded research and public healthcare at St Vincent's Hospital are nurtured.

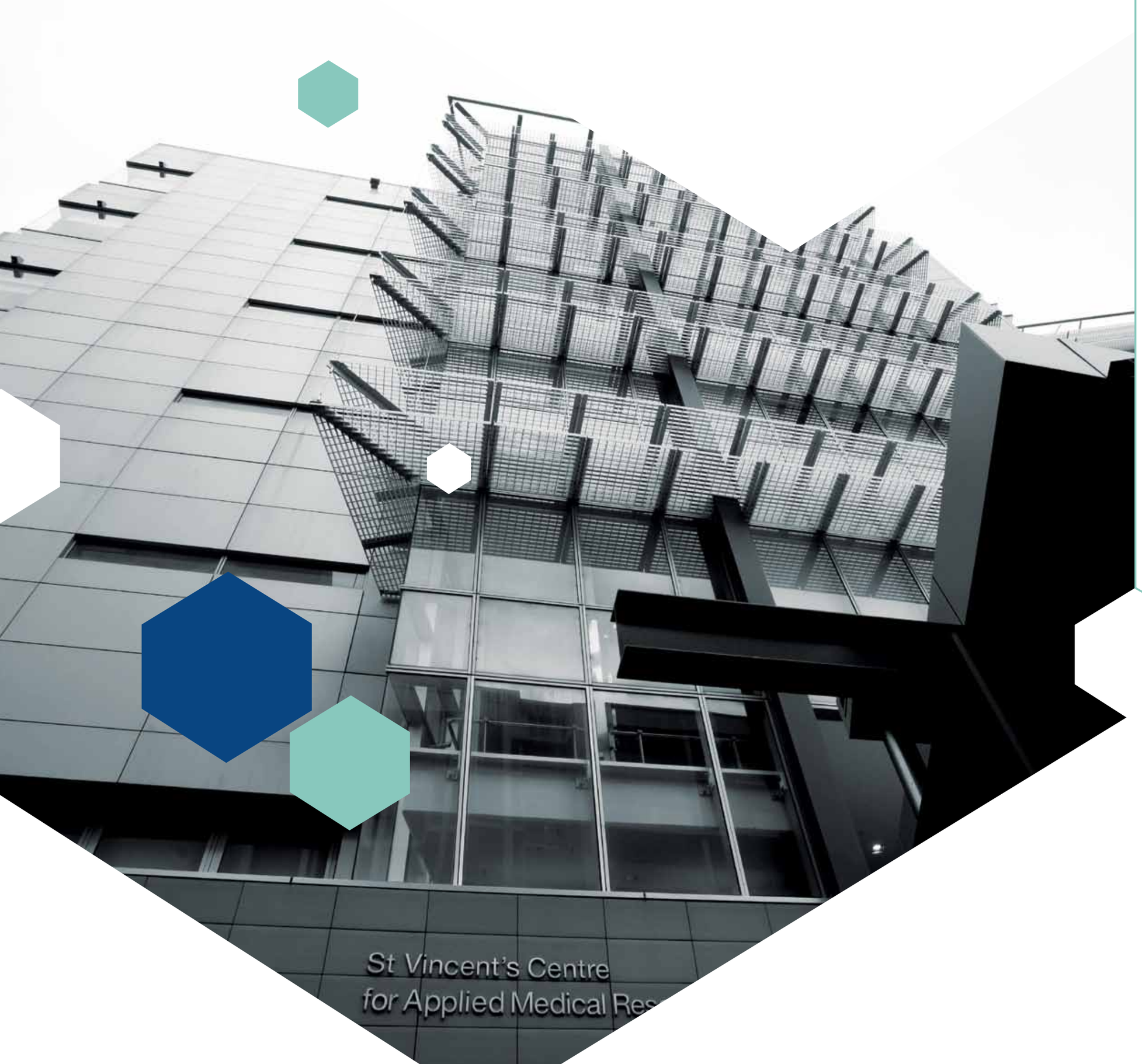
The work of the group involves molecular biology and tissue culture experiments analysing the impact of anti-HIV gene constructs. These gene constructs are targeted to both HIV and cellular factors required for HIV infection and replication. The work progresses through the stages of

i) engineering the anti-HIV constructs themselves,
ii) producing self-inactivating lentiviral vectors containing the constructs,
iii) introducing the constructs (transduction) to relevant cell populations (T cell lines, peripheral blood mononuclear cells, haematopoietic stem cells),
iv) analysing the transduced cell populations for anti-HIV gene expression and function, including HIV challenge,
v) and determining impact of the anti-HIV gene constructs in humanized mouse models and non-human primates.

This approach follows classical drug development but is somewhat more complicated as it deals with cell delivery. Thus characterisation of the product is the phenotype of the cell and potency is the ability to perform the anti-HIV function. The pre-clinical data is now complete and clinical trials have been approved by the Food and Drug Administration, FDA (USA) and the Therapeutic Drug Administration, TGA (Australia) The clinical trial in the USA has commenced and that in Australia will initiate shortly.

Clinical trials are designed around the introduction of the anti-HIV agents into appropriate target cells – CD4+ T lymphocytes or CD34+ haematopoietic stem cells outside the body and their re-infusion to the individual. The concept being tested is that these gene protected cells will form a new population of blood cells resistant to HIV and its pathogenic effects acting to reduce viral load and increase T cell count in the individual. This will potentially be a one-time or infrequent treatment and reduce fully or partially the need for anti-retrovirals. The latter must be taken daily for life and have significant co-morbidity issues.

The HIV Gene Therapy Program works closely with the HIV Immunovirology Program, with shared laboratory and office space ensuring knowledge is shared and collaborative research projects are forged with the goal of improving the delivery of healthcare to the poor, sick and disadvantaged. •



WHETHER OR NOT YOU COME FROM A MEDICAL OR SCIENCE BACKGROUND, AT AMR, YOU ARE ENCOURAGED IN A POSITIVE WAY TO LEARN FROM EVERYONE WITHIN YOUR LAB AND ALSO ON THE WIDER ST VINCENT'S CAMPUS

DARLINGHURST CAMPUS RESEARCH FACILITIES

In recent times, AMR programs have actively participated in the Darlinghurst campus capital master planning process. One of the major outcomes is the overwhelming need to realign and focus on the development of structures and processes to integrate all Darlinghurst-based research and teaching initiatives. The Darlinghurst campus, one of Australia's largest and most successful bio-medical research hubs, will support and enable a greater focus on translational research where there is an intersection of clinical and research expertise.

During this time of continued transition the facilities of St Vincent's Research Precinct are working together, under the direction of AMR, on the Darlinghurst Campus Translational Research Steering Committee. The likely result of this review is that AMR will cement its position as the peak research body for the campus, while recognising the important contributions of the co-located but independent Garvan Institute of Medical Research and Victor Chang Cardiac Research Institute. Their close physical proximity reflects the strong working relationships of these organisations, with many core facilities being shared among the University of New South Wales, the Kirby Institute, VCCRI and Garvan.

AMR is the lead precinct partner for the provision of the cryogenics essential shared service facility which incorporates the St Vincent's Biobank. This facility was purpose built to address many of the workplace health and safety issues associated with handling cryogenic fluids, pressurised gases, extremely low temperatures (as low as -196°C), and samples which may be biologically hazardous, including infectious microorganisms and genetically modified organisms.

Other shared essential services on the St Vincent's Research Precinct are stores and loading dock services, glass washing and media preparation. Pooling these resources from each partner organisation on the precinct enables lead partners to focus and excel on their allocated service and realising valuable cost efficiencies. These shared services are further leveraged with the opening of the Kinghorn Cancer Centre, a joint initiative between St Vincent's Hospital and the Garvan Institute. Researchers and clinicians will be co-located within this building to create an integrated translational research facility where research findings move quickly into clinical care, and clinical challenges drive laboratory research. With the commencement of operations of this Centre, there will be further opportunities for research to excel on the precinct.

The ultimate aim to be achieved from this initiative is the critical mass required to support quality translational research, world class research talent and greater research funding. The vision is to create a world-leading health services and research campus that conducts a continuum of high quality applied and translational, discipline-based and multidisciplinary research, that is mission aligned and contributes actively to the relief of human illness and suffering. The combined efforts of AMR and the Kirby Institute to form a single unincorporated joint venture and successfully qualified for State Medical Research Support Program infrastructure funding, ranking in the top three of the funded organisations in NSW. This partnership has an independent board of management, housed within magnificent facilities on the St Vincent's Research Precinct.

The PC3 laboratory within the Lowy Packer Building, managed by AMR, is a modern purpose built and modular facility giving researchers the flexibility to handle a number of infective organisms and genetically modified organisms at any one time.
The facility was primarily designed to handle human immunodeficiency viruses (HIV-1) and houses a cell sorting flow cytometer which allows researchers to safely study cell populations from individuals with HIV and viral hepatitis infections.

In addition to the flow cytometer, we have installed a seven parameter, high-resolution live cell microscope within our facility. The sensitivity and resolution of this microscope has enabled our researchers to track single viral particles over time. The system is also compatible to read and acquire high throughput data and thus ideal in screening anti-HIV compounds/ strategies. This facility is the only PC3 facility with such capacity and enables unique research into the immunology, natural history and pathogenesis of these infections. This facility is certified by the Federal Government Office of the Gene Technology Regulator (OGTR) ensuring the standards and work practices are complied with and permits research involving genetically modified microorganisms (GMO) to be carried out.

The St Vincent's BioBank, also managed by SVCAMR, was established in 2010 to provide researchers with high quality biological tissues and samples that will translate to better health outcomes for patients. The biorepository is a significant resource that carefully manages many of the issues around ethics and compliance that pertain to the use of human blood and tissues in medical research.

The BioBank has the capacity for over five million samples which are all stored in 'suspended animation' which enables future biomedical research on living cells and tissue. It also is the home for a number of valuable 'tissue banks' which holds specimens collected from patients with a variety of diseases including cancer, HIV, viral hepatitis and heart disease. Tissue banks are valuable resources which enable researchers to study diseased samples with a view to develop treatments and better diagnostic tests. Demand for this premium service has increased significantly during 2012, resulting in the impending commissioning of a new vapour phase. •

FUNDING AND DONORS

AMR would like to thank the generosity of our funders and donors. With your valued support, we have been able to conduct leading edge research and adopt effective new technologies to realise the Vision of St Vincent's Hospital as being a leading healthcare organisation. The research we conduct enables the poor and vulnerable in our community to benefit from innovative healthcare.

2012 has seen an increase in the value of research grants awarded to AMR, a reflection of the quality, importance and productivity of the projects investigated by our researchers. This is also a reflection of the time and effort our researchers put into numerous grant applications to ensure their investigations are financially supported over the long-term.

GOVERNMENT, NON-PROFIT AND INDIVIDUALS

Arrow Bone Marrow Transplant Foundation
Australian Research Council
Cancer Council NSW
Cancer Institute
Curran Foundation – St Vincent's Hospital
Department of Health and Ageing, Australian Government
Fondation Jérôme Lejeune
Multiple Sclerosis Society
National Health and Medical Research Council
NSW Ministry of Health, Office of Medical Research
NSW Ministry of Health, Applied Spinal Cord Injury Research Fellowships
Peter Duncan and Family
Rebecca L Cooper Medical Research Foundation
Royal Thai Government
St Vincent's Clinic Foundation
St Vincent's Clinical School
St Vincent's Hospital Sydney
Sydney Foundation for Medical Research
Thomas Christopher Wright
University of New South Wales

BIOMEDICAL AND PHARMACEUTICAL INDUSTRY

Aveo Pharmaceuticals
Bristol-Myers Squibb
Merck, Sharpe and Dohme Australia
Gilead Sciences
GlaxoSmithKline
INCResearch/Kindle
Janssen-Cilag
Life Healthcare
Medtronic
Novartis
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Parexel International
Pfizer
Quintiles
Roche Products
ViiV Healthcare
Wyeth Australia •

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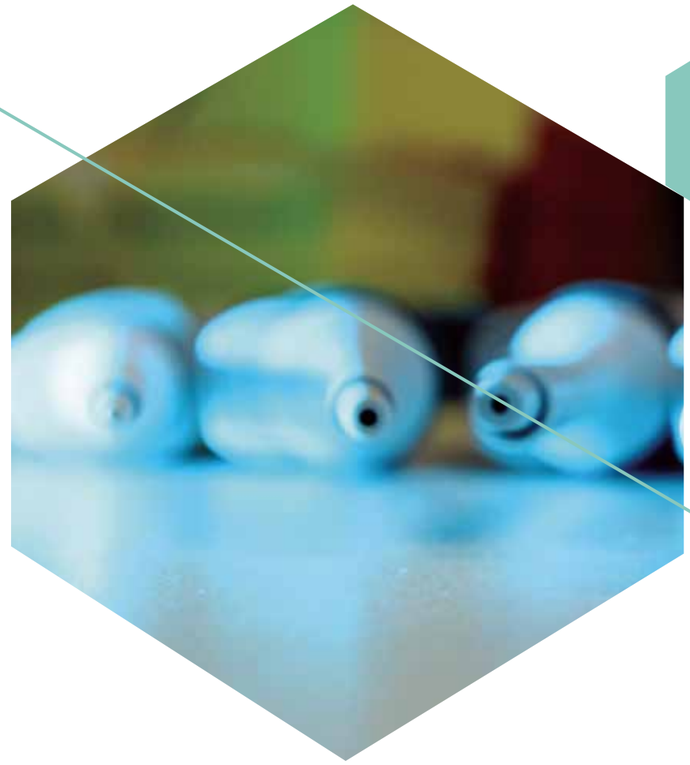

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St Vincent's Hospital is nationally and internationally recognised as one of Australia's leading and technologically advanced hospitals, enhanced by the teaching and research conducted by our highly skilled and experienced scientists at AMR. To continue the hospital's achievements in connecting research with healthcare, AMR provides clinicians with the opportunity to be relieved from their clinical duties and dedicate a period towards research. This enables staff to acquire the latest skills and knowledge in their respective disciplines, in turn providing innovative and technically sophisticated services to the patients of St Vincent's Hospital and the wider community.

Through the extensive global collaborations of AMR programs, we have been referred many PhD candidates who seek to be supervised by the vast array of our internationally renowned researchers. We promote an abundance of learning opportunities for our students through working closely with the Kirby Institute and the UNSW St Vincent's Clinical School. Weekly seminar series are conducted to allow students to draw upon the knowledge of their peers, and also provides the chance for students to receive support and feedback when presenting their findings. AMR provides additional financial assistance to PhD students in receipt of peer-reviewed and competitive scholarships to attract candidates at the top of their respective fields.

SVCAMR research programs also support Independent Learning Project (ILP) medical students. This initiative aims to promote lifelong learning patterns and skills which enable prospective clinicians to approach future medical challenges in their careers with a rigor and depth not possible without a detailed knowledge of the formal processes of research, literature appraisal, data collection, analysis and presentation. The aim of the ILP is to acquire knowledge of research principles and methods applicable to the discipline and its professional practice, and develop cognitive, technical and creative skills to investigate, analyse and synthesise complex information, problems, concepts and theories and to apply established theories to different bodies of knowledge or practice. Some of our senior scientists also supervise Masters and Honours students from the University of Sydney, Macquarie University and Notre Dame University.

DOCTORATES AWARDED

Seray Adams
Kynurenine pathway in the persistence of brain tumours
Supervisor: Gilles Guillemin

Nady Braidy
NAD metabolism in aging and degenerative diseases
Supervisor: Gilles Guillemin

Mee Ling Munier
The role of HIV-specific CD4+ T-cells at primary infection
Supervisors: Tony Kelleher, Bill Sewell, John Zaunders

Gayathri Sundaram
New treament for multiple sclerosis based on trypophan metabolism
Supervisor: Gilles Guillemin

Chris Weatherall
Characterisation of B-lymphocyte responses in primary HIV infection-neutralising antibodies and immune tolerance
Supervisors: David Cooper, Tony Kelleher

PHD STUDENTS

Laura Cook
Characterisation of T regulatory cells
Supervisors: Tony Kelleher; Nabila Seddiki

Araluen Freeman
Identification of biomarkers in Barrett's oesophagus and oesophageal adenocarcinoma
Supervisor: Reginald VN Lord

William Hey-Cunningham
Delineation of the latent HIV reservoir with subpopulations of Memory CD4 T cells
Supervisors: Tony Kelleher, Kersten Koelsch, John Zaunders

Hila Haskelberg
Antiretroviral toxicity in HIV-infected patients
Supervisors: Andrew Carr, Sean Emery, Janaki Amin

Mahsoud Hassanpour
The role of MIC-1/GDF15 and CEBPD in spinal cord injury
Supervisor: David Brown

Denise Chee Hsu
Using novel biomarkers to define the role of TV specific effector T cell and TB specific regulatory T cells in patients with Mycobacterium tuberculosis (TB) and HIV co-infection
Supervisors: David Cooper; Jintanat Ananworanich (HIVNAT); Tony Kelleher

Tina Iemma
The role of dynamin-II in HIV pathogenesis
Supervisors: Stuart Turville, Phillip Robinson

Brendan Jacka
Viral epidemiology of multiple Hep C infections in international high risk populations
Supervisors: Tanya Applegate, Jason Grebely, Greg Dore

Scott Ledger
The effects of anti-attachment and fusion inhibitor gene-therapies in the protection of HIV susceptible cells
Supervisors: Geoff Symonds, John Murray

Frederick Lee
Complications of antiretroviral therapy
Supervisor: Andrew Carr

Allison Martin (Humphries)
Toxicities associated with antiretroviral treatment of HIV-1 antiretroviral treatment effects on HIV infection
Supervisors: Andrew Carr, Sean Emery, Janaki Amin

Samantha McAllery
Proteomics of True de novo HIV in the context of productive infection
Supervisor: Stuart Turville

Kristin McBride
Studies of the latent reservoirs of HIV-1
Supervisors: David Cooper, Tony Kelleher, Kersten Koelsch

Catalina Mendez
Defining the role of RNAi transcriptional silencing of HIV-1
Supervisors: Tony Kelleher, Kazuo Suzuki

Daniel Murray
The role of microRNA in HIV-1 progression
Supervisor: Tony Kelleher

Andrew Mynott
Structural investigations of CLIC proteins and importin-β recognition of nuclear localisation signals
Supervisor: Paul Curmi

Rebecca Akao Oyomopito
HIV-1 drug resistance in treatment-naïve and combination antiretroviral therapy exposed patients in Asia
Supervisors: Matthew Law, Tony Kelleher, Suzanne Polis

Juanita Phang
Structural studies of CLIC protein complexes
Supervisors: Paul Curmi, Krystyna Wilk, Anthony Duff

Chansavath Phetsouphanh
Re-characterising CD4+ T cell responses to HIV
Supervisors: Tony Kelleher; Nabila Seddiki

Kanin Salao
The role of CLIC-1 in immune/inflammatory response
Supervisor: Samuel Breit

Ivy Shih
Characterisation of HIV spread between physiologically relevant cell targets of the immune system
Supervisors: Stuart Turville, Najla Nasr

Winnie Tong
Measurement of immune responses to clinically significant viral pathogens in immunocompromised adults
Supervisors: Andrew Carr, Tony Kelleher

James Walsh
Control of Prokaryotic Cell Division via Turing Mechanisms
Supervisors: Paul Curmi, Chris Angstmann, Iain Duggin

Yin Xu
How does SIV enter follicular helper T cells?
Supervisor: Tony Kelleher

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Nadine Dermody
What are the most reliable quantitative neuropsychological methods to assess cognitive change? A review Study Paper: Assessing three different quantitative neuropsychological methods for the determination of cognitive change in a sample of HIV-negative individuals.
Supervisor: Lucette Cysique

Jody Kamminga
The prevalence of neurocognitive disorder in a primary care HIV positive cohort compared to a HIV negative control cohort: criterion validity for CogState vs. standard neuropsychological testing.
Supervisors: Lucette Cysique, Jennifer Batchelor

Grace Lu
HIV Dementia Scale re-test reliability and association with demographic and clinical predictors of HIV-associated neurocognitive disorders.
Supervisor: Lucette Cysique

James Soares
Striato-frontal and corpus callosum volumetry and white matter integrity in a cohort of middle-aged HIV+ and HIV- individuals.
Supervisor: Lucette Cysique

ILP STUDENTS

Anoosha Aslam
An investigation of the Relationship Between Antiplatelet Drug Therapy and Platelet Microparticle Formation and Procoagulant Activity in Patients with Cardiovascular Disease
Supervisor: David Ma

Joohye (Grace) Kim
The development of an air-liquid interface cell culture model
Supervisors: Richard Harvey, Janet Rimmer

Teck Khai Lim
MicroRNA-155 gene expression in Haematopoietic progenitors and its function in Acute Myeloid Leukaemia
Supervisor: David Ma

Arthur Wong
Detection of Hepatitis C Mixed Infection in People Who Injects Drug
Supervisor: Tanya Applegate •

COLLABORATORS

INTERNATIONAL

Aaron Diamond AIDS Research Center, New York, USA

AIDS Research Alliance, Los Angeles, California, USA

AIDS Research Institute irsiCaixa, Badalona, Spain

Asociación Civil IMPACTA Salud y Educacion, Lima, Peru

Beijing Mental Health Institute, Peking University, Beijing, China

Biostatistics and Bioinformatics Branch, National Institute of Child Health and Human Development, NIH, Bethesda, Maryland, USA

British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada

Calimmune Inc. United States

Cardiovascular Institute, Mount Sinai Hospital, New York, New York, USA

Centre for Aging and Regeneration, Faculty of Biological Sciences, P. Catholic University of Chile, Santiago, Chile

Centre National de la Recherche Scientifique, UMR 8199, Pasteur Institute, Université Lille Nord de France, Lille, France

Centro Interdiciplinario de Neurociencia de Valparaiso, Facultad de Ciencias, Universidad de Valparaiso, Valparaiso, Chile

Changi General Hospital, Singapore

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Developmental Neuroscience Lab, NYSIBR, New York, USA

Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

Guy's and St Thomas' NHS Trust, London, United Kingdom

HIV Netherlands Australia Thailand Research Collaboration, Thai Red Cross AIDS Research Centre, Bangkok, Thailand

HIV Neurobehavioral Research Center, University of California San Diego, San Diego, California, USA

Howard University College of Medicine, Washington District of Columbia, USA

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National Center for AIDS/STD Control and Prevention, Beijing, China

NeurogesX, Inc, San Mateo, California, USA

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Ohio State University College of Medicine, Columbus, Ohio, USA

Oregon Health and Science University, Portland, Oregon, USA

Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University, Boston, Massachusetts, USA

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The Pennsylvania State University, University Park, Pennsylvania, USA

The Salk Institute for Biological Studies, California, USA

Unidad de VIH, Servicio de Medicina Interna, Hospital U. La Paz, Madrid, Spain

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Contact Information and Acknowledgements

St Vincent's Centre for Applied Medical Research
Level 4 Lowy Packer Building
405 Liverpool Street
Darlinghurst NSW 2010
P +61 2 8382 4900
F +61 2 8382 4901
www.amr.org.au

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