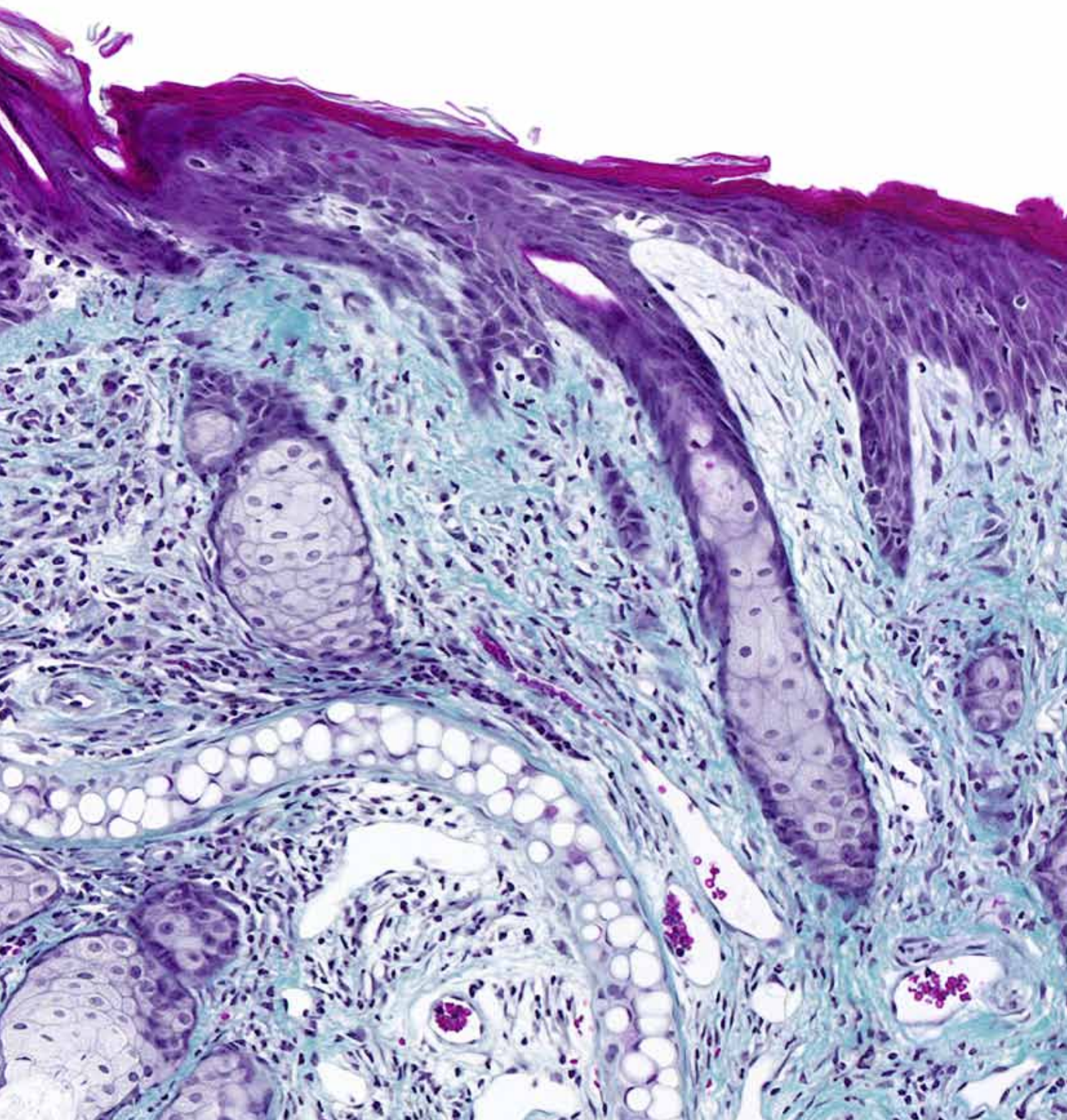
2012

Annual Report

Centre for Cancer Biology



2012
Annual Report

Centre for Cancer Biology

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cover image
mMCP4 protects against chronic UVB-induced ulceration and neoplasia development
Cross-section of chronically UVB-irradiated ear of mast cell-deficient c-*Kit*$^{W/W-v}$ mouse.
Section stained with Masson's trichrome

Organisational Chart

Executive Director SA Pathology
Mr Ken Barr

Research Director SA Pathology
Professor Heddy Zola

Co-Director Centre for Cancer Biology
Professor Angel Lopez

Co-Director Centre for Cancer Biology
Professor Sharad Kumar

Acute Leukaemia Laboratory
Professor Richard D'Andrea

Cell Signalling Laboratory
Dr Yeesim Khew-Goodall

Cytokine Receptor Laboratory
Professor Angel Lopez

Gastroenterology Research Laboratory
Assoc Prof Andrew Ruszkiewicz

Gene Regulation Laboratory
Professor Greg Goodall

Haematology Clinical Research Unit
Professor Luen Bik To

Hepatitis C Virus Research Laboratory
Assoc Professor Michael Beard

Leukaemia Biology Group
Professor Junia V. Melo

Leukaemia Unit, Genetics and Molecular Pathology
Assoc Professor Susan Branford

Lymphatic Development Laboratory
Assoc Professor Natasha Harvey

Mast Cell Laboratory
Assoc Professor Michele Grimbaldeston

Melissa White Memorial Laboratory: Clinical
Professor Timothy Hughes

Melissa White Memorial Laboratory: Research
Assoc Professor Deborah White

Molecular Pathology Research Laboratory
Professor Hamish Scott

Molecular Regulation Laboratory
Professor Sharad Kumar

Molecular Signalling Laboratory
Assoc Professor Stuart Pitson

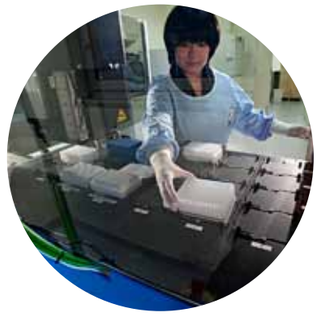
Myeloma Research Laboratory
Professor Andrew Zannettino

Neurovascular Research Laboratory
Dr Quenten Schwarz

Tumour Microenvironment Laboratory
Dr Michael Samuel

Vascular Biology and Cell Trafficking
Dr Claudine Bonder

ACRF Cancer Genomics Facility



ACRF Cancer Genomics Facility
Ming Lin operates a Caliper Sciclone NGS Workstation robot to select or capture the ~2% of the human genome (genes encoding proteins) that we understand most to load onto the DNA sequencer.

SA Pathology Executive Director's Report

It gives me great pleasure to present the third Annual Report of the Centre for Cancer Biology (CCB) of SA Pathology and to reflect on its successes in 2012.

Since its establishment in 2009 as a hub of cancer research excellence, the Centre for Cancer Biology has steadily grown. New laboratory heads have been recruited, new technologies brought in and new facilities have been established. This growth has energised a virtuous cycle with a significant rise in competitive research grants, Fellowships and infrastructure funding for the CCB.

As you will see in this Annual Report, 2012 has been yet another highly successful year for the CCB. The membership of its Faculty has grown, several new Fellowships and research grants have been won, and the CCB has earned and received donations for much needed state-of-the-art equipment that ensures our researchers continue to be competitive which facilitates the translation of discoveries into better cancer treatments.

Having arrived last year from the National Health Service in the UK where health care is strongly linked to excellence in scientific research, I have been impressed with the integration of the CCB with the rest of SA Pathology. The close association of our pathologists with CCB researchers helps maintain the high quality of our diagnostic pathology services whilst giving our CCB researchers access to the most relevant pathology samples needed to make their cancer discoveries. The further integration of the CCB work with our own clinicians and clinicians at the Royal Adelaide Hospital provides reciprocal benefits to research and clinical care.

This close association between diagnostic and research activities is further boosted with the opening of the ACRF Cancer Genomics Facility, creating a wonderful formula that is already helping further advance the personalised cancer care provided by SA Pathology in South Australia, as well as boosting cancer, genomics and bioinformatics research for the CCB, our University of Adelaide partner and the SA research community in general.

As you will also see in this Annual Report the CCB enjoys a wonderful association with the rest of the research community and in particular with the two neighbouring universities: the University of Adelaide and the University of South Australia, with which it shares students, equipment, library facilities and seminar programs. Of note also are the CCB links to industry that facilitate the commercialisation of many of its inventions and their development for clinical use.

As I reflect on the future of health care for the State, I cannot fail to appreciate how well SA Pathology and the CCB fit with the recently released McKeon report and its Strategic Review of Health and Medical Research commissioned by our Federal Government. Its motto of 'Better health through research' could not better epitomise what we are doing in SA Pathology today. The McKeon Report mirrors our vision and gives us further considered evidence of the benefits to be gained by facilitating and strengthening the excellent work of the CCB.

Ken Barr
Executive Director, SA Pathology

Centre for Cancer Biology Directors' Report

Professor Sharad Kumar MSc PhD FAA

Professor Angel Lopez MBBS PhD FRCPA

We are delighted to present the third Annual Report of the Centre for Cancer Biology. As in previous years, the CCB continued to achieve significant landmarks in 2012, with the opening of the $6.5 million ACRF Cancer Genomics Facility being one of the highlights. This new facility was inaugurated on October 2 by the Right Honourable Minister John Hill, SA Minister for Health and Ageing, and Mr Tom Dery, Chairman of the Australian Cancer Research Foundation Board of Directors. This unique facility in South Australia is already being used to annotate the DNA of patients' cancers to enable researchers and physicians to categorise and define cancers more accurately for better and more personalised ways of treating each patient. This is being used by South Australian and CCB investigators in discovery, translational research (eg clinical trials) and standard cancer care.

Research at the CCB continued to encompass basic understanding of why and how cells become malignant, how they spread, what keeps them alive and sometimes makes them resistant to killing by therapeutic drugs, as well as advanced translational and clinical work focused on improving treatments. Given the wide scope of cancer research being performed at the CCB, our scientists made significant advancements in the fundamental understanding of tumourigenesis as well as in personalised treatment of certain cancers.

CCB researchers published 110 scientific articles in the 2012 calendar year. There were many research highlights and we include a small selection here. In a collaborative study published in the *Journal of Clinical Investigation*, Professor Greg Goodall and colleagues from the MD Anderson Cancer Centre in the US (Dr Don Gibbons and Dr Jonathan Kurie) identified several miR-34a target genes required for tumour cell invasion. Their findings provide a strong rationale to develop miR-34a as a therapeutic agent in a distinct group of cancer patients. In a study published in the prestigious *Journal of Clinical Oncology*, Associate Professor Susan Branford's laboratory provided new data on the optimal response to therapy after diagnosis of CML, which has direct implications in the clinical management of this blood cancer. In a publication in *Molecular Psychiatry*, Dr Quenten Schwarz and Professor Angel Lopez discovered that 14-3-3 proteins, previously shown to be important for regulating blood cell signalling, are central players in schizophrenia. In another high profile paper in the *Journal of Clinical Investigation*, Dr Michael Samuel, in collaboration with colleagues at the Beatson Institute for Cancer Research in the UK and the Ludwig-Maximilians Universität in Germany, showed that the genetic ablation or pharmacological inhibition of the chemokine receptor CXCR2 suppresses tumour growth in several mouse models of skin and intestinal cancer. Their work suggests that targeting of CXCR2 may have therapeutic utility in the treatment of intestinal and skin cancers.

One of the key thrusts of the CCB is to maintain cancer research excellence. This can be measured in high quality publications, as well as in public health outcomes. The research excellence is also evident in the success of CCB scientists in obtaining peer reviewed funding and fellowships from local, national and international sources. We were delighted to see many of our new investigators receiving project grants as well as the more established ones. In the latest round of the highly competitive NHMRC Project Grants, CCB researchers won eight. They also won 31 grants from several other funding bodies. Those who were awarded project grants in the 2012 NHMRC round included Professor Sharad Kumar and Dr Hayley Ramshaw, two grants each; Associate Professor Richard D'Andrea, Associate Professor Stuart Pitson, Professor Andrew Zannettino, and Dr Quenten Schwarz, one grant each. Associate Professor Michael Beard was a member of a team who were awarded an NHMRC Program Grant.

We take much pleasure in reporting that one of our new members, Dr Michael Samuel received a prestigious Future Fellowship from the Australian Research Council. In addition, Associate Professor Stuart Pitson was awarded an NHMRC Senior Research Fellowship; Professor Timothy Hughes, an NHMRC Practitioner Fellowship; Dr Hayley Ramshaw a Peter Nelson Leukaemia Research Fund Senior Research Fellowship; Dr Simon Conn, a Florey Fellowship; Dr Kate Vandyke, a Mary Overton Fellowship; Dr Jacqueline Noll, a Veronika Sacco Postdoctoral Clinical Cancer Research Fellowship; Dr Wendy Parker, a Postdoctoral Fellowship; and Dr Melissa Pitman, a Royal Adelaide Hospital Research Fellowship.

Top: ACRF Cancer Genomics Facility
Rosalie Kenyon using a *Sequenom MassARRAY RS1000 Nanodispenser*, a DNA spotting robot which prepares for analyses the parts of cancer genomes that direct personalised medicine.

Right: Dr Janice Fletcher; Professor David Vaux; Dr Sally Martin recipient of the Early Career Investigator Award, 2012 Centre for Cancer Biology Prize, and Qiagen sponsor representative Mr Brad Duncan

In 2012 we welcomed three new members to the CCB Faculty: Professor Michael Brown, Dr Michael Samuel and Associate Professor Andrew Ruszkiewicz. These members greatly enhance both basic and clinical research capabilities of the CCB and we look forward to new productive collaborations as a result of these appointments.

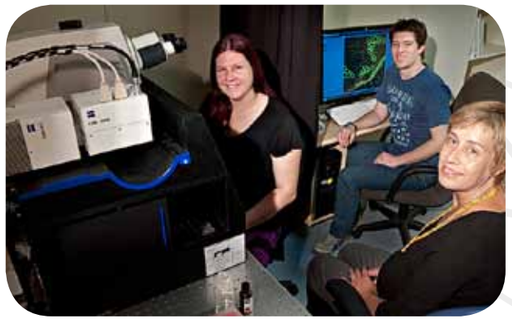
On 14 June 2012, the CCB held its Annual General Meeting. Professor David Vaux, Assistant Director of Walter and Eliza Hall Institute, Melbourne, presented a special guest lecture where he praised the research efforts of the scientists at the CCB and outlined the importance of fundamental and discovery research in the development of new diagnostics and more tailored types of treatment for cancer patients. Professor Vaux presented a number of research excellence awards to the staff and students of the CCB, including the Best Primary Research Publication Award to Dr Chris Hahn; the Best Student Primary Research Publication Award to Ms Tamara Leclercq, and the CCB Early Career Investigator Award to Dr Sally Martin. The CCB takes special pride in training and mentoring junior scientists and graduate students. As Directors of the CCB, the achievements of our younger scientists always give us great delight.

CCB scientists played a major role in the organization of ComBio 2012, the major annual combined conference of the Australian Society for Biochemistry and Molecular Biology (ASBMB), the Australia and New Zealand Society for Cell and Development Biology and other scientific societies. Associate Professor Stuart Pitson was the convenor of a highly successful ASBMB meeting, whereas Professors Greg Goodall and Sharad Kumar served as the Program Chair and Deputy Program Chair, respectively. Many other CCB members served as members of the organising committee, thematic or session chairs and speakers.

This report gives us an opportunity to thank our supporters and collaborators including the Australian Cancer Research Foundation, Novartis, the Cooperative Research Centre for Biomarker Translation, CSL Ltd, Therapeutic Innovation Australia, Health Services Charitable Gift Board, eResearch SA, The University of Adelaide and The University of South Australia. Keeping up with the state-of-the-art technological platforms that facilitate our research is a key part of our strategy. To this end, we are grateful for the provision of $900,000 that helped us expand our Imaging Facility with the installation of a 2-photon microscope.

As in previous years, we have had strong support from SA Pathology and this is an opportunity for both of us to thank Mr Ken Barr, Executive Director of SA Pathology and Professor Heddy Zola, Research Director of SA Pathology, for their continued commitment to cancer research and the CCB Faculty. Professor Zola has greatly facilitated the smooth running of the CCB with great attention to detail and ever present good humour. Our thanks also go to the RAH Research Foundation, led by Mr Mark Goldsmith, for their enthusiasm in bringing our scientific successes to the South Australian community and for raising valuable funds for the work of the CCB so that it can continue to pursue its main aim of fighting and defeating cancer.

Professors Sharad Kumar and **Angel Lopez**
Co-Directors, Centre for Cancer Biology

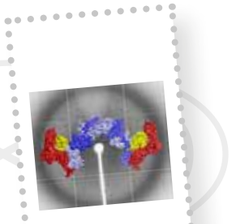


The Zeiss LSM710 2-photon microscope installed in the ACRF Cancer Genomics Facility. CRC-BT staff Ms Michaelia Cockshell and Dr Lachlan Moldenhauer work with Dr Claudine Bonder to better understand endothelial progenitor cells in neovascularisation *in vivo*.

Top left: Launch of ACRF Cancer Genomics Facility
Mr Stephen Gerlach, Chancellor, Flinders University; Prof Angel Lopez; Mr Tom Dery, Chair, Australian Cancer Research Foundation Board; The Right Hon John Hill MP; Dr Janice Fletcher, Deputy Director, SA Pathology; Prof Sharad Kumar; Prof Hamish Scott

Top right: The latest DNA sequencer, *Illumina HiSeq 2500*, which can generate 100 human genomes worth of DNA sequence in two weeks, being loaded by Mark van der Hoek.

Right, above: Professor David Vaux, Assistant Director, Walter and Eliza Hall Institute



Right, below: Special edition stamp
Part of the series released by Australia Post, celebrating 100 years of X-ray crystallography, used to determine the structure of DNA. The image shows the 3D structure of the GM-CSF receptor complex.

Acute Leukaemia Laboratory

Professor Richard D'Andrea PhD

Associate Professor Ian Lewis MBBS PhD FRACP FRCPA

A major research focus of the group is the identification and characterisation of genes involved in the myeloid lineage and in myeloid disease including Acute Myeloid Leukaemia (AML) and the Myeloproliferative Neoplasms (MPN).

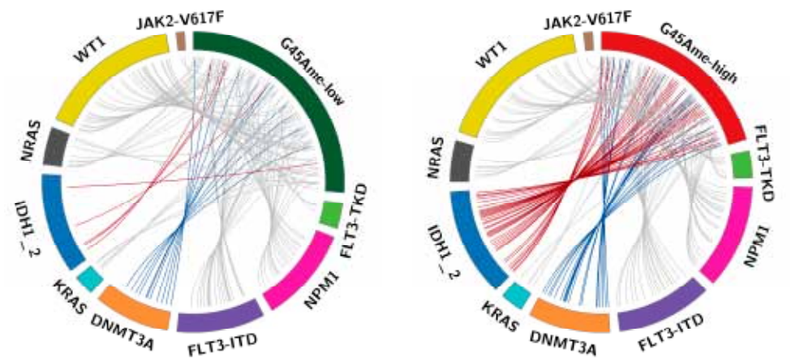
Utilising myeloid cell line models, we have described a novel role for *TCF4* in specifying macrophage lineage differentiation. Making use of a large cohort of AML patient samples, we have also recently published studies showing the prognostic impact in AML of *KLF5* promoter methylation, and silencing of the *GADD45A* tumour suppressor by promoter methylation. To investigate further the role of *Klf5* we are currently characterising a conditional haemopoietic-specific knockout model of *Klf5*.

Our interest in the molecular genetics of MPN has led us to identify somatic mutations in patient samples in genes including *DNMT3A*. In collaboration with other groups, we have investigated the occurrence of *NPM1* mutations in Chronic Myeloid Leukaemia (CML) and reported the cooperation of Evi1 with AP-1 transcription factors in solid tumours.

We also focus on the mechanisms of cytokine receptor signalling and the role of aberrant signalling in leukaemia. Specifically, we have reported the frequency and prognostic significance of the FLT3-TKD mutation in the core binding factor (CBF) AMLs. In collaboration with other groups, we have described the use of novel systems to dissect signalling pathways associated with GM-CSF and IL3 receptors. In addition, we are exploring the link between IL-3 signalling and β-catenin activity in AML associated with HOX gene over-expression or MLL gene translocations.

We have explored new treatments for AML and the Philadelphia chromosome negative MPN. For both groups of diseases, we have identified novel pathways that may have potential to be targeted to induce death of disease cells. We have identified Dequalinium Chloride (DECA) as a potential agent able to target the subgroup of AML with translocations of the MLL gene; this group of AML patients have a particularly poor prognosis and new targeted therapies are desperately needed.

We have shown that DECA activity in this subtype is associated with its ability to induce changes in mitochondrial activity and we are investigating this activity further in xenograft AML models. We have also identified somatic mutations in the *EGFR* gene in MPN patients suggesting a potential important role for aberrant EGFR signalling in MPN.



Circos diagrams showing co-occurrence of mutations in AML with low Gadd45A methylation (*G45A*me^{low}) and high Gadd45A methylation (*G45A*me^{high})

Top Sarah Bray | Anna Brown | Sonya Diakiw | Grant Engler
Middle Diana Iarossi | Chung Hoow Kok | Nick Li | Kyaw Zeya Maung
Below Michelle Perugini | Nisha Rao | Teresa Sadras | Nur Hezrin Shahrin | Amilia Wee

Key discoveries 2012

Prognostic Significance and Role for *GADD45A* in AML
To test the clinical significance of *GADD45A* promoter hyper-methylation in an AML patient cohort (167 AML patients) we measured DNA methylation at 4 CpG residues previously shown to be methylated in numerous cancers. This showed that *GADD45A* promoter methylation is predictive of poor survival overall in AML, and particularly in normal karyotype AML. This is the first study to link *GADD45A* promoter methylation to patient outcome in cancer (*Leukemia* doi: 10.1038/leu.2012.346 2012). Our analysis also revealed a positive correlation between *GADD45A* promoter methylation status and the presence of *IDH1*/*IDH2* and *DNMT3A* mutations suggesting this mark may be detecting a broader epigenetic phenotype. We also showed that *GADD45A* promoter methylation segregated outcome in the important intermediate-risk group of patients that are negative for *FLT3-ITD*, but positive for *NPM1* mutations; a group of patients in which it is difficult to determine prognosis and therefore treatment options.

Role of IL-3 mediated β-catenin activation in HOX gene mediated myeloid transformation and AML
β-catenin has previously been shown to be stabilised in AML, however the molecular mechanisms that underlie the β-catenin activity in AML remain poorly understood. We have investigated the link between IL-3 signalling and β-catenin expression/stabilisation in AML. We have now shown that IL-3 signalling induces dose-dependent β-catenin accumulation and activation in murine and human myeloid cell lines. In a murine model of HOX transformation (FDM cells) we have used Cre-mediated deletion of β-catenin to demonstrate a requirement for β-catenin in IL-3 mediated growth and survival. Using gene expression profiling and QPCR we have shown that IL-3 activates distinct early and late responses in primary AML cells with activation of β-catenin gene signatures and target genes associated with the late response. Thus IL-3 signaling is associated with activation of β-catenin, which may provide signals critical for survival and self-renewal in the context of HOX gene transformation of myeloid cells.

Outcomes for the Community

Our results above provide important leads for therapy of myeloid malignancies. For example a role for EGFR signaling in MPN suggests that therapy with existing clinical EGFR inhibitors may benefit MPN patients and we anticipate that these results can be rapidly translated to clinical trial in selected patients showing evidence of EGFR activation. The response observed with DECA in the MLL subtype of AML suggests potential therapeutic strategies using rational combinations of drugs that are in advanced clinical development. This subtype is associated with a particularly poor outcome and translation of findings toward a definitive phase I/II MLL-AML trial can be rapid.

Cell Signalling Laboratory

Dr Yeesim Khew-Goodall PhD

Top Leila Belle | Sam Dyer | Freya Gehling | Nick Hauschild
Below Xiaochun Li | Ana Lonic | James Paltridge | Emily Paterson

The interest of the Cell Signalling Laboratory is to understand how signals that are normally generated to maintain homeostasis, when dysregulated, give rise to disease.

Our disease model is breast cancer metastasis and our long term focus is to understand what turns a benign cancer cell which remains local and treatable into a malignant cell capable of spreading to multiple organs. In solid tumours, which make up ~80% of human cancers, metastasis is the main cause of death.

An ongoing interest of the Cell Signalling Laboratory is the interactions of the cancer cell with its microenvironment. Cells secrete factors that can act upon themselves or on other cells for normal maintenance or homeostasis. Cancer cells, through mutations, can have an altered composition of secreted factors which can act to alter their immediate microenvironment, turning it from one that suppresses cancer progression to one that supports metastasis and resistance to chemotherapy. Recent studies have shown that the cancer 'secretome' can also prepare a metastatic niche in secondary organs to facilitate their ability to embed in those organs.

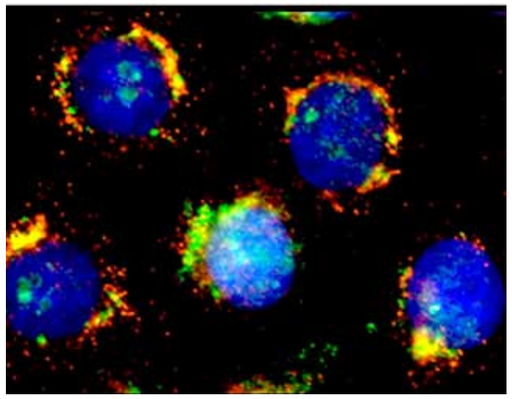
To date, however, little is known about the mechanism(s) by which the cellular secretome is regulated or how this regulation might be altered in cancer cells. We have shown that the protein tyrosine phosphatase Pez, a protein which we have studied for many years, regulates TGFβ secretion. In some cells, increased Pez expression resulting in TGFβ secretion can cause them to undergo an epithelial-mesenchymal transition, an early step deemed necessary for the dissemination of breast cancer cells.

In addition to our interest in breast cancer, the Cell Signalling Laboratory (in collaboration with Professor Greg Goodall, Dr Susanna Proudman and Dr Pravin Hissaria) also has an interest in identifying microRNAs that are altered in scleroderma, a debilitating fibrotic disease with no cure. Ongoing work will go towards establishing the role(s) these microRNAs play in establishment or progression of scleroderma.

Key discoveries 2012

Identification of novel functions of Pez
Mutations to Pez have been identified in various cancers including breast and colorectal cancers, but limited knowledge of its substrates or biological functions has hampered studies to identify how Pez mutations affect cancer progression. We have identified novel functions of Pez that indicate how dysregulation of Pez could affect cancer progression and novel substrates for Pez that could help us understand the normal physiological functions of this protein. Importantly, these findings could be a key to understanding how mutations in this protein that have been identified in cancers may facilitate metastasis or oncogenesis.

Identification of differentially expressed microRNAs
Using scleroderma patient samples, we have identified microRNAs that are differentially expressed between normals and scleroderma patients and also between patients with limited and diffuse disease. Consistent with current notions that limited and diffuse forms of scleroderma have different aetiologies, our data suggest that the two different forms of scleroderma have arisen through different mechanisms. Exploring the mechanisms by which the changes in mircoRNA expression patterns are regulated, we found correlations between expression of certain microRNAs with pro-inflammatory cytokines that are elevated in scleroderma patients.



Pez localisation to the perinuclear golgi in breast cancer cells
Pez *red*; Golgi *green*

Outcomes for the Community

Solid tumours make up the majority of human cancers whereby the progression to metastasis is the main cause of morbidity and mortality in these patients. Currently, there is little effective treatment for metastatic disease. In part, this is due to our lack of understanding of the way metastatic cells spread, survive and colonise secondary organs and become resistant to standard chemotherapy. Our studies aim to increase knowledge of these processes using multiple strategies so that we may identify and open up avenues for new therapeutics to be developed.

Cytokine Receptor Laboratory

Professor Angel Lopez MBBS PhD FRCPA

Cytokine receptors are the conduit between the extracellular milieu and the cell's internal machinery that allows cells to respond in a variety of ways such as maintenance of viability or proliferation.

Abnormalities such as extended cell viability or survival, and enhanced cell proliferation are hallmarks of cancer. Understanding the molecular basis of cytokine receptor signalling in health and disease is vital for the design of new forms of therapy for leukaemia and some chronic and debilitating inflammatory conditions such as asthma and rheumatoid arthritis.

Cytokines or growth factors regulate the function of cells in the body by binding to specific receptors on the cell surface. This initial binding triggers cytokine receptor activation which in turn generates multiple biochemical events that signal to the cell how to divide, where to migrate, what to secrete, etc. Our laboratory focuses on a particular set of cytokines named β_c cytokines because their receptors share the major signalling subunit called β_c. These include GM-CSF, IL-3 and IL-5, cytokines that by and large regulate the function of many blood cells and as such are important in normal blood formation, malignant haemopoiesis (leukaemia) as well as diseases such as rheumatoid arthritis, multiple sclerosis, asthma and autoimmune diseases.

To understand how the β_c cytokines signal, we are studying receptor proximal events, namely how the receptor complex assembles on the cell surface to initiate downstream signalling. In collaboration with Professor Michael Parker and his team (St Vincent's Institute of Medical Research), we are establishing how GM-CSF and IL-3 interact with their receptors to form a binary complex and how this interaction then dictates how higher order complexes are assembled that initiate signalling. Defining the key molecular interactions is important to design specific forms of therapeutics. In collaboration with Professor Paul Ekert and his team, we are studying the signalling mechanisms activated following receptor assembly.

A second approach is to understand why some cytokine receptors such as the IL-3 receptor is upregulated in some leukaemias. In collaboration with Professor Richard D'Andrea and Professor Hamish Scott (Centre for Cancer Biology), we are defining the consequences of increased IL-3 receptor expression in terms of genetic programs and the biological advantages that leukaemic cells gain from this. In collaboration with Professor Greg Goodall and Dr Cameron Bracken (Centre for Cancer Biology), we are studying the mechanisms at the microRNA level that control IL-3 receptor expression.

As blood cells are also involved in diseases such as asthma, we are characterizing their role in this disease. In collaboration with Associate Professor Michele Grimbaldeston (Centre for Cancer Biology) and with CSL Ltd, we are examining how β_c cytokines stimulate mast cells and how this stimulation may be tamed. As mast cells are important not only in asthma but in many other inflammatory conditions and in some solid cancers, it may be possible to regulate their function to better control disease. Interestingly, the actions of β_c cytokines do not seem to be restricted to blood cells. In collaboration with Dr Quenten Schwarz (Centre for Cancer Biology), we have found an unexpected role in neuronal development and function, and in collaboration with Dr Claudine Bonder (Centre for Cancer Biology), a possible pathogenic role in breast cancer.

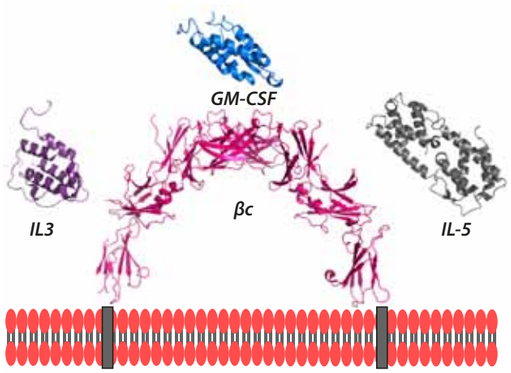
As we learn more about β_c cytokines and how their receptors work, opportunities arise to apply this knowledge. A few years ago, we generated a monoclonal antibody that blocks the IL-3 receptor, rapidly being appreciated as a marker of acute myeloid leukaemia stem cells. CSL Ltd has now improved this antibody (CSL362) so that it can kill these stem cells better, a result that has led to clinical trials currently being carried out in Australia and the US to examine the therapeutic potential of CSL362. In collaboration with Professor Timothy Hughes and Associate Professor Deborah White teams (Centre for Cancer Biology), we are also examining this antibody for its usefulness in chronic myeloid leukaemia.

Top Emma Barry | Nicole Christie | Mara Dottore | Zarina Greenberg
Middle Sue Heatley | Tim Hercus | Winnie Kan | Barbara McClure
Below Melanie Pudney | Hayley Ramshaw | Frank Stomski | Rebecca Wright

Key discoveries 2012

Molecular assembly and signalling of the β_c receptor family
In collaboration with Prof Parker and his team, we have assembled the GM-CSF and IL-3 receptors in solution, have crystallised the complexes, and their 3-dimensional structure is being solved. Already a distinct pattern of receptor assembly has emerged which reveals the sequential steps required and the critical protein interacting sites (*Immunological Reviews* 250: 277-302, 2012). In collaboration with Professor Ekert and his team, we found a novel signalling mechanism that promotes cell survival which is mediated by the IKK complex (*Cell Death Differ* 19: 633-41, 2012).

The dimer interface of the 14-3-3 family of proteins regulates its function
We have found that the dimer interface of 14-3-3 proteins is held together by a distinct set of amino acids. Using this information and knowledge of the structure of the dimer interface has allowed us to identify, in collaboration with Professor Parker's team and Associate Professor Stuart Pitson (Centre for Cancer Biology), a set of compounds that regulate dimer formation leading to cell death. This is of practical significance as many cancers express too much 14-3-3 which may lead to uncontrolled growth. These unique compounds are currently being tested in chronic myeloid leukaemia in collaboration with Professor Hughes and Associate Professor White with very promising results.



The β_C cytokines and their shared β_C receptor subunit

Outcomes for the Community

We are understanding more and more how many cancers arise by focusing on signals transmitted from the very surface of the cell all the way to the cell nucleus. As the players in this cellular circuitry are revealed and the problems that they cause are understood, we are faced with a clearer picture of what goes awry in some cancers. Because in many cases we are obtaining very clear, three-dimensional views, of how these circuits work, we have a realistic opportunity to modulate them by designing and testing new and more specific anti-cancer drugs.

Gastroenterology Research Laboratory

Associate Professor Andrew Ruszkiewicz MD FRCPA

Most colorectal cancers (CRCs) arise from conventional adenomas, however up to 30% of cancers may develop from 'serrated' polyps which until recently were regarded as innocuous lesions without malignant potential.

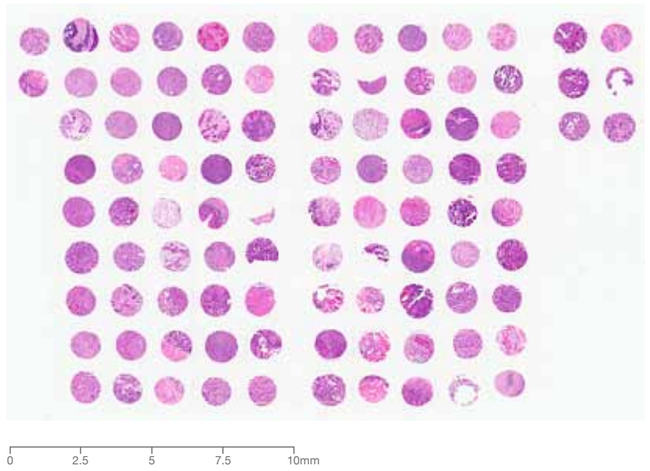
The emergence of 'serrated' polyps as a class of precursor lesion of CRC presents a major challenge for the early detection and management of colorectal cancer and its precursors

This alternate, so called 'serrated pathway', of CRC presents added complexity in our attempts to understand disease progression, in particular the transition from premalignant to malignant disease. The serrated polyps are notoriously difficult to visualize endoscopically and may not be detected on routine colonoscopic examination. There is growing evidence that failure to identify serrated polyps during colonoscopy may explain the occurrence of 'interval' colon cancers in patients with previous 'negative' colonoscopic examinations.

Additionally, the serrated polyps with malignant potential often have overlapping morphological features with benign hyperplastic polyps making their recognition in routine histological examination difficult.

We are using –omics technologies to detect and characterise the underlying molecular alterations in order to understand the biology of early precursor lesions and the potential factors that influence the rate of progression of these lesions to carcinoma.

Our research requires high quality biological samples from patients with colorectal cancer and clinical data. The Gastroeneterology Research Laboratory is responsible for establishing and managing the Colorectal Cancer Tissue Bank which holds samples of colorectal cancers and other gastrointestinal tumours, colorectal polyps and normal tissues, matching blood and clinical data from patients treated in various hospitals in Adelaide. This material is used for research projects conducted by us and other researchers at the Centre for Cancer Biology.

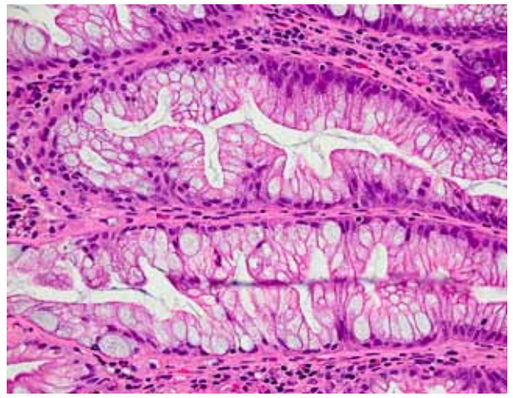


TMA HE Tissue Microarray
TMA consists of paraffin blocks which contain up to several hundred separate cores of tumour tissue from several patients assembled in array fashion allowing a robust, cost effective interrogation of numerous patients in a single experiment. Haematoxylin and Eosin stain.

Top Kay Taylor | Teresa Tin
Below Maria Caruso | Ross Hamilton

Key discoveries 2012

We have previously demonstrated over-expression of *Cathepsin E* and *Trefoil Factor 1* in sessile serrated adenomas but not in conventional adenomas of the colorectum which is indicative of molecular differences between these types of colorectal polyps. Our recent gene expression data has shown that a unique molecular profile exists which distinguishes hyperplastic polyps and sessile serrated adenomas at the molecular level. Our gene expression profiling of hyperplastic polyps and sessile serrated adenomas revealed a strong correlation between Claudin1 (CLDN1) expression and BRAF V600E mutation status in a subset of serrated colorectal polyps. Results of our study identify CLDN1 as a potential biomarker of the serrated pathway.



Morphology of sessile serrated adenoma, precursor of substantial percentage of colorectal cancer. Haematoxylin and Eosin stain.

Outcomes for the Community

Our work towards better characterisation of precursor lesions of colorectal cancer results in better understanding of the biology behind serrated polyps and subsequently will enhance early detection, pathological diagnosis and treatment strategies for colorectal cancer.

Gene Regulation Laboratory

Professor Greg Goodall PhD

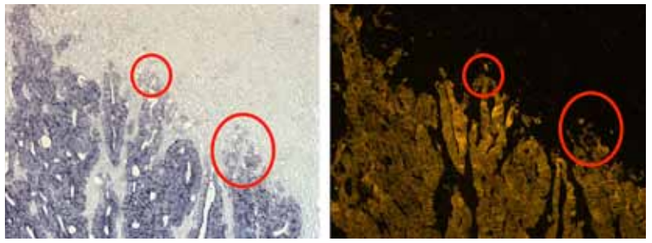
The majority of solid cancers, including most lung, breast, colon, prostate and liver cancers, arise from epithelial cells. Most deaths from these cancers are due to metastasis, which involves the transition of the cancer to an invasive form.

This process involves a recapitulation of the developmental process known as epithelial to mesenchymal transition (EMT), which normally occurs during embryogenesis and during wound healing. The recent discoveries that cancer stem cells have EMT-like features and that EMT typically confers resistance to chemotherapy, place studies on the mechanisms that control EMT at the nexus of investigations of the cause of cancer progression and therapy resistance.

EMT is driven by coordinated changes in the expression of hundreds of structural and regulatory proteins. These changes are determined by integrated gene expression networks that themselves involve numerous components. We have identified microRNAs that play a central role in controlling and coordinating the regulatory networks that underlie EMT in cancer cells.

Our current work focuses on developing our understanding how microRNAs control EMT and examining their consequences for cancer progression. The project areas include:

- investigating the mechanisms that regulate expression of microRNAs in EMT
- identifying authentic targets of microRNAs involved in EMT
- identifying coordinated effects of microRNAs on EMT pathways
- discovering other EMT pathways controlled by microRNAs
- identifying microRNAs controlling the maintenance and properties of cancer stem cells



Staining of the invasive front of a colorectal cancer showing miR-200 (left panel) and the tumour marker β-catenin (right panel). Circles show invading cells that have reduced miR-200 levels.

Outcomes for the **Community**

Our work is identifying new molecules and pathways that drive metastasis, the primary cause of death of cancer sufferers. These discoveries open up new avenues for potential therapeutic exploitation and for development of new diagnostics.

Top Matthew Anderson | Victoria Arnet | Joanne Attema | Andrew Bert
Middle Cameron Bracken | Phil Gregory | Kimi Honma | Corine Neilsen | Katherine Pillman | Francisco Sadras
Below Marika Salmanidis | Rosemary Sladic | Suraya Roslan | Daniel Thomson

Key discoveries 2012

ZEB1 induces widespread changes in the miR transcriptome and controls biological processes other than EMT and stem-ness through repression of miR-34a

Metastatic cancer is extremely difficult to treat, and the presence of metastases greatly reduces a cancer patient's likelihood of long-term survival. The ZEB1 transcriptional repressor promotes metastasis through downregulation of microRNAs that are strong inducers of epithelial differentiation and inhibitors of stem cell factors. In collaboration with Don Gibbons and Jonathan Kurie at the MD Anderson Cancer Center, we have investigated additional roles of ZEB1 in metastasis using a mouse model of human lung adenocarcinoma metastasis driven by ZEB1, human lung carcinoma cells, and human breast carcinoma cells. Transcriptional profiling studies revealed that ZEB1 controls the expression of numerous oncogenic and tumour-suppressive miRs, including miR-34a. Ectopic expression of miR-34a decreased tumour cell invasion and metastasis, inhibited the formation of promigratory cytoskeletal structures, suppressed activation of the RHO GTPase family, and regulated a gene expression signature enriched in cytoskeletal functions and predictive of outcome in human lung adenocarcinomas. We identified several miR-34a target genes, including Arhgap1, which encodes a RHO GTPase activating protein that was required for tumour cell invasion. These findings demonstrate that ZEB1 drives prometastatic actin cytoskeletal remodelling by downregulating miR-34a expression and provide a compelling rationale to develop miR-34a as a therapeutic agent in lung cancer patients (*J Clin Invest* 122 :3170-83, 2012).

Down-regulation of the miRNA-200 family at the invasive front of colorectal cancers with degraded basement membrane indicates EMT is involved in cancer progression.

Cancer progression is a complex series of events thought to incorporate the reversible developmental process of epithelial-to-mesenchymal transition (EMT). *In vitro*, the microRNA-200 family maintains the epithelial phenotype by post-transcriptionally inhibiting the E-cadherin repressors, ZEB1 and ZEB2. We have used *in situ* hybridization and immunohistochemistry to assess expression of miR-200 and EMT biomarkers in formalin-fixed paraffin-embedded human colorectal adenocarcinomas.
In addition, laser capture microdissection and quantitative real time polymerase chain reaction (qPCR) were employed to quantify levels of miR-200 in the normal epithelium, tumour core, invasive front, and stroma. We found that miR-200 is down-regulated at the invasive front of colorectal adenocarcinomas that have destroyed and invaded beyond the basement membrane. However, regional lymph node metastases and vascular carcinoma deposits show strong expression of miR-200, suggesting this family of miRNAs is involved in the recapitulation of the primary tumour phenotype at metastatic sites. In contrast, adenomas and adenocarcinomas with intact basement membranes showed uniform miR-200 expression from the tumour core to the tumour-host interface. Taken together, these data support the involvement of EMT and mesenchymal-to-epithelial transition (MET) in the metastasis cascade and show that miR-200 is down-regulated in the initial stages of stromal invasion but is restored at metastatic sites (*Neoplasia*, accepted 17 Dec 2012).

Haematology Clinical Research Laboratory

Professor Luen Bik To MBBS (HK), MD (Adel), MRCP (UK), FRCPA, FRACP PhD

Associate Professor Ian Lewis MBBS (Adel), PhD (Adel), FRCPA, FRACP

The Haemostasis Program studies the laboratory as well as the clinical aspects of bleeding and clotting problems, ranging from diagnostic and monitoring to treatment.

The Clinical Research Unit encompasses a number of research groups in the Royal Adelaide Hospital Department of Haematology including both cancer and non-cancer related research. The Haemostasis Program studies the laboratory as well as the clinical aspects of bleeding and clotting problems, ranging from diagnostic and monitoring to treatment.

A major new initiative is the South Australian Cancer Research Biobank which was funded by the Beat Cancer Project as well as MedVet Science Pty Ltd. The setting up of a tumour bank to facilitate researchers in SA is a major and far-reaching project. The external funding allows the expansion of the RAH Blood Disease Tumour Bank first set up in the 1980s to cover collection from all major public teaching hospitals in SA. The original bank has already been a significant enabler of research leading to multiple publications. We expect that the new bank will have double the collection rate and will therefore be even more important for discovery research in South Australia.

The investigators in the Clinical Research Unit are also active collaborators with other researchers in the Centre, particularly in the conduct of translational research projects in leukaemias and myeloma.

Through a coordinated research programme, the Haematology Clinical Research Unit has a strong commitment to improving the treatment of patients with blood diseases

Outcomes for the **Community**

The clinical research unit has a core focus of improving the treatment of patients with malignant and non-malignant diseases of the blood. This is achieved by a core interest in fundamental research, involvement in clinical trials utilising novel agents and provision of infrastructure to allow these activities to expand. The active clinical trial program gives patients with haematological malignancies the opportunity to receive novel therapeutic agents which may not otherwise be available to them. The prospective storage of leukaemia and myeloma specimens is a valuable resource which underpins a number of research projects that will have many benefits for the community.

Top Debbie Bennetta | Carolyn Butcher | Devendra Hiwase | Smita Hiwase
Middle Simon McRae | Kerry Munro | Silvana Niutta | Thanh Nguyen
Below Sunayana Patel | Naranie Shanmuganathan | Judy Stevens | Michael Vo | Agnes Yong

Key discoveries 2012

Haemostasis Program Report
The Haemostasis Program comprises applied clinical and diagnostic projects. Our broad theme is to introduce new, or improve current, haemostasis tests with the aim of developing better tools to diagnose and manage patients with bleeding or clotting disorders. Currently, the projects include:

- Study of Protein S deficiency (inherited or acquired) as a cause of thrombosis, and its impact on thrombin generation (TGT) in the presence and absence of thrombomodulin. This work has included experiments to assess the impact of various pre-analytical variables on the TGT, a neglected area in the development of this potential diagnostic test.

- Investigation of the coagulation factors that may contribute to thrombosis in patients with myeloma, especially during chemotherapy. Our aim is to determine parameters that predict which patients are more likely to develop thrombosis so that anticoagulants can be prescribed before the thrombosis occurs. Samples have also been collected from patients with MGUS (monoclonal gammopathy of unknown significance), a precursor to myeloma, as a patient control group. A future project to study polycythemia vera using a similar approach is also planned.

- The study of thrombin generation in mild haemophilia A, to better understand the different bleeding phenotypes of this disorder and to relate this to genotype. This project is near completion and shows interesting differences between sub-groups. This may allow better prediction of treatment needs.

- The study of pharmacokinetics of Factor VIII treatment products in haemophilia, in order to ascertain half-life and plan for required therapy during and after surgery. This project has the potential to save unnecessary use of expensive products by tailoring dosage to half-life, and also to ensure sufficient dose is given to those patients needing a higher dose.

- The study of methods to diagnose Factor XIII deficiency. This project has identified a novel cause of false positive results in commonly used screening tests and will recommend a change in practice for all laboratories that screen for and manage this rare disorder.

- Study of tests to assess the effect of new oral anticoagulant drugs on the coagulation pathway, and to monitor the effect of reversal agents. This includes introduction of diagnostic tests to measure drug levels and research to investigate their impact on thrombin generation. This work will help those patients with excessive bleeding as a drug side effect, or those requiring emergency surgery.

Hepatitis C Virus Research Laboratory

Associate Professor Michael R Beard PhD









Top Amanda Aloia | Nick Eyre | Guillame Fiches | Adriana Gaeguta | Karla Helbig
Below Erin McCartney | Kate Muller | Sumudu Narayana | Kylie van der Hoek

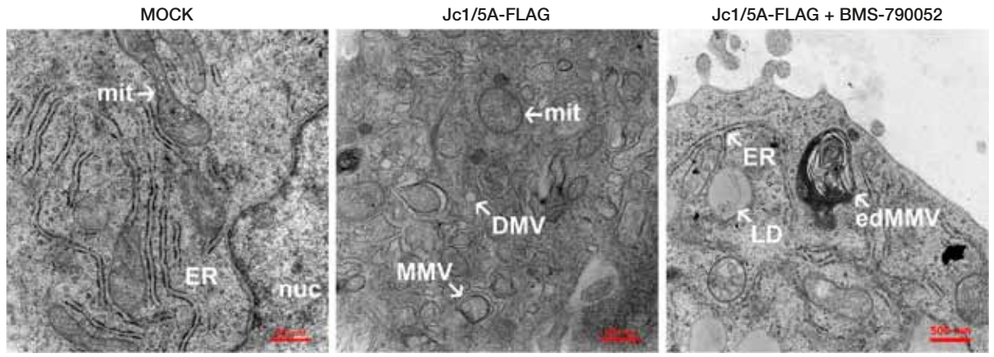
HCV specifically infects liver cells (hepatocytes) and the main focus of our laboratory is to define the host response to infection with HCV using both laboratory based models and clinical samples.

The hepatitis C virus (HCV) that infects over 170 million people worldwide results in significant liver disease (fibrosis/cirrhosis) and liver cancer (hepatocellular carcinoma) in many of those infected. In fact, infection with HCV is now the leading indication for liver transplantation in many countries including Australia.

Recent development of direct acting antiviral (DAA) compounds show great promise in the treatment of hepatitis C, however these are often expensive, have significant side effects and are not available to all infected with HCV. Thus new therapies and a greater understanding of the pathogenesis of hepatitis C are required.

HCV specifically infects liver cells (hepatocytes) and the main focus of our laboratory is to define the host response to infection with HCV using both laboratory based models and clinical samples. We also have a focus on developing models to study the HCV-host interaction in living cells. Through these approaches we hope to add to our understanding of how HCV causes disease and identify novel therapeutic targets. Specific areas of research include:

- Investigating the interferon stimulated gene response (ISG) in HCV infection and the identification and characterization of novel ISGs. We are specifically interested in ISG control of the positive RNA strand flavivirus family and specifically investigate HCV, Dengue (in collaboration with Dr Jill Carr, Flinders University) and West Nile virus (with Dr Sonja Best, NIH, USA).
- Understanding the dynamics of viral replication at the cellular level using a live cell imaging approach to study HCV replication in real time. This is achieved by using a small (6–12 amino acid) genetically encoded tetracysteine peptide sequences that can be introduced into viral proteins and labelled by fluorescent dyes. We are also interested in visualising HCV RNA in real time and have engineered HCV genomes containing the bacteriophage MS2 detection system.
- Understanding the efficacy of the recently developed DAAs that target the HCV NS3/4a protease and the emergence of resistance mutations and how they impact that action of the protease inhibitors and HCV replicative fitness.



Electron microscopy analysis of Huh-7.5 hepatoma cells infected with hepatitis C virus (HCV; Jc1/5A-FLAG) induces rearrangements of cytoplasmic membranes to support the replication of its genome (middle panel). These virus-induced rearrangements are dramatically altered by antiviral drugs that target the HCV NS5A protein (BMS-790052, right panel)

Key discoveries 2012

Host control of viral replication
Viral infection of cells results in a host response that attempts to limit viral replication through the induction of specific antiviral proteins. However the complete spectrum of these antiviral proteins has not been characterized. Our laboratory specifically focuses on the host interferon stimulated gene, viperin and it role in limiting a number of medically important viruses. We have shown that viperin exerts its antiviral effect through a direct interaction with the HCV NS5A protein and the pro viral host factor VAP-A to disrupt HCV replication within the HCV replication complex. Interestingly viperin also limits replication of the closely related *flavivirus*, Dengue. In this instance viperin interacts with the dengue NS3 protein that is also a key component of the dengue virus replication complex. Furthermore in collaboration with the Westmead Millennium Institute, Sydney we have also shown that viperin inhibits the replication of HIV (*Blood* 120:778-88, 2012). Thus viperin has antiviral activity against a number of important viruses and our work adds to the understanding of how we respond to control viral infections.

Dynamic imaging of the HCV life cycle
Using a combination of fluorescent labelling approaches (tetracysteine tags, fluorescent proteins and SNAP tags) we have developed techniques to image the localization and dynamics of the HCV proteins, NS5A and core, HCV RNA and relevant host cell factors in living virus-producing cells. Specifically, we are interested in the role of NS5A in the biogenesis and function of HCV replication complexes (RCs) that harbour active replication of HCV RNA and how these structures associate with core-coated cytoplasmic lipid droplets; the sites of infectious virus particle assembly. We have demonstrated that NS5A-positive cytoplasmic structures (putative RCs) traffic throughout the cytoplasm in a process that depends on an intact microtubule network and, at least in part, on the dynein motor protein complex.

Additionally, we have demonstrated that both relatively static and highly motile RCs are enriched with fluorescently labelled HCV RNA and the host cell factors VAP-A and Rab5A and suggest that Rab5A may be a key determinant of RC formation and motility. Finally we have visualised the association of NS5A-positive RCs with core-coated lipid droplets in the context of a productive infection and demonstrated the interaction of these proteins by proximity ligation assays. Through the use of pharmacological inhibitors of cellular pathways and viral protein function we are now in a position to further dissect aspects of the HCV life cycle in real-time.

STAT3 plays a role in HCV replication
Host factors play an important role in all facets of the HCV life cycle and one such host factor is the transcription factor STAT3. We have established that STAT3 is actively phosphorylated in the presence of replicating HCV. Expression of a constitutively active form of STAT3 leads to marked increases in HCV RNA levels, whereas conversely, chemical inhibition and siRNA knockdown of STAT3 leads to significant decreases in HCV RNA levels. As a transcription factor, up-regulation of a distinct set of STAT3 dependent genes may create an environment that is favourable for HCV. However, we have recently shown that STAT3 may exert is effect on the HCV life cycle via positive regulation of microtuble dynamics, via sequestration of the microtubule depolymerising protein Stathmin1. We have demonstrated that STAT3 plays a role in the HCV life cycle and have clarified the role of STAT3 as a pro-viral host factor. As activated STAT3 has been implicated in the pathogenesis of hepatocellular carcinoma (HCC) our findings may provide a rationale basis for the role of HCV initiated STAT3 activation in the development of HCC.

Outcomes for the Community

Chronic hepatitis C often results in serious liver disease including the development of liver cancer and places a significant burden on our health system. Our work investigating the host response to infection with HCV has significant implications in that a greater understanding of how the liver combats HCV infection is essential for the development and implementation of new therapeutic strategies. Furthermore, our work with with the new HCV DAAs will inform therapeutic strategy in particular with HCV genotype 6 that predominates in Asia.

Leukaemia Biology Group

Professor Junia V. Melo MD PhD FRCPath

The main area of interest of the Leukaemia Biology Group (LBG) is the molecular biology and cell kinetics of chronic myeloid leukaemia (CML), related myeloproliferative disorders (MPDs) and myelodysplastic syndrome (MDS), aiming at identifying new molecular targets for the treatment of these diseases.

CML is a paradigm of cancer of the haemopoietic system, in which cells that would normally develop into neutrophils, basophils, eosinophils, and monocytes become cancerous. It was the first human disease to be associated with a consistent molecular abnormality, the Bcr-Abl fusion protein, a constitutively activated tyrosine kinase that is produced as a consequence of a reciprocal t(9;22) chromosomal translocation. With the introduction of targeted tyrosine kinase inhibitors (TKI), CML has been transformed from a disease with median survival of five years to one compatible with normal life expectancy if patients comply with daily oral medication for life. This is a first in cancer therapy and has brought entirely new problems of management. Although a relatively rare malignancy, effective therapy has dramatically changed its prevalence. In fact, for an increasingly large population of patients, CML has become a chronic illness, like hypertension, diabetes or AIDS.

CML affects all age groups with a median age of onset in the mid-50s. It is not unreasonable to assume that the average life span of these patients after diagnosis is now 30 years. With estimated TKI costs of AUD 30,000–50,000 per annum per patient, each successive year adds at least AUD 900 million in projected costs. Unfortunately, despite the impressive success of TKIs for CML, a significant proportion of patients do not achieve optimal response, and many more relapse under this form of treatment. The reasons for this are still largely unknown. It is vital therefore to devise a treatment strategy which allows complete eradication of the leukaemic clone, leading ultimately to total cessation of treatment. This can only be achieved through thorough investigations on the molecular mechanisms of leukaemogenesis, as we are undertaking in our laboratory. If successful in CML the discoveries could have a far ranging applicability in other chronic illnesses.

The main focus of our research is to understand how the mutant gene BCR-ABL is regulated, so that we can build a way to switch it off. It's still early days in this investigation, when we are looking broadly at large regions of the gene, before narrowing down to specific parts where we hope to fine tune a cure.

Specific questions that are currently being addressed are:

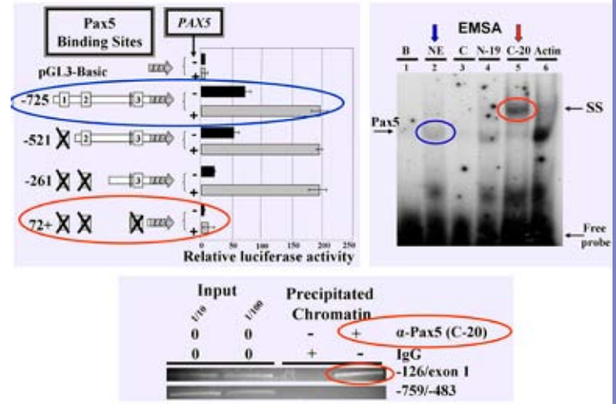
- What comes 'before' the *BCR-ABL* fusion gene: Genetic 'lesions' preceding CML.
- What regulates *BCR-ABL*: how *BCR-ABL* gene expression is controlled.
- What is regulated by Bcr-Abl: downstream genes / proteins essential for the leukaemic (chronic phase) phenotype.
- What adds to/replaces Bcr-Abl signalling to result in disease progression: mechanisms of blastic transformation.
- What determines the difference in disease progression rate and response to treatment: establishment of prognostic and predictive gene expression signatures.
- What determines CML stem cell quiescence and possibilities to reverse it: identification of genes differentially expressed (in comparison with normal stem cells) which can be therapeutically targeted.

Top Debora Casolari | Bradley Chereda
Below Stanley Cheung | Annabel Good

Key discoveries 2012

We have dissected the pathway of regulation of the Bach2 gene, which is repressed by BCR-ABL. This repression prevents Bach2 from making sure leukaemic cells with additional genetic abnormalities and, thus, more malignant, are induced to undergo apoptosis (i.e., these cells remain alive, and give rise to an acute transformation of CML). Our work showed that BCR-ABL utilises the Pax5 transcription factor in this regulation, a protein previously linked to other types of leukaemia. Such 'mapping' of the network of interactions between proteins in the leukaemic cell helps to pave the way to new forms of therapy. This was published by Debora Casolari and co-workers from the LBG and Imperial College London (*Leukemia* doi: 10.1038/leu.2012.220, Epub Aug 4 2012).

The cancer stem cell (CSC) concept has important therapeutic implications, but its investigation has been hampered both by a lack of consistency in the terms used for these cells and by how they are defined. Together with a panel of experts in CSC biology, we reviewed several issues related to their phenotype and functional properties, and proposed a conceptual and practical framework for CSC terminology (*Nature Reviews* in Cancer 12: 767-775, 2012). More precise reporting of the parameters that are used to identify CSCs, and to attribute responses to them was recommended as key to accelerating an understanding of their biology and developing more effective methods for their eradication in patients.



Pax5 induces BACH2 transcription

Outcomes for the Community

We have already found a region of DNA that acts as part of the BCR-ABL switch and we are investigating which proteins bind to this region for the switch to be on. The next step will be to devise a drug that can inhibit these binding proteins. Turning off the switch may work to help stop the leukaemic process from the start, or when the Bcr-Abl protein cannot be inactivated by current treatments. Furthermore, this knowledge could be used to design similar strategies to turn off other genes which are implicated in the origin of different types of leukaemia and solid tumours, with the potential to revolutionise the treatment of these diseases

Leukaemia Unit, Department of Molecular Pathology

Associate Professor Susan Branford PhD, FFSc (RCPA)

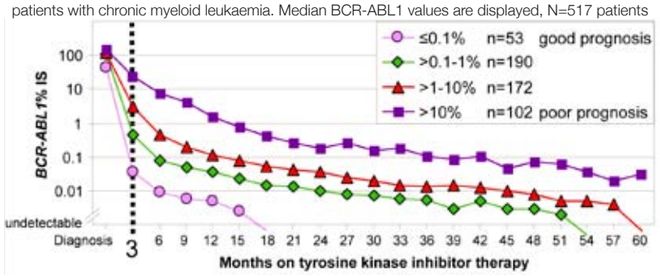
Tyrosine kinase inhibitor therapy has remarkably changed the course of disease for patients with chronic myeloid leukaemia (CML) and most achieve long-term remission. However, responses to inhibitor drugs are highly heterogeneous in terms of the rate of clearance of leukaemic cells after the initiation of therapy and some patients develop drug resistance.

Our laboratory investigates the molecular response to therapy by an examination of the *BCR-ABL1* oncogene. This abnormal gene causes the leukaemia and can be effectively targeted by drugs that inhibit *BCR-ABL1*. We investigate factors associated with clinical response and resistance to the targeted therapy. Failure to achieve certain reductions of leukaemia at specific time-points predicts suboptimal response or treatment failure.

The aim of therapy is to have a rapid *BCR-ABL1* reduction within the first three to 12 months to achieve an optimal response and long term survival. Failure to achieve these responses leads to a change of therapy to improve the chances of survival. It is important to identify patients at early stages of relapse before the disease develops into an acute leukaemia that may rapidly lead to death. Our molecular methods can predict pending relapse by an increase in the *BCR-ABL1* levels. We also search the *BCR-ABL1* gene for changes in the DNA (mutations) that indicate a patient is developing drug resistance.

These acquired mutations can interfere with drug binding and reduce its efficacy. We have developed a very sensitive method to detect these mutations and have found that some mutations can lie 'dormant' for many years and cause resistance with a change of therapy. The type of mutation we detect is important and guides the subsequent therapy selection. Some mutations cause resistance to other tyrosine kinase inhibitor drugs and it is therefore very important that a clinician knows the resistance profile of any mutations their patient may have. We are currently using the latest mutation detection technology to improve the detection of resistance and to expand our search for mutations in other genes that may cause relapse.

The *BCR-ABL1* transcript value at three months of therapy provides prognostic information for patients with chronic myeloid leukaemia. Median BCR-ABL1 values are displayed, N=517 patients



The initial molecular response measured at three months of therapy can provide long-term prognostic information. The graph shows levels of the leukaemia specific gene, BCR-ABL1, measured over five years of drug therapy. As early as three months of therapy the outcome for patients can be predicted. Those with a rapid initial reduction have the best outcomes and the highest chance and earliest opportunity to stop therapy. Some patients who stop therapy can maintain their response and may have an effective cure.

Top Sunil Abraham | Haley Altamura | Emma Channon | Zoe Donaldson | Linda Fletcher | Jasmina Georgievski
Below Mary Leong | Wendy Parker | Stuart Phillis | Brad Sullivan | Alexandra Yeoman | David Yeung

Key discoveries 2012

Some patients have many *BCR-ABL1* mutations below the level of detection by standard techniques and these can cause poor response to therapy

Using a sensitive mutation analysis technique we searched for mutations within the *BCR-ABL1* gene that we could not detect using the conventional technique of the laboratory. Surprisingly, we detected many mutations in some patients (up to ten mutations). The most we had detected by standard techniques was four mutations. Most patients only have one mutation, which is sufficient to cause resistance. Usually a change of therapy can overcome the resistance caused by mutations since most are sensitive to more potent tyrosine kinase inhibitors. However, we discovered that patients who had many low level mutations had a very high risk of failing to respond to more potent inhibitors (*Blood* 119: 2234-38, 2012). This was even though all of their mutations were predicted to be sensitive to the more powerful drugs. This was important information for clinicians to help with their decisions regarding the best therapy for their patients.

The initial molecular response to therapy can indicate the long-term outcome for patients

Studies have demonstrated that the rate of reduction of leukaemia in response to tyrosine kinase inhibitors can determine whether patients will achieve an optimal response to therapy after diagnosis of CML. For patients who develop drug resistance, some of them can be treated with more powerful tyrosine kinase inhibitor drugs. However, only about 50% of the patients respond and identifying which patients were going to respond was not possible for most patients. We examined the initial molecular response for patients who had failed their first therapy and were treated with another drug. Those patients who achieved the most rapid reductions in the first 3 months of therapy had a very good long term treatment response (*J Clin Oncology* 30: 4323-29, 2012), whereas those who only had a minor reduction were highly likely to fail therapy. This information has meant that clinicians now examine the initial molecular response to therapy as a guide to the potential outcome for their patient. Those with a rapid reduction can be reassured that their response may be very good. Other patients may benefit from an early change of therapy.

The dynamics of a *BCR-ABL1* rise after a response to therapy may help to identify a patient who has stopped taking their medication

A rise in *BCR-ABL1* is the molecular marker for potential loss of response. However, we have determined that it can also occur when a patient stops taking their drug. We have found very rapid increases in *BCR-ABL1* levels when a patient completely loses response to kinase inhibitor therapy and progresses to the terminal, acute leukaemia phase of the disease, which is also known as blast crisis. We have characterised the rise as the number of days over which the *BCR-ABL1* level doubles; the doubling-time. With progression to blast crisis, the doubling time is very short and is on average nine days. For patients who relapse but do not have sudden blast crisis, the doubling-time is much longer and is on average 48 days. For these patients there is time to consider therapeutic options for rescue since their relapse is slow. Surprisingly we found that patients who stopped taking their therapy for any reason also had a very rapid rise that was as rapid as the patients who progressed to blast crisis, however, these patients did not develop an acute leukaemia and were responsive when therapy was recommenced (*Blood* 119: 4264-71, 2012). Some patients stop taking their drug without telling their doctor, but in the long run it can lead to a poor response and possible shortening of life. Our molecular test and assessment of BCR-ABL1 doubling-times now provides an indication to clinicians that their patient may have stopped taking their drug. In the absence of blast crisis a fast doubling-time may identify a non-adherent patient.

Outcomes for the Community

Our research has benefited patients by providing guidance for clinicians when determining the most appropriate therapy after drug resistance. We regularly test patients using a sensitive technique to enable us to identify resistance causing mutations, which would otherwise go undetected. This avoids costly and time consuming trials of inappropriate kinase inhibitor drugs. We have also demonstrated the importance of the initial rapid reduction of leukaemia in the first months of therapy and established criteria for determining whether a patient is non-adherent to therapy. It is important that a clinician is alerted to non-adherence since this can lead to long-term suboptimal response for their patient.

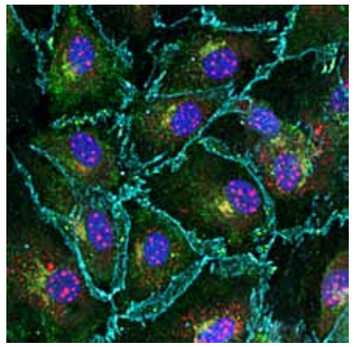
Lymphatic Development Laboratory

Associate Professor Natasha Harvey PhD

The cardiovascular system, comprised of the heart, blood vessels and lymphatic vessels, is the first organ network to develop in the vertebrate embryo. While blood vessels are essential for the delivery of oxygen and nutrients to the tissues, lymphatic vessels are crucial for returning tissue fluid and protein to the bloodstream.

Lymphatic vessels also play key roles in directing immune cell trafficking throughout the body and absorbing dietary fats from the digestive tract. The growth and development of lymphatic vessels (lymphangiogenesis) 'goes wrong' in a large catalogue of human disorders; insufficient or abnormal lymphangiogenesis manifests in conditions including lymphoedema and vascular malformations, while excessive lymphangiogenesis is associated with inflammatory diseases and cancer.

The major goal of research in the Lymphatic Development Laboratory is to identify and characterise signals important for the construction, maturation and function of lymphatic vessels, with the aim that they may prove to be targets for the generation of novel therapeutics able to promote, or inhibit lymphangiogenesis. Pro-lymphangiogenic agents should prove valuable for repairing hypoplastic or damaged lymphatic vessels and thereby treating lymphoedema, while anti-lymphangiogenic agents are likely to provide novel therapeutics for the prevention of tumour metastasis and treatment of inflammatory diseases.



Lymphatic endothelial cells grown in culture and stained with markers of the nucleus (blue), subcellular compartments (red, green) and cell membrane (cyan).

Top Kelly Betterman | Jan Kazenwadel | Genevieve Secker
Below Drew Sutton | Sebastien Tabruyn

Key discoveries 2012

Defining signals important for lymphatic vessel growth and remodelling in the mouse mammary gland

Despite the key roles of lymphatic vessels in breast cancer metastasis, little is known regarding the cellular sources of signals that drive lymphatic vascular growth and patterning in this tissue. By employing high resolution, three-dimensional imaging technology, we revealed that lymphatic vessels in the postnatal mouse mammary gland share an intimate spatial association with epithelial ducts and large blood vessels. Moreover, we demonstrated that the lymphatic vasculature is dynamically remodelled during mammary gland morphogenesis; growth of the lymphatic vessel network accompanied expansion of the mammary epithelial tree during pregnancy and was followed by regression during involution. Our work found that epithelial cells, in particular myoepithelial cells, are a rich source of growth factors including VEGF-C and VEGF-D that promote lymphatic vessel growth and development and that levels of these growth factors in the mammary gland peaked preceding a burst in lymphatic vessel growth during pregnancy. Our work sheds new light on the location of lymphatic vessels in the mouse mammary gland and the cellular sources of growth factors responsible for patterning the lymphatic vasculature during development. In addition, our work suggests a new explanation for the propensity of metastatic breast tumour cells to gain access to the lymphatic vasculature (*Am J Pathol* 181: 2225-38, 2012).

The growth factors FGF2 and VEGF-C play distinct roles in lymphangiogenesis

Primary mouse endothelial cells have traditionally proven difficult to culture and as a consequence, few assays have been developed to dissect gene function and signal transduction pathways in these cells *ex vivo*. Having established methodology for the purification, short-term culture and transfection of primary blood (BEC) and lymphatic (LEC) vascular endothelial cells isolated from embryonic mouse skin, we optimised robust assays able to measure primary embryonic LEC proliferation, migration and three-dimensional tube forming ability *in vitro*. We then used these assays to dissect the roles of established pro-lymphangiogenic growth factors FGF2 and VEGF-C in cellular processes important for lymphatic vessel development. Our work demonstrated that FGF2 promotes LEC proliferation directly via FGF receptors and independently of VEGF receptors in primary embryonic LEC. Further investigation revealed that FGFR1 was by far the predominant FGF receptor expressed by primary embryonic LEC and was important for FGF2 mediated LEC proliferation. While FGF2 potently promoted LEC proliferation and migration, three dimensional tube formation assays revealed that VEGF-C primarily promoted LEC sprouting and elongation, illustrating that FGF2 and VEGF-C play distinct, cooperative roles in lymphatic vascular morphogenesis. These assays provide useful tools able to dissect gene function in cellular events important for lymphangiogenesis and implicate FGFR1 as a key player in developmental lymphangiogenesis *in vivo*. (*PLoS One* 7(7):e40497, 2012).

Outcomes for the Community

Lymphatic vessels are of major importance to cancer patients. Cancer cells exploit lymphatic vessels as a route of metastasis and can either enter pre-existing lymphatic vessels, or promote the growth of new lymphatic vessels in order to access the lymphatic vascular network. Lymphatic vascular damage following lymph node resection often results in secondary lymphoedema, a major problem for many cancer patients. There are currently no effective, curative treatments for lymphoedema. By understanding the signals that control the growth and development of lymphatic vessels, we hope to design new therapeutics that either block, or promote the growth of lymphatic vessels. Such agents should prove invaluable for the inhibition of tumour metastasis, or for the repair of lymphatic vessel damage and treatment of secondary lymphoedema.

Mast Cell Laboratory

Associate Professor Michele Grimbaldeston PhD

Mast cells are unique immunocytes that normally reside in tissues, particularly those that are exposed to the external environment such as the skin, gut and lung.

Historically, they are depicted as major effector cells of asthma and other IgE-associated allergic disorders and immune responses to parasites. However, in addition to their ability to initiate and amplify inflammation, mast cells can also regulate such responses to protect against pathological effects of excessive inflammation and aide the processes of restoring tissue homeostasis.

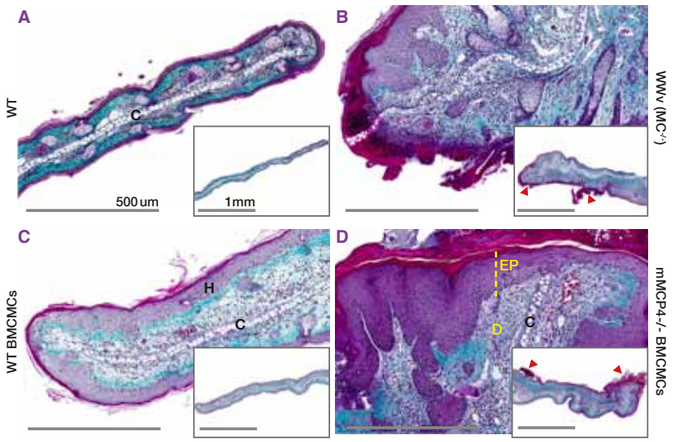
Research being undertaken by the Mast Cell Laboratory focuses on the novel regulatory abilities of mast cells, with an emphasis on how this dynamic cell contributes to the regulation of inflammation associated with allergy and skin cancer development. In a recent paper (*J Exp Med* 207: 455-63, 2010), we identified the molecular basis for the protective effects of mast cell-dependent limitation of chronic ultraviolet B (UVB) irradiation-induced skin damage.

Key to the beneficial capabilities of mast cells in this setting, is their ability to produce the anti-inflammatory cytokine, IL-10, in response to vitamin D_3. For over 80 years vitamin D_3 has been recognised as the 'sunshine' vitamin. Although it can be sourced from dietary intake, the skin also plays a crucial role in its synthesis; a process initiated by and dependent on exposure of the skin to UVB radiation, a component of sunlight. The findings from this study provided the first *in vivo* evidence of a regulatory axis between vitamin D_3 and mast cells.

In collaboration with Dr Michael Samuel (Centre for Cancer Biology) and Professor Gunnar Pejler (Uppsala, Sweden), we are investigating the important question of whether mast cell function at the peri-lesional interface provides a permissive tumourigenic environment or guards against rapid neoplastic progression during skin carcinogenesis.

At the molecular level we have identified that at certain stages of UVB-induced neoplastic progression, mast cells protect against detrimental inflammation and tissue changes by secreting IL-10 and the chymotrypsin-like protease, mast cell protease 4.

Another important aspect of our studies is to identify agents that can harness the negative regulatory ability of mast cells and thereby alter their activation state from a nefarious pro-inflammatory one to that of a beneficial anti-inflammatory one. In 2012, CSL Ltd and our laboratory, together with Professor Angel Lopez (Centre for Cancer Biology), set up a collaboration to develop therapeutics that specifically target the overactivity of mast cells without causing loss of their viability. Already we have identified a number of molecules with such efficacy *in vitro* and we are now investigating them for their therapeutic potential utilising humanised mouse models of nasal polyp growth.



mMCP4 protects against chronic UVB-induced ulceration and neoplasia development. Cross-sections of chronically UVB-irradiated mouse ears from (A) wild-type, (B) mast cell-deficient c-*Kit*$^{W/W-v}$ mice, and c-*Kit*$^{W/W-v}$ mice engrafted with (C) wild type or (D) mMCP4-deficient bone marrow derived mast cells. Sections stained with Masson's trichrome. *C*: cartilage; *EP*: epidermis; *D*: dermis; *H*: epidermal hyperplasia; *Red Arrowheads*: ulceration and necrosis

Top Alicia Chenoweth | Nicholas Hauschild | Natasha Kolesnikoff
Below Houng Taing | Svetlana Vassilieva | Dave Yip

Key discoveries 2012

Vitamin D_3 suppresses IgE-mediated mast cell activation
Mast cells have long been recognized as active participants of the allergic response at specific sites. Whether in the skin or the lung, the binding and cross-linking of IgE on the surface of mast cells stimulates the release of inflammatory mediators that exacerbate the allergic response. Our new findings demonstrate that the pro-inflammatory properties of MCs in certain IgE-dependent immune settings can be reduced upon vitamin D_3 administration. Utilizing the powerful tool of mast cell-deficient c-kit mutant mice, that can be successfully repaired of their mast cell deficiency by selective engraftment of bone marrow-derived cultured mast cells, we observed that topical cutaneous application of vitamin D_3 significantly curtails ear swelling responses associated with IgE-mediated passive cutaneous anaphylaxis. Notably, this effect required the presence of dermal mast cells and their expression of vitamin D receptors.

Outcomes for the Community

Our research extends from basic discovery in mouse models through to drug development for clinical settings. The emergence of the notion that mast cells also possess 'anti-inflammatory' potential and that they exhibit a level of 'plasticity' in response to the signals they receive from the tissue in which they reside, points to the possibility that 'harnessing' mast cell functions will be clinically beneficial.
Our finding that vitamin D_3-induced mast cell activation can initiate anti-inflammatory responses, suggests that by identifying potential druggable targets that engage the negative regulatory propensity of mast cells will enable new therapies to emerge.
Such endeavours will be of paramount importance, for example, to people who suffer with allergic disease, a setting where mast cells can exacerbate the extent of the pathology.

Melissa White Memorial Laboratory

Clinical Laboratory: Professor Timothy Hughes MD FRACP FRCPA MBBS

Research Laboratory: Associate Professor Deborah White PhD FFSc(RCPA)

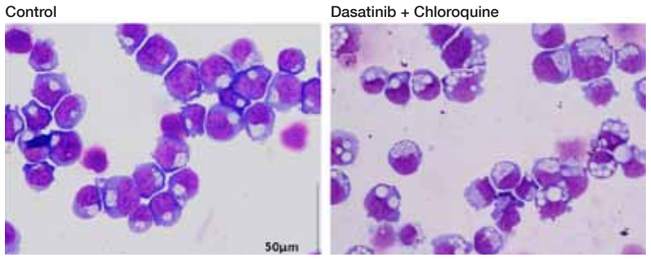
Chronic myeloid leukaemia (CML) is characterised by the Philadelphia chromosome which results from a reciprocal translocation between the long arms of chromosome 9 and 22.

This translocation results in a fusion of the BCR and ABL1 genes, and this gene fusion encodes a constitutively active tyrosine kinase Bcr-Abl which results in excess proliferation and reduced death of white blood cells. If left untreated, the disease progresses from the chronic phase (CP) into blast crisis, which resembles an acute leukaemia and is invariably fatal. The development of first and second generation tyrosine kinase inhibitors (TKIs: imatinib, nilotinib and dasatinib) has revolutionised targeted therapy and markedly improved treatment outcomes for CP-CML patients. However, there are a group of patients who respond poorly, and intolerance, development of TKI resistance and progression to blast crisis remain of major concern. Even in patients who show good clinical responses to first line drugs, the disease is rarely fully eradicated, thus patients currently expect to be on TKI therapy for life.

In order to identify patients who will respond poorly to imatinib, we have developed assays to measure a patient's sensitivity to the drug (IC50 assay) and to measure the activity of the organic cation transporter 1 (OCT-1), which is responsible for active influx of imatinib into cells. We have previously shown that patients with very low OCT-1 activity are at greatest risk of suboptimal response to imatinib. We are currently exploring different biomarkers, at the gene expression, epigenetic regulation and protein level, to aid the easy identification of those poor responders prior to therapy to enable their treatment to be individualised to ensure the best outcome is achieved.

Nilotinib, dasatinib and the third generation TKI ponatinib, which is effective against the T315I BCR-ABL kinase domain mutation that confers resistance to first and second generation TKIs, are studied in our laboratory. In particular, we investigate the differences in cellular transport and efficacy compared to imatinib. These studies led, for example, to the discovery of a novel nilotinib efflux transporter. Another focus of our lab is to recapitulate TKI resistance development in *in vitro* models and to thereby identify critical resistance mechanisms, such as the emergence of BCR-ABL mutations and other, BCR-ABL-independent, mechanisms that can potentially be targeted with combination therapies. To this end, autophagy and cytokine signalling have been highlighted and targeting the transcription factor STAT5 became, for instance, another promising approach to be assessed.

Vacuole morphology was assessed by May–Giemsa stain following cytospin K562 cells cultured with or without a combination of dasatinib and chloroquine for 24 h. The increase in vacuoles with chloroquine treatment indicates inhibition of autophagy.



Outcomes for the **Community**

With current approaches, complete responses are infrequently achieved in CP-CML patients and resistance and intolerance remain significant clinical issues. Research in our laboratory addresses the urgent need to better understand the underlying biology of CML, and to explain why some patients respond poorly to TKI therapy. Furthermore, we are ideally placed internationally to evaluate the potential clinical application of novel targeted therapies. Our overarching aim is to improve the outcome and quality of life of patients with CML.

Top Stephanie Arbon | Bron Cambareri | Phuong Dang | Laura Eadie | Amity Frede | Jarrad Goyne
Middle Devendra Hiwase | Chung Hoow Kok | Oi-Lin Lee | Liu Lu | Jenny McLean | Eva Nievergall
Below Verity Saunders | Lisa Schafranek | Carine Tang | Ljiljana Vidovic | Dale Watkins | Jackie Wong

Key discoveries 2012

A monoclonal antibody against the IL-3 receptor α (CD123) effectively depletes CML progenitor and stem cells

It has been reported that TKI therapy does not effectively target the leukemic stem and progenitor cell (LSPC), thus a pool of LPSC remain and have the potential to repopulate blood and marrow with leukaemic cells even after optimal response or in cases of therapy withdrawal. Protection by cytokines, such as IL-3 and GM-CSF, provides a potential mechanism for LPSC to escape TKI mediated cell death. In a project undertaken in collaboration with CSL Limited and the group of Angel Lopez we have demonstrated that the expression of the IL-3 receptor α (CD123) is elevated in CML LSPC compared to normal haematopoietic stem and progenitor cells. These findings are similar to others reported in acute myeloid leukemia (AML). Exploiting this further, we have utilised the monoclonal antibody CSL362, which blocks IL-3 signalling and directs NK cells to lyse CD123-expressing cells, and demonstrated effective targeting of CML LSPCs. Of clinical importance, CML patients' own NK cells were able to execute CSL362-mediated LSPC killing *in vitro* and the combination of nilotinib and CSL362 showed an additive benefit when compared to either agent alone. CSL362 is currently in a clinical trial for the treatment of AML and may hold a potential for CML therapy in the future (*ASH* abstract 32, 2012).

The non-steroidal anti-inflammatory drugs (NSAIDs) diclofenac and ibuprofen differentially affect active imatinib uptake into leukaemic cells

NSAIDs are frequently used by CML patients to manage musculoskeletal complaints. To investigate their impact on OCT-1 activity, we performed a systematic functional analysis of 12 commonly used NSAIDs in CML cell lines and CP-CML patients' cells. Interestingly, we found that ibuprofen significantly reduced OCT-1 activity and reduced imatinib effectiveness, while diclofenac was found to increase OCT-1 activity and improve imatinib potency in leukaemic cells. These studies demonstrated that patient cells can be pharmacologically manipulated to increase OCT-1 functional activity, and importantly, exploration of the underlying mechanism of action of diclofenac has revealed previously unidentified biological differences between patients with low and high OCT-1 activity. The results of these studies may have a significant impact not only for imatinib treated patients, but also those treated with other TKIs (*Br J Cancer* 106: 1772-78, 2012).

Inhibition of autophagy enhances TKI-induced cell death in chronic myeloid leukemia cells

Autophagy is a means by which cells adapt their metabolism to environmental stresses, facilitating survival during unfavourable metabolic circumstances; and has recently attracted interest as a mechanism of resistance to several cancer therapies. Combination of TKI-induced blockade of survival pathways and inhibition of autophagy by chloroquine has previously been shown to restore sensitivity of TKI-resistant CML cells to TKI-induced cell death. We have now confirmed the role of autophagy in CML and have identified the antibiotic clarithromycin as a potent autophagy inhibitor. Clarithromycin is one of several macrolide antibiotics that has been demonstrated to inhibit cancer cell growth. A recent case report suggested clarithromycin dramatically reduces BCR-ABL levels in TKI-resistant patients. Our results indicate that clarithromycin may be equally as effective as chloroquine at inhibiting autophagy and therefore enabling TKI-induced cell death (*Leukemia & Lymphoma* doi: 10.3109/10428194.2012.698737, Epub July 6 2012).

Molecular Pathology Research Laboratory

Professor Hamish S Scott PhD, FFSc (RCPA)

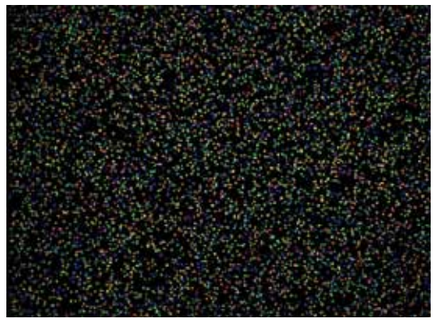
All disease processes in humans have a genetic component. This can be either inherited (familial and germline), or acquired by somatic mutation during cell division. The identification of genes and mutations that cause or predispose families to diseases, or mutations in genes acquired during disease progression are important as diagnostic and prognostic markers, as well as providing direct targets and biological pathways for therapeutic intervention.

Our research program spans basic to applied genetic research. It takes advantage of existing and emerging technologies, and resources unique to our research team and collaborators, such as patient collections and mouse models. We are interested in how and why genetic mutations occur, how these changes cause diseases or disease predisposition such as cancer and autoimmunity, and ways of better treating and monitoring these diseases. Our model diseases are typically, blood cell diseases, such as leukaemias, lymphomas and autoimmunity (eg arthritis). These diseases are mechanistically linked, being caused by excessive clonal expansion of a specific blood cell type, and may often occur together. We also work on rare, or orphan diseases, with unmet clinical need, such as genetic diagnoses for family planning.

Identification of the AutoImmune REgulator (AIRE) gene as being responsible for the human monogenic organ specific autoimmune disease, Autoimmune Polyendocrine Syndrome Type 1 (APS1), and subsequent studies, have revolutionised our knowledge of central tolerance in immunology and autoimmunity. Studies in both humans and mice with mutations in the *AIRE* gene have firmly established its role as a master regulator of the expression of RNAs encoding proteins normally restricted to specific tissues or cell types. This occurs in thymic medullary epithelial cells (mTECs) where these tissue specific antigens (TSAs) can then be presented to self-reactive T cells which are subsequently eliminated (negative selection). In the absence of Aire, self-reactive T-cells leave the thymus and, if they encounter self-antigen (Ag), T-cell and B-cell activation, auto-antibody (Ab) production and tissue damage follow.

Rare cases of genetic diseases including predisposition to leukaemias and lymphomas, infection and autoimmunity can provide insights into the initiation and progression of these diseases. With international and national collaborators as well as the South Australian Familial Cancer Service, we collect samples from rare families with predispositions to haematological malignancies (HMs) and attempt to determine which genes are mutated to cause these disease predispositions.

These studies are increasingly using the revolutionary 'next generation sequencing' technologies that have reduced the price of whole genome sequencing (sequencing a persons entire DNA composition or genome) to only a few thousand dollars. We have introduced these technologies and skills locally to South Australia. Identification of disease genes have immediate and direct implications for affected families and individuals and are beneficial for counselling, family planning and, ultimately, choices of therapy. The genes responsible for familial HMs to date are also of considerable importance in sporadic HMs.



Illumina Next Generation Sequencing. Each dot represents an individual DNA sequencing reaction and each color represents a different nucleotide that has just been incorporated into the sequencing reaction. The image shows only a fraction of the millions of sequencing reactions that can be performed simultaneously.

Top Milena Babic | Peter Brautigan | Chan Eng Chong | Chris Hahn
Below Manuela Klingler-Hoffmann | Young Lee | Nathalie Nataren | Parvathy Venugopal

Key discoveries 2012

Post-Aire maturation of thymic medullary epithelial cells
Aire regulated expression of TSAs by mature mTECs is an essential mechanism in the induction of central tolerance. Recent data suggest that the survival of mTECs extends beyond the stage of Aire expression to form a post-Aire mTEC population and Hassall's corpuscles (HCs). The nature and function of these post-Aire mTECs and structures, however, have remained unidentified. Here, we characterized in detail the end-stage development of mTECs and HCs in both Aire-sufficient and Aire-deficient mice. Using a transgenic mouse model in which the LacZ reporter gene is under the control of the endogenous Aire promoter, we purified and analyzed the post-Aire mTECs to characterize their function. We showed that the end-stage maturation of mTECs closely resembles that of keratinocytes and that the lack of Aire results in a marked block of mTEC differentiation, which is partially overcome by ligands for RANK and CD40. We also provide evidence that, during mTEC development, Aire is expressed only once and during a limited 1-2 day period. Loss of Aire expression is followed by a quick downregulation of MHC class II and CD80, and of most of the Aire-dependent and Aire-independent TSAs, with the exception of keratinocyte-specific genes. In the final stage of maturation, mTECs lose their nuclei to become HCs and specifically express desmogleins (DGs) 1 and 3, which, via cross-presentation by APCs, may contribute to tolerance against these pemphigus vulgaris-related TSAs (*Frontiers in Immunology* 3, 2012).

Genomic, proteomic and metabolomic analyses of a mouse model of Leigh syndrome
Eukaryotic cells generate energy in the form of ATP, through a network of mitochondrial complexes and electron carriers known as the oxidative phosphorylation system. In mammals, mitochondrial complex I (CI) is the largest component of this system, comprising 45 different subunits encoded by mitochondrial and nuclear DNA. Humans diagnosed with mutations in the gene NDUFS4, encoding a nuclear-encoded subunit of CI (NADH dehydrogenase ubiquinone Fe-S protein 4), typically suffer from Leigh syndrome, a neurodegenerative disease with onset in infancy or early childhood. Mitochondria from NDUFS4 patients usually lack detectable NDUFS4 protein and show a CI stability/assembly defect. We described a recessive mouse phenotype caused by the insertion of a transposable element into Ndufs4, identified by a novel combined linkage and expression analysis. Designated Ndufs4(fky), the mutation leads to aberrant transcript splicing and absence of NDUFS4 protein in all tissues tested of homozygous mice. Physical and behavioural symptoms displayed by Ndufs4(fky/fky) mice include temporary fur loss, growth retardation, unsteady gait and abnormal body posture. Analysis of CI in Ndufs4(fky/fky) mice revealed the presence of a faster migrating crippled complex. This crippled CI was shown to lack subunits of the 'N assembly module', which contains the NADH binding site, but contains two assembly factors not present in intact CI. Metabolomic analysis of the blood by tandem mass spectrometry showed increased hydroxyacylcarnitine species, implying that the CI defect leads to an imbalanced NADH/NAD(+) ratio that inhibits mitochondrial fatty acid beta-oxidation (*J Biol Chem* 287: 20652-63, 2012).

Outcomes for the Community

We continue to study rare genetic diseases and cancers. These studies are elucidating important biological pathways and disease processes. Our studies are actively guiding the therapeutic choices of patients with various cancers including leukaemia, lung and adrenal cancer.

Molecular Regulation Laboratory

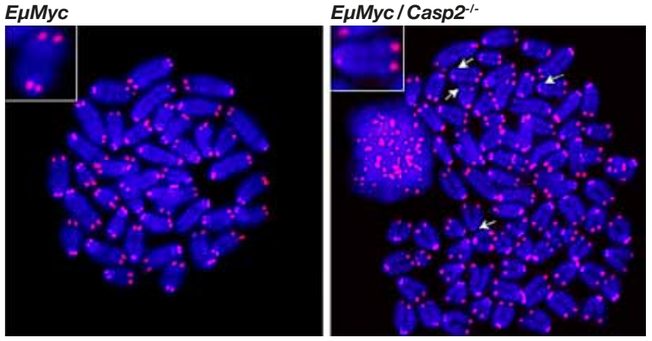
Professor Sharad Kumar MSc PhD FAA

Our broad research focus is on cellular and molecular biology of disease, with an emphasis on cancer biology. Our two major interests are: (1) the study of programmed cell death and its role in cancer and ageing, and (2) understanding the regulation of cellular homeostasis by ubiquitination.

Millions of cells in the human body die every minute as part of normal homeostasis by programmed cell death. Programmed cell death, mediated by specific cellular pathways such as apoptosis, necrosis and autophagy, plays a fundamental role in cell and tissue homeostasis and too little or too much of it can lead to many human diseases including cancer.

Given the essential role of cell death in normal functioning of the human body, deciphering the mechanisms that mediate cell death is essential for understanding disease processes and to design effective treatment strategies for pathologies which arise due to inappropriate cell death. We study the mechanisms and regulation of cell death in normal homeostasis and during animal development, with a particular emphasis on the roles of the cell death and survival machinery in cancer and ageing.

Ubiquitination (attachment of ubiquitin to a target protein) is a common type of protein modification that is involved in the regulation of protein stability, degradation, localisation and trafficking. Ubiquitination is a major regulator of many ion channels, receptors and transporters. We are studying the functions of a group of ubiquitin-protein ligating enzymes (Nedd4 family of ubiquitin ligases), which are implicated in the ubiquitination of a number of proteins mentioned above. We use a variety of molecular, cellular and gene knockout approaches to study the physiological functions of these enzymes and establish their roles in human diseases.



Loss of caspase-2 leads to telomere shortening and increased aneuploidy
Telomere FISH of metaphase spreads from *EμMyc* and *EμMyc/Casp2*$^{-/-}$ lymphoma cells, with small arrows indicating loss of telomere staining. 20x magnification

Top May Thandar Aung-Htut | Natasha Boase | Alyshea Collaco | Donna Denton
Middle Loretta Dorstyn | Natalie Foot | Kimberly Mackenzie | Jantina Manning | Kathryn Mills | Shannon Nicolson
Below Pranay Goel | Joey Puccini | Sonia Shalini | Claire Wilson | Tianqi Xu

Key discoveries 2012

The cell death protease, caspase-2, functions in the DNA damage response and is required for genome stability
Caspases are cysteine proteases that function as critical regulators of apoptosis and inflammation. Recently we have found roles for caspase-2 in apoptotic and non-apoptotic signalling pathways including tumour suppression and ageing. We demonstrated that loss of caspase-2 enhances oncogene-induced cell transformation and augments lymphomagenesis in the EμMyc mouse tumour model. In a recent publication we reported that *caspase-2-deficient (Casp2*$^{-/-}$*)* cells exhibit defective DNA damage signalling response and accumulate excessive damage to DNA, including increased DNA breaks and aberrant chromosomal separation (*Cell Death Differ* 19: 1288-98, 2012). Consistent with these observations, we observed that loss of caspase-2 leads to aneuploidy and genomic instability which likely contributes to the increased tumour potential of *Casp2*$^{-/-}$ cells. Thus, our work provides evidence that caspase-2 is a regulator of the DNA damage response and is involved in maintaining genome stability.

Caspase-2 deficiency leads to increased oxidative stress and early onset of ageing in mice
In another paper published in *Cell Death Differ* (19: 1370-80, 2012) we reported that loss of caspase-2 causes early ageing which is due to its involvement in the oxidative stress response pathway. We found that caspase-2 knockout (*Casp2*$^{-/-}$) mice have a shorter maximum lifespan, show early hair greying, reduced fat content and increased bone loss compared to wild type (WT) mice all of which are indicative of early ageing. Aged *Casp2*$^{-/-}$ mice show enhanced oxidative stress accompanied by reduced activity of antioxidant enzymes and increased DNA damage. Interestingly, in the aged *Casp2*$^{-/-}$ animals expression of FoxO family members (FoxO1 and FoxO3a) and some of its target genes were significantly reduced. Our work thus demonstrates that increased DNA damage and oxidative stress associated with caspase-2 deficiency are the causal factors leading to early onset of ageing related traits in *Casp2*$^{-/-}$ animals.

Growth arrest is required for autophagy during cell death
The catabolic process of autophagy is important for both cell survival and programmed cell death (PCD). The seemingly paradoxical functions are highlighted by the complex role of autophagy in tumourigenesis. Our previous studies using the *Drosophila* larval midgut as a model system demonstrated that caspases have little influence on PCD, whereas inhibition of autophagy severely delays midgut removal. In a recent paper (*Cell Death Differ* 19: 1299–1307, 2012) we showed that growth arrest is required for midgut removal and altered growth signalling affects autophagy and midgut degradation. Our data also revealed that induction of autophagy during cell death occurs in response to similar signals as survival-induced autophagy. Together our data indicates that autophagy and the growth regulatory pathways that have been implicated in oncogenesis have an important relationship during midgut PCD.

Outcomes for the Community

Our research will provide a better understanding of disease mechanisms and the functioning of the human body. For example, deciphering the mechanism of Caspase-2 action is important to the fundamental understanding of DNA damage response pathways, ageing and tumour progression, with the potential to discover new disease markers and novel therapeutic targets.

Molecular Signalling Laboratory

Associate Professor Stuart Pitson PhD

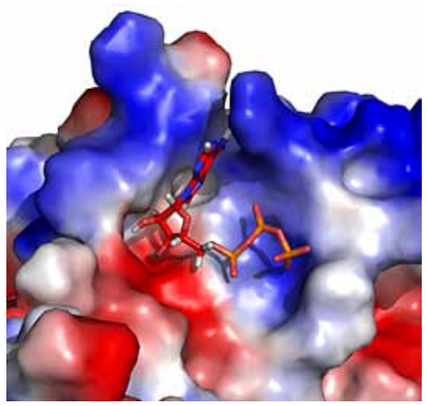
The Molecular Signalling Laboratory examines sphingolipid-mediated cell signalling pathways, and how they contribute to cancer and other diseases. In particular, the primary focus of our work is the enzyme sphingosine kinase, that controls the cellular levels of the important signalling molecules, ceramide, sphingosine and sphingosine 1-phosphate.

Ceramide, sphingosine and sphingosine 1-phosphate regulate a diverse range of cellular processes by acting as intracellular second messengers, while sphingosine 1-phosphate also acts as a ligand for a family of sphingosine 1-phosphate-specific cell surface receptors. Of greatest interest to our laboratory are findings that elevated cellular sphingosine kinase prevents programmed cell death (apoptosis), enhances cell proliferation, and leads to neoplastic cell transformation. This indicates an oncogenic role for sphingosine kinase, which is further supported by recent data from us, and others, showing elevated sphingosine kinase in a variety of human cancer cells, and inhibition of tumour growth *in vivo* by genetic or chemical suppression of sphingosine kinase.

In addition to this role in tumourigenesis, sphingosine kinase and sphingosine 1-phosphate appear central players in many other cellular processes, including; vascular endothelial cell activation, a hallmark of inflammatory diseases; enhancing blood vessel construction, and; enhancing constriction of airway smooth muscle cells. Thus, sphingosine kinase is also a potential target for therapeutic intervention in inflammation and atherosclerosis, hypertension and asthma.

Recent work in the Molecular Signalling Laboratory has concentrated on identifying the mechanisms regulating sphingosine kinase, the (patho-)physiological functions of signal transduction pathways controlled by this enzyme, and in developing small molecule inhibitors as anti-cancer agents.

In particular we have made several major breakthroughs in understanding how this enzyme in activated, relocalised to the plasma membrane, and deactivated, which have provided novel therapeutic targets to control cancer. We have also identified that the substrate of sphingosine kinase, sphingosine, is a key regulator of the pro-survival 14-3-3 proteins. Indeed, our work suggests that inactivation of 14-3-3 by sphingosine is a key control mechanism that if deregulated can enhance tumourigenesis. Thus, this pathway also represents novel therapeutic target that may be exploited to control cancer.



Structural model of the ATP-binding site of sphingosine kinase with ATP inserted

Top Watson Chan | Carl Coolen | Lori Davies | Julia Dobbins
Middle Helen Dockrell | Briony Gliddon | Paul Moretti | Heidi Neubauer | Melissa Pitman
Below Jason Powell | Haiwei Qu | Jo Woodcock | Layla Zhu

Key discoveries 2012

Development of new anti-cancer sphingosine kinases inhibitors

Sphingosine kinase shows considerable promise as a target for anti-cancer therapy in a diverse range of solid tumours and leukaemias. To date, however, no clinically useful sphingosine kinase inhibitors have been developed. Using a structure-based approach we have recently developed novel sphingosine kinase inhibitors that show considerable promise as anti-cancer agents. These inhibitors are highly specific the sphingosine kinases and in pre-clinical studies these agents show efficacy blocking the progression of a number of different human cancers *in vivo*.

Sphingosine kinase ameliorates insulin resistance

Obesity is associated with the development of insulin resistance and type 2 diabetes, which is a major health concern. In collaborative work with Professor Mark Febbraio (Baker IDI Heart and Diabetes Institute) we have recently identified that sphingosine kinase is an important regulator of insulin action and can reduce the development of obesity-induced insulin resistance (*Diabetes* 61: 3148-55, 2012). Specifically, we found that increased sphingosine kinase activity in skeletal muscle results in improved insulin sensitivity in mice fed a high fat diet.

Outcomes for the Community

Cancer continues to have a major human and economic impact on the community, with new therapeutic options desperately needed to combat this disease. Our research has not only helped to determine the molecular basis for the development, progression and chemotherapeutic resistance of some cancers, but also identified new targets for therapeutic intervention in the treatment of these cancers

Myeloma Research Laboratory

Professor Andrew Zannettino PhD

Our laboratory focuses on multiple myeloma (MM), an incurable haematological malignancy characterised by the clonal proliferation of malignant plasma cells (PC) within the bone marrow (BM).

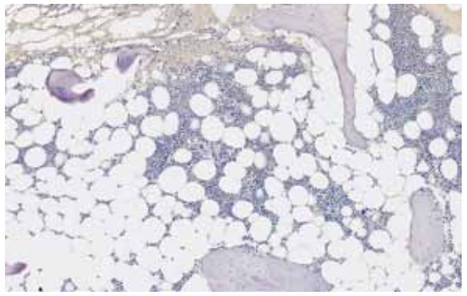
Multiple myeloma is the second most common haematological malignancy after non-Hodgkin's Lymphoma, with approximately 1,400 newly diagnosed patients each year in Australia. Despite recent advances in treatment, MM remains almost universally fatal with a five year survival rate of approximately 30%. The main clinical manifestations of MM are the development of osteolytic bone lesions, bone pain, hypercalcaemia, renal insufficiency, suppressed immunoglobulin production and increased BM angiogenesis. It is now widely accepted that most, if not all, multiple myeloma is preceded by a premalignant MGUS (monoclonal gammopathy of uncertain significance) stage. However, the genetic factors that trigger the progression from asymptomatic MGUS to overt malignant MM remain to be determined.

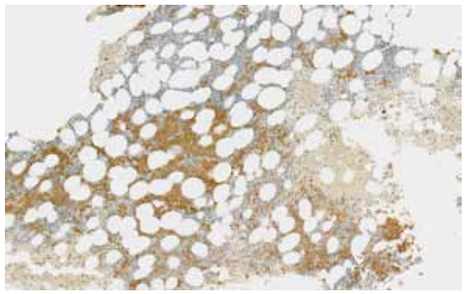
Our current projects are focused on:

Identifying key genetic changes that 'drive' the progression from asymptomatic MGUS to overt malignant MM.

Identifying novel BM microenvironmental factors that contribute to MM disease progression.

Identifying novel signalling pathways with roles in mesenchymal stem cell differentiation which may be manipulated to increase bone formation in MM patients.





Top: Bone marrow trephine sections recovered from a healthy donor

Below: Section from patient with myeloma stained with an antibody to CD138 to detect plasma cells (brown staining)

Top Chee Man Cheong | Annie Chow | Lachlan Cooper | Stephen Fitter | Catherine Gan | Duncan Hewett
Middle Tony Le | Natalia Martin | Sally Martin | Mary Matthews
Below Krzysztof Mrozik | Jacqueline Noll | Sharon Paton | Kate Vandyke | Vicki Wilczek | James Richardson, absent

Key discoveries 2012

Imatinib is a tyrosine kinase inhibitor that has been successfully used to treat Philadelphia chromosome-positive chronic myeloid leukemia (CML) and Kit(+) gastrointestinal stromal tumors

We have previously shown that imatinib therapy is associated with an increase in trabecular bone volume. We performed a prospective analysis of bone indices in imatinib-treated CML patients to determine the mechanism responsible for this altered bone remodeling using serum markers of bone remodeling, dual-energy x-ray absorptiometry analysis of bone mineral density (BMD) and micro-computed tomography analysis on bone trephine biopsies. We showed that the increase in trabecular bone volume and trabecular thickness after imatinib treatment was associated with a significant decrease in osteoclast numbers, accompanied by a significant decrease in serum levels of a marker of osteoclast activity. In contrast, osteoblast numbers were not altered by up to 24 months of imatinib treatment. Notably, we also found that imatinib caused a site-specific decrease in BMD at the femoral neck (*J Clin Endocrinol Metab* 10.1210/jc.2012-2426). Further long-term investigations are required to determine the causes and consequences of the site-specific decrease in BMD at the femoral neck.

Chronic low-back pain of discal origin is linked strongly to disc degeneration

In this study, we examined the capacity of ovine mesenchymal precursor cells (MPCs) to restore the extracellular matrix of degenerate discs in an ovine model. We found that injection of MPCs into degenerate intervertebral discs contributed to the regeneration of a new extracellular matrix and disc restoration (*J Neurosurg Spine*. 2012 May; 16(5):479-88).

Elevated N-cadherin expression in MM PC is associated with poor prognosis and can be used as a novel prognostic marker of high-risk myeloma patients

N-cadherin (cadherin 2, type 1, N-cadherin (neuronal); CDN2) is a homotypic adhesion molecule that is upregulated in breast, prostate and bladder cancer. These studies, for the first time, highlight the prognostic significance of upregulated N-cadherin expression in multiple myeloma (MM). The levels of circulating N-cadherin were elevated in a subset of patients with MM (n = 81; mean: 14·50 ng/ml, range: 0-146·78 ng/ml), relative to age-matched controls (n = 27; mean: 2·66 ng/ml, range: 0-5·96 ng/ml). Notably, patients with abnormally high levels of N-cadherin (>6 ng/ml) had decreased progression-free survival (P = 0·036; hazard ratio: 1·94) and overall survival (P = 0·002; hazard ratio: 3·15), when compared with patients with normal N-cadherin levels (≤6 ng/ml). Furthermore, multivariate analyses revealed that the combination of N-cadherin levels and International Staging System (ISS) was a more powerful prognostic indicator than using ISS alone. Collectively, our studies demonstrate that circulating N-cadherin levels are a viable prognostic marker for high-risk MM patients (*Br J Haematol* Feb 2013 doi: 10.1111/bjh.12280).

Outcomes for the Community

One contribution to the community was through the 'Clinical Practice Guidelines for Myeloma' (coordinated by Dr Hang Quach and Professor Miles Prince) prepared by the Medical and Scientific Advisory Group of the Australian Myeloma Foundation. These guidelines provide direction to treating physicians (haematologist/oncologists) as to the most effective treatment strategies for MM. These guidelines are freely accessible on the Myeloma Foundation of Australia Inc website: www.myeloma.org.au

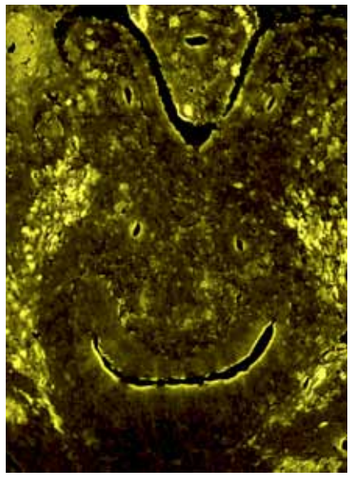
Neurovascular Research Laboratory

Dr Quenten Schwarz PhD

Understanding development and integration of the neuronal and vascular systems at the molecular level presents a major challenge to developmental biologists.

Recent advances, including our own, conclusively show that similar molecules are recruited by both systems to coordinate their development. Our laboratory is particularly interested in understanding the signaling pathways controlling neural stem cell development with the aim of identifying molecular defects underlying neurodevelopmental disorders including neuronal tumours, neurocristopathies and neuropsychiatric illness. Together, these disorders affect over 5% of the population and arise from aberrant neuronal development.

We have recently identified several key signaling molecules in neuronal development and are now using genome-wide studies in association with an array of genetic animal models to characterise the function of these proteins in neuronal migration, stem cell maintenance and differentiation.



Transverse section of an E12.5 embyo in which all neural crest cells (yellow) are labelled in our lineage tracing mouse model. Neural crest cells migrate around the urogenital ridge to form chormaffin cells of adrenal gland

Top Zarina Greenberg | Samuela Kabbara | Rachael Lumb
Below Peter McCarthy | Eiman Saleh | Sophie Wiszniak | Xiangjun Xu

Key discoveries 2012

Distinct stem cell precursors of sympathetic and sensory neurons

Neuroblastoma is the most prevalent extracranial solid tumour in childhood and is widely believed to arise from aberrant differentiation of sympathoadrenal neural crest stem cell precursors of sympathetic neurons and adrenal chromaffin cells. Our work has recently identified the cell surface receptor neuropilin 1 as a marker of sympathoadrenal neural crest cells. We have created unique animal models to specifically mark these cells and now using them to provide insight to the differentiation programs of these cells during normal development. Such data is aimed at identifying novel molecules to induce differentiation of tumour stem cells.

Identification of a central mediator of neural crest stem cell identity

Upon emigration from the neural tube neural crest cells exist as a pool of fate specified precursors and multipotent stem cells. Our work has identified a molecule that integrates extracellular signalling events with the coordination of several transcription factor networks to control stem cell identity. This finding has direct relevance to the survival of neural stem cells and to cancer stem cells.

A key signalling molecule in neurodevelopment and schizophrenia

Schizophrenia is a devastating psychiatric disorder affecting ~1% of the population and is one of Australia's major medical issues. Although recent advances in the aetiology of schizophrenia provide resounding evidence of a neurodevelopmental origin, the vast majority of underlying defects remain unknown.
We recently demonstrated that the regulatory protein 14-3-3ζ is essential for neuronal development by interacting with the schizophrenia risk factor, DISC1. Our findings provide the first cause and effect relationship between deficiency of 14-3-3ζ and neurodevelopmental disorders such as schizophrenia (*Molecular Psychiatry* 17: 45166, 2012).

Outcomes for the Community

Disorders arising from aberrant neuronal development affect a significant proportion of the population. Despite multimodal therapies that mask some clinical symptoms there remains a large degree of morbidity and mortality. It is therefore essential to identify the mechanisms underpinning these disorders so that definitive diagnostics and alternative therapies may be devised. We are currently translating our findings in to the clinic by creating and testing unique tools as diagnostic markers for neurodevelopmental disorders.

Tumour Microenvironment Laboratory

Dr Michael Samuel PhD



Anthony Pollard | Natasha Pyne | Kaitlin Scheer

The microenvironment profoundly influences the tumour phenotype and there is accumulating evidence of its utility as a prognostic tool as well as a therapeutic target.

Our laboratory works to identify the mechanisms by which the cellular and extra-cellular matrix (ECM) components of the tumour microenvironment impact on the initiation and progression of cancers, and conversely how the cancer acts to remodel its microenvironment, resisting the organism's attempt to normalise it.

The Rho signalling pathway is well-known to promote cell motility by its ability to regulate the contractility of the cellular actomyosin cytoskeleton. Less well-understood is its role in remodelling the normal tissue microenvironment. Our laboratory uses murine models in which the Rho signalling pathway can be conditionally activated, to determine the mechanisms by which this pathway modifies the ECM.

Using one of these models, we have previously demonstrated that activation of the Rho-signalling pathway within the skin causes an increase in the deposition collagen, a major ECM protein of the dermis.

The resulting increase in the stiffness and density of the ECM, disrupted normal tissue homeostasis, promoted tumourigenesis, increased the number and size of lesions and the rate of conversion to malignant carcinoma in a model of cutaneous papillomagenesis and squamous cell carcinoma (SCC) (*Cancer Cell* 19: 776-91, 2012). We are now working on determining how signalling through the Rho pathway effects these changes within the ECM.

The 14-3-3 family of phospho-serine binding proteins have roles in various cellular processes as a result of their ability to function as adaptor proteins or molecular chaperones. They have also been implicated as modulators of the Rho signalling cascade, which contains several proteins that are regulated by serine phosphorylation. Our laboratory uses mice deficient in 14-3-3ζ to determine the role of this protein in regulating Rho signalling, tissue homeostasis, tumourigenesis and tumour progression.

Outcomes for the **Community**

The progression of cancer from benign to metastatic form is directly responsible for the majority of cancer deaths. While the cost to health and wellbeing is immense, the economic cost of cancer equates to around a tenth of our country's economy. The major outcome from our work is a greater understanding of the mechanisms by which tumours hijack normal physiological processes to facilitate their growth. In identifying these mechanisms, we uncover key signalling nodes within both the tumour and the tumour microenvironment, against which therapeutic agents could be targeted in order to halt tumour progression and minimise the social and economic cost of the disease.

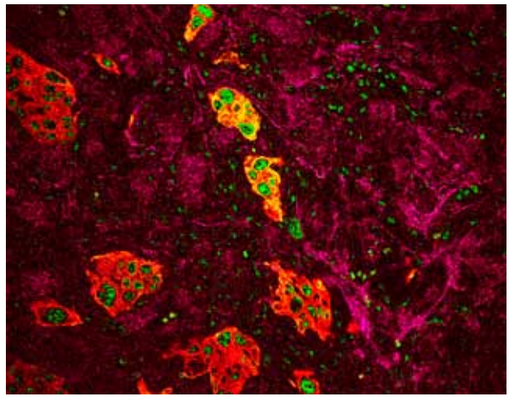
Key discoveries 2012

The Rho-signalling pathway regulates the deposition of ECM proteins in human cutaneous SCC

Following on from our work on Rho-mediated elevation of tissue stiffness and density, we have shown that this signalling pathway not only regulates the deposition of collagen within the ECM, but also the production of other key ECM components such as fibronectin and periostin, which have been previously demonstrated to exhibit pro-tumourigenic properties. Furthermore, in collaboration with Dr Jan Ibbetson of SA Pathology and using primary human cutaneous SCC samples, we have established that the Rho signalling pathway is progressively activated during tumour progression within cells of the tumour as well as the cells of the tumour microenvironment such as immune cells and fibroblasts. Activation of the Rho signalling pathway is accompanied by the increased deposition of collagen, fibronectin and periostin within the tumour microenvironment. It therefore appears that the Rho signalling pathway has a key role in establishing a tumour microenvironment that strongly promotes tumour progression.

CXCR2 inhibition suppresses tumourigenesis

CXCR2 is a chemokine receptor that exhibits context-dependent properties in either promoting or inhibiting the development of tumours. In collaboration with colleagues at the Beatson Institute for Cancer Research, the University of Glasgow UK and the Ludwig-Maximilians Universität, Germany, we have shown that expression of CXCR2 on the surface of neutrophils is required for their recruitment to sites of tumourigenesis, where they act as key members of a pro-tumourigenic inflammatory response that is driven by the incipient tumour. Genetic ablation or pharmacological inhibition of CXCR2 suppressed tumour growth in several murine models of skin and intestinal neoplasia (*J Clin Invest* 122: 3127-44, 2012). This discovery suggests that antagonising CXCR2 may have therapeutic utility in the treatment of intestinal and skin cancers.



Immunofluorescence analysis of a primary human cutaneous squamous cell carcinoma
Cancer cells (red) invade through the extra-cellular matrix on collagen (magenta fibres), accompanied by cells of the tumour microenvironment. The green label indicates activation of the Rho signalling pathway. Pathway activation is evident both within cells of the tumour microenvironment (small green cells) as well as the cancer cells.

Vascular Biology and Cell Trafficking Laboratory

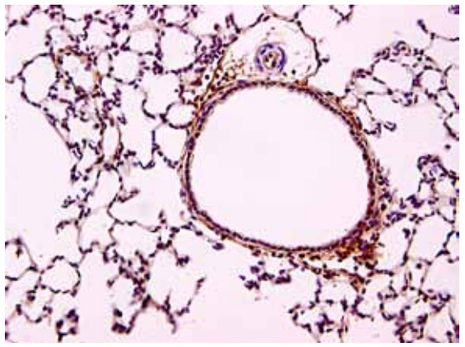
Dr Claudine Bonder PhD

Endothelial cells (ECs) line the lumen of all blood vessels and thus play a pivotal role in maintaining vascular homeostasis. This dynamic interface services an enormous array of functions including the regulation of inflammation, coagulation, arterial tone, permeability, and vessel growth.

More specifically, leukocyte recruitment to sites of inflammation is tightly regulated by ECs which, when activated, express several types of adhesion molecules. Controlling these adhesion molecules is critical to combating diseases such as allergy, cancer and heart disease.

Endothelial progenitor cells (EPCs) directly contribute to blood vessel formation (vasculogenesis) in physiological 'repair' processes of wound healing and foetal development as well as the pathological settings of cardiovascular disease, cancer, diabetes, arthritis and ischemia/reperfusion injury.

A major focus of the Vascular Biology and Cell Trafficking Laboratory is to (i) investigate the blood vasculature in normal and disease states, and (ii) identify markers that define a purified population of EPCs as well as the genetic profile which regulates their differentiation, survival and recruitment.



Identification of blood vessels in tissue using anti-CD-31 antibodies and immunohistochemistry allows for distinction between normal and diseased tissues

Outcomes for the **Community**

With a focus on immune dysfunction and disease we study the intricate network of blood vessels that carry white blood cells throughout our body. Blood vessels contribute to life threatening diseases but are also essential for tissue regeneration and organ transplantation. Our work may provide new opportunities to, on the one hand, augment blood vessel development in patients with cardiovascular disease and on the other hand, ablate blood vessel development in cancer patients.

Top Minky Cockshell | David Dimasi | Lisa Ebert | Lachlan Moldenhauer
Below Kate Parham | Wai Sun | Lih Tan | Emma Thompson | Nikhil Thyagarajan

Key discoveries 2012

Identification of a new target to treat allergic inflammation
Rapid recruitment of neutrophils to a site of inflammation is associated with allergic diseases, such as asthma and anaphylaxis. Although anti-histamines and steroids are the mainstay of treatment for symptomatic relief, their effectiveness is varied; thus, a better understanding of acute allergic reactions is required. We have examined the role of sphingosine kinase (SK) mediated P-selectin expression on ECs for the rapid recruitment of neutrophils. SK is a highly conserved lipid kinase that catalyses the phosphorylation of sphingosine to form sphingosine-1-phosphate. Two isoforms of SK exist, SK-1 and SK-2, they are ubiquitously expressed but stored at varying levels in different cell types. In collaboration with Associate Professor Stuart Pitson, we recently identified that (i) histamine-induced P-selectin expression on human umbilical vein ECs is SK-1 dependent and (ii) histamine-induced neutrophil rolling along the vasculature *in vitro* and *in vivo* is SK-1 dependent. Of great interest is that administration of FTY720 (approved pro-drug for treatment of multiple sclerosis) attenuates histamine-induced neutrophil recruitment *in vivo* (*Am J Pathol* 180: 1740-50, 2012).

Defining a new EPC signature
Current protocols for endothelial progenitor cell (EPC) identification employ combinations of progenitor markers (CD133 and CD34) and the EC marker vascular endothelial cell growth factor receptor 2 (VEGFR2). Using this protocol, EPCs have been isolated from diverse tissues, including bone marrow, umbilical cord blood (UCB) and peripheral blood. However, it is not currently known what proportion of the CD34+CD133+VEGFR2+EPCs in each tissue are in fact bona fide endothelial progenitors with one or more of CD34, CD133 and VEGFR2 described in haematopoietic, fibroblast and cancer cell populations. We recently identified a new population of immature, non-adherent EPCs (naEPCs) (*PLoS ONE* 7: e46996, 2012). These cells are distinct from 'currently used' EPCs by their non-adherence and immature phenotype which will support vascular repair and development across vascular lineages and thus vascular beds. Moreover, naEPCs likely represent the 'true' circulating EPCs which constantly survey the vasculature, ready to respond to vascular injury for repair with novel biomarkers (Patent application PCT/AU2011/001415). Our new protocols provide novel expansion methods to generate ~10^9 naEPCs in a serum free medium which provides better therapeutic opportunities for vascular repair.

Blood vessels are critical for pancreatic islet function
Pancreatic islet transplantation is an emerging cure for Type 1 Diabetes but success is limited by death of insulin producing beta cells post-transplantation. Vasculogenic endothelial progenitor cells (EPCs) have the potential to improve islet engraftment, and may also improve islet graft function. In collaboration with Dr Claire Jessup and Associate Professor Toby Coates we have combined EPC and islets into functional mosaic clusters *in vitro* and assessed the interactions between islets and EPC *in vitro* and *in vivo* in a diabetic mouse model of islet transplantation. To date we have shown that mosaic islet clusters can form successfully, using both rat and mouse cells and using confocal microscopy we have demonstrated distribution of EPC throughout rat mosaic islet clusters and glucose stimulation index function was superior to clusters comprised of islet cells only (*Islets* 3: 1-7, 2011). In 2012 we demonstrated that co-transplantation of islets and EPCs into diabetic mice significantly increased the cure rate when compared to islets alone.

The Australian Cancer Research Foundation Cancer Genomics Facility

Joel Geoghegan BSc, MSc

Dr Andreas Schreiber PhD

Over the last 10 years numerous technological developments have greatly accelerated our understanding of genetics and genomics of both inherited diseases and cancer. Advancements in microarray, microfluidics and next-generation sequencing (NGS) technologies have ushered in a new era of personalised medicine.

The Australian Cancer Research Foundation (ACRF) Cancer Genomics Facility was opened in October 2012 by the Hon John Hill, MP, South Australian Minister for Health. The Facility is the result of a number of generous grants, initiating with $3.5 million from the ACRF, and other grants from the State Government of South Australia, Therapeutics Innovation Australia (TIA) SuperScience Fund (Federal Government), MedVet Laboratories, the Cancer Council of South Australia, the Co-operative Research Centre for Biomarker Translation and through a partnership of SA Pathology and the University of Adelaide.

Over the last ten years numerous technological developments have greatly accelerated our understanding of genetics and genomics of both inherited diseases and cancer. Advancements in microarray, microfluidics and next-generation sequencing (NGS) technologies have ushered in a new era of personalized medicine. Emerging data on the structure and function of the human genome are revealing the molecular basis of disease providing opportunities to improve human health through new approaches to diagnostics and therapy. These advances are impacting all aspects of human health including diagnoses of cancer and cancer predisposition, genetic disorders, and many other chronic disorders.

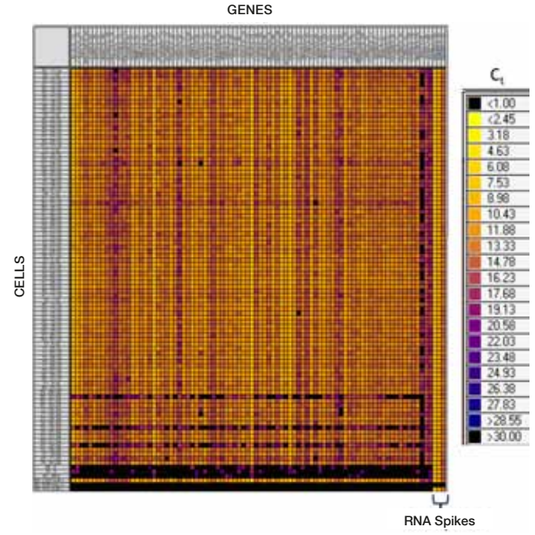
For example, cancers have, traditionally, been classified and subsequently treated based on where they occur, for example lung cancer; and their pathology, such as non-small cell lung cancer. Increasingly however, cancers are being classified and treated based not only on their location, but on their genetics. Recent advances in the power of NGS technologies, together with the discovery of genetic lesions in particular cancers, and the ability to specifically target those mutations with specialised drugs, forms the basis of personalised medicine which will become the standard of patient care in the near future.

Funding has been used to refit new lab space and bring a number of key technologies to the Centre for Cancer Biology and the South Australian research community including NGS from Illumina, Ion Torrent and Roche; microarrays from Affymetrix and Illumina; as well as Fluidigm equipment for the study of single cells. We have substantive automation, and have been first in Australia for several of these technologies, such as automation of epigenomics.

For example, through the ACRF Cancer Genomics Facility, it is now possible to sequence an individual's genome for a few thousand dollars, and equally important the protein coding genes that form the basis of personalised medicine can now be sequenced for hundreds of dollars in just a few days. This can be of importance in diagnosis and choice of therapy for both cancer and genetic diseases.

Importantly, in collaboration with eResearch SA, South Australia's high performance computing node, we have started to build our in-house capability to analyse and interpret the vast amounts of data generated by these new technologies. This includes not only 'super'-computer infrastructure, but also bioinformaticians, people skilled in analysing and interpreting this data. The prominence and promise of studies using these technologies is shown in high profile international publications, which are changing cutting edge clinical practice for both inherited genetic diseases including cancer predisposition, and many forms of 'sporadic' cancer.

Top Frank Feng | Rosalie Kenyon | David Lawrence
Below Ming Lin | Anna Tsykin | Mark van der Hoek



Expression heat map from Fluidigm BioMark HD real time PCR system
From a starting pool of about thousand K562 cells (immortalised leukaemia cell line), 96 cells were isolated using Fluidigm's C1™ Single-Cell AutoPrep System. RNA from the individual cells was converted to cDNA and loaded onto the BioMark along with assays for 96 genes. The heat map is culmination of 9,216 total real time PCR reactions (96 samples x 96 genes). image © Fluidigm

Outcomes for the Community

We are now major participants in cutting edge international studies in the causes of cancer and genetic diseases with in-house capacity and training. Up until now, many of these studies, with the vast amounts of data that these technologies generate, have been outsourced outside the State, or indeed outside Australia, in terms of both laboratory manipulations and data analyses.
We continue to developed in-house genetics, genomics and bioinformatics capacity, which helps local researchers and clinicians understand both the promise and demands in applying these new technologies to answer fundamental biological questions and specific clinical problems.
We are working closely with researchers and clinicians in basic science at the Centre for Cancer Biology, clinical translational research (for example, genetic diagnoses and molecular oncology, Centre for Cancer Biology and SA Pathology) as well as working towards implementation of our new technologies into standard health care via the Centre for Cancer Biology, SA Pathology and SA Health.

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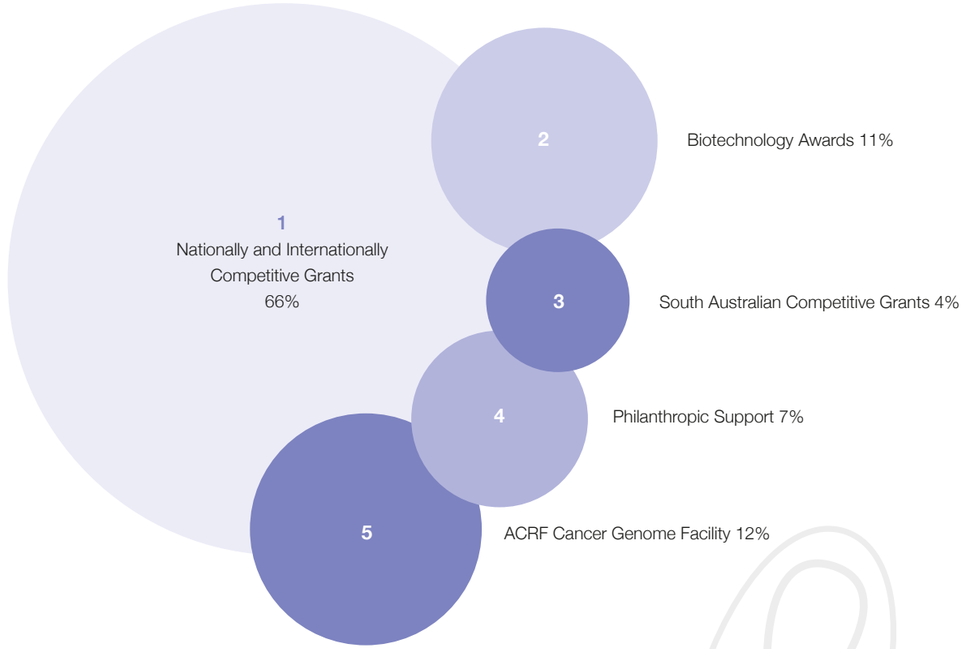
Financial Highlights

Research Income 2012

1	Nationally and Internationally Competitive Grants		11,818,528
2	Biotechnology Awards		1,988,186
3	South Australian Competitive Grants		778,850
4	Philanthropic Support		1,226,804
5	ACRF Cancer Genome Facility		2,100,000
	Total	AUD	17,912,368

All amounts shown are in Australian currency



New Grants and Fellowships Awarded in 2012

Investigator	Title	Granting Body
Andrews R, Ramshaw H, Cranmer S	A newly identified role for 14-3-3zeta protein in thrombosis and platelet procoagulant activity	National Health and Medical Research Council
Bonder C, Lopez A	A new target to combat breast cancer	Cancer Council South Australia
Branford S, Hughes T, Scott H, Schreiber A	Identification of molecular signatures at diagnosis of chronic myeloid leukaemia by an examination of the entire expressed leukaemic transcriptome to distinguish poor risk patients	Health Services Charitable Gifts Board The Ray and Shirl Norman Cancer Research Trust
Branford S	Evaluation of a major BCR-ABL mRNA assay for patients with CML for consistent interpretation of individual patient response to TKI therapy	Otsuka Pharmaceuticals
Byrne S, Halliday G, Grimbaldeston M	How does sunlight protect from autoimmunity?	Multiple Sclerosis Research Australia
Carr J, Pitson SM	Roles and regulation of sphingosine kinase 1 during dengue virus infection	National Health and Medical Research Council
Conn S	Florey Fellowship	Royal Adelaide Hospital
D'Andrea RJ	Molecular characterisation of Diamond Blackfan Anaemia	Channel 7 Children's Research Foundation
D'Andrea RJ, Gonda T, Brown AL, Lewis ID	Identification and characterisation of novel FLT3-ITD co-operating mutations	National Health and Medical Research Council
D'Andrea RJ, To LB	Dissecting the blood cell defect in Diamond Blackfan Anaemia	Captain Courageous
Ebert L, Brown A, Bonder C	A new molecule involved in the development of blood vessels within tumours	Cancer Council South Australia
Dorstyn L, Kumar S	Deciphering the mechanisms of a caspase mediated tumour suppressor pathway	Association for International Cancer Research
Grimbaldeston M, Samuel M, Gebhardt T	Mast cells are key negative regulators of skin tumourigenesis	Cancer Council South Australia
Grimbaldeston M	Commercial in Confidence funding	CSL Ltd
Gronthos S, Zannettino A	Mesenchymal Stem Cell maintenance and recruitment during skeletal repair and bone disease are dependent on EphB-ephrinB signaling	National Health and Medical Research Council
Harvey N, Scott H	Defining the role of GATA2 in lymphatic vascular development as a means to understanding how GATA2 mutations predispose to human lymphoedema	Cancer Council South Australia
Hiwase D, Hahn C, To LB, Bardy P, Scott H, Melo J	Mutation detection in MDS patients using mass spectrometry: Predicting response to therapy and long-term outcome	Royal Adelaide Hospital Contributing Haematologists' Committee
Hughes T	Practitioner Fellowship	National Health and Medical Research Council
Jessup C, Coates P, Bonder C	The importance of cell-to-cell interactions in juvenile (Type 1) diabetes	Channel 7 Children's Research Foundation
Jessup C, Peiris H, Keating D, Bonder C	The role of the calcineurin regulator RCAN1 in pancreatic islet function	Diabetes Australia Research Trust
Kumar S	Autophagy and growth signalling in developmentally programmed cell death	National Health and Medical Research Council
Kumar S, Dorstyn L	Deciphering the function of caspase-2 in DNA damage response and tumour suppression	National Health and Medical Research Council
Lewis ID, D'Andrea RJ	Investigation of dysregulated HGF/MET signalling in AML	Royal Adelaide Hospital Contributing Haematologists' Committee
Lewis ID, D'Andrea RJ, Brown AL	Gene expression consequences of altered KLF5 activity in poor prognosis	Royal Adelaide Hospital Contributing Haematologists' Committee
Li J, Liu L, Pei J, Goodall GJ,	Developing novel data mining methods to reveal complex group relationships from heterogeneous data	Australian Research Council
Lloyd A, Dore G, George T, Beard M	Program Grant: Hepatitis C infection: epidemiology pathogenesis and treatment	National Health and Medical Research Council
McRae S, Foster D	Pharmacokinetic based dosing of patients with severe haemophilia A	ACHDO Clinical Excellence Fund
McRae S, Ross D, Rodgers S, Dale B	Laboratory assessment of thrombotic risk in myeloproliferative neoplasms	Royal Adelaide Hospital Contributing Haematologists' Committee
Melo JV, Whitelaw M, Hughes TP	Transcriptional and post-transcriptional regulation of the BCR-ABL gene in chronic myeloid leukaemia	Cancer Council South Australia
Melo JV, Hughes TP, Johnson BV	Transcriptional regulation of the BCR-ABL Oncogene	Royal Adelaide Hospital Contributing Haematologists' Committee
Noll J	Veronika Sacco Postdoctoral Clinical Cancer Research Fellowship	University of Adelaide Florey Foundation
Parker W	Postdoctoral Fellowship	Leukaemia Foundation of Australia / Cure Cancer Australia Foundation
Pitman MR	Royal Adelaide Hospital Research Foundation Fellowship	Royal Adelaide Hospital Research Foundation
Pitson SM	Senior Research Fellowship	National Health and Medical Research Council
Ramshaw H, Ekert P	Does CD123 provide a biological advantage to Leukaemia stem cells?	National Health and Medical Research Council
Ramshaw H	Senior Research Fellowship	Peter Nelson Leukaemia Research Fund
Reynolds P, Curiel D, Bonder C	Development of novel gene and cell therapies for pulmonary hypertension	Heart Foundation
Samuel M	Future Fellowship	Australian Research Council
Samuel M, Lopez A, Grimbaldeston M, Ramshaw H	Skin tumourigenesis and tumour progression: A new function for 14-3-3zeta?	Cancer Council of South Australia
Schwarz Q	Defining the role of Nedd4 in neural crest cell development	National Health & Medical Research Council
Steinberg G, Bliss T, Grimbaldeston M	NIH 1R21 Grant Meningeal mast cells: key effectors of stroke pathology	National Institutes of Health, USA
To LB, Hughes T, Lopez A, Zannettino A, Scott H, D'Andrea R, Kuss B, Lewis I, Cambareri T, White D	South Australian Cancer Research Biobank (ongoing support)	SAHMRI Beat Cancer Project Infrastructure Funding
Vandyke K	Mary Overton Fellowship	Royal Adelaide Research Foundation
White D, Mullighan C, Hughes T, Sutton R	Screening for recently defined genetic lesions in poor risk adult and childhood ALL, and development treatment approaches to target causative pathways	National Health and Medical Research Council
White D, Mullighan C	Childhood Ph-like ALL: Improving diagnostic screening and therapeutic rationale	Leukaemia Foundation
White D, Mullighan C, Hughes T	Investigating the prevalence of druggable novel gene fusions, detectable by phospho-flow analysis in high risk adult B-ALL	Australasian Leukaemia and Lymphoma Group
White D, Mullighan C, Hughes T	Assessing the cause and drug susceptibility of adult high-risk ALL	Cancer Council of South Australia
Yong A, Hughes T	Characterisation of immune responses in CML patients on nilotinib and interferon alpha	Leukaemia Foundation

Seminar Program

Assoc Prof Richard Lake
Tumour Immunology Group-Research
University of Western Australia, Perth
Chemoimmunotherapy for mesothelioma: from mouse to man 8/03/12

Dr Dagmar Wilhelm
Institute for Molecular Bioscience
University of Queensland, Brisbane
Towards a new understanding of the reproductive system, a tale of ncRNAs and ovaries 15/03/12

Dr Daniela Stock
Laboratory Head, Structural and Computational Biology Division, Victor Chang Cardiac Research Institute, Sydney
Structure and dynamics of molecular rotary motors 22/03/12

Prof Michael Good (AO)
Head, Laboratory of Vaccines for the Developing World
Australia Fellow, Institute for Glycomics
Griffith University, Griffith, Queensland
A novel strategy to develop a malaria vaccine 29/03/12

Prof Shudong Wang
Professor in Medicinal Chemistry, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide
Discovery and early clinical development of cell-cycle kinase inhibitors as anti-cancer agents 05/04/12

Prof David Vaux (FAA)
Head, Cell Signalling and Cell Death Division,
Assistant Director, Walter and Eliza Hall Institute, Melbourne
Inhibitor of apoptosis proteins (IAPs) and a deal with the Devil 19/04/2012 and *Ten rules for the presentation and interpretation of data in publications* 20/04/12

Prof David James (FAA)
Director, Diabetes and Obesity Program
Garvan Institute, Sydney
Dissecting the AKT network 26/04/12

Prof Carola Vinuesa
Head, Pathogens and Immunity Dept, John Curtin School of Medical Research, Australian National University, Canberra
Antibody Responses: the Good, the Bad and the Ugly 03/05/12

Prof Christina Mitchell
Dean, Faculty of Medicine, Nursing and Health Sciences
Monash University, Melbourne
Role of PI3K regulating enzymes in development 10/05/12

Dr Greg Neely
Pain Research Group, Neuroscience Program
Garvan Institute, Sydney
Genomics approaches in the fruit fly to validate novel human disease genes 17/05/12

Prof Martin Lavin
Acting Director, Queensland Institute of Medical Research Brisbane
Dual role for senataxin, defective in ataxia oculomotor apraxia type 2, in protecting the genome 24/05/12

Assoc Prof John Pimanda
Prince of Wales Clinical School
University of New South Wales, Sydney
Embryonic haematopoietic stem cell enhancers are active in leukaemic cells and predict clinical outcome 31/05/12

Assoc Prof Carol Wicking
Molecular Genetics and Development, Institute for Molecular Bioscience, University of Queensland, Brisbane
Using mouse models to understand human ciliopathies 07/06/12

Prof Arthur Christopoulos
Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences and Dept of Pharmacology
Monash University, Melbourne
Allosteric and biased ligand drug discovery at G protein-coupled receptors 21/06/12

Assoc Prof Susan Branford
Head, Leukaemia Unit, Genetics and Molecular Pathology
Centre for Cancer Biology, Adelaide
Biomarkers of response and drug resistance in chronic myeloid leukaemia; from single mutant mRNA levels and proliferation rate, to clonal diversity 28/06/12

Prof Peter Leedman
Head, Laboratory for Cancer Medicine
Deputy Director, WA Institute for Medical Research, Perth
microRNAs and cancer: insights and challenges 05/07/12

Mr Joel Geoghegan and **Dr Andreas Schreiber**
Bioinformatics Group,
ACRF Cancer Genomics Facility, Adelaide
Overview of the new ACRF SA Cancer Genome Facility: detailing technologies, analyses and bioinformatics for research programs 12/07/12

Prof Don Newgreen
Senior Research Fellow, Embryology Laboratory,
Cell Biology, Development and Disease
The Murdoch Childrens Research Institute, Melbourne
Simple rules for a 'simple' nervous system? Biomathematical approaches to enteric nervous system formation and malformation 19/07/12

Dr Craig Wallington-Beddoe
Westmead Institute for Cancer Research
The University of Sydney, Sydney
identification of sphingosine kinases as therapeutic targets in B-lineage acute lymphoblastic leukaemia 26/07/12

Prof Michaela Kress
Dept of Physiology and Medical Physics
Innsbruck Medical University, Austria
Proinflammatory cytokines: neuroimmune regulators for pathological pain 02/08/12

Prof Peter Currie
Head, Developmental and Regenerative Biology
Deputy Director, ARMI, Monash University, Melbourne
Modelling muscle disease and regeneration in zebrafish 09/08/12

Assoc Prof Ruth Arkell
Head, Early Mammalian Development Laboratory; Research School of Biology, The Australian National University, Canberra
Is the genomic arrangement of the Zic genes critical for their function? 16/08/12

Dr Raelene Endersby
Senior Research Fellow, Brain Tumour Laboratory
Telethon Institute for Child Health Research
University of Western Australia, Perth
Paediatric Brain Tumours: from mouse modelling to preclinical trials 23/08/12

Dr Louise Cheng
Peter MacCallum Cancer Centre, Melbourne
Food for thought: Brain-sparing under nutrient restriction in Drosophila 30/08/12

Dr Archa Fox
Cancer Gene Regulation, WA Institute for Medical Research, Perth
Paraspeckles: Dynamic nuclear bodies formed by key long noncoding RNA-protein interactions 06/09/12

Assoc Prof Narci Teoh
ANU College of Medicine, Biology and Environment
Australian National University, Canberra
Liver carcinogenesis: from bench to bedside, and back again 20/09/12

Dr Annemiek Beverdam
Brain Growth and Regeneration Laboratory,
University of Queensland, Brisbane
YAP controls stem/progenitor cell proliferation and differentiation in the epidermis 28/09/12

Prof Nick Hayward
Laboratory Head, Oncogenomics
Queensland Institute of Medical Research, Brisbane
Towards dissecting the genetic landscape of melanoma through population, family and tumour sequencing 04/10/12

Dr Jose Polo
Larkins Fellow and Group Leader, Monash Immunology and Stem Cell Laboratories, Monash University, Melbourne
Unveiling the reprogramming process 11/10/12

Prof Alvin C Powers
Director, Vanderbilt Diabetes Center
Professor of Medicine; Molecular Physiology and Biophysics;
Vanderbilt University, Nashville, USA
VEGF-A and vascular networks in pancreatic islets 18/10/12

Prof Georges Grau
Chair of Vascular Immunology, Dept of Pathology
Medical School, University of Sydney
Microparticles: from infectious diseases to cancer 25/10/12

Prof Andreas Villunger
Biocenter, Division of Developmental Immunology,
Innsbruck Medical University, Innsbruck, Austria
Tumour suppression by BH3-only proteins: fact or fiction? 30/10/12

Prof Robert Parton (FAA)
NHMRC Australia Fellow, Cell Surface in Health and Disease
Institute for Molecular Bioscience, Brisbane
New insights into the formation and function of caveolae 01/11/12

Dr Stuart Brierley
NHMRC Career Development Fellow
Nerve-Gut Research Laboratory
Discipline of Medicine, University of Adelaide
Mechanisms underlying chronic visceral pain 08/11/12

Dr Ian Majewski
Research Fellow, Cancer and Haematology Division
Walter and Eliza Hall Institute, Melbourne
Targeted questions for the cancer genome 15/11/12

Prof Matt Trau
Deputy Director Nanotechnology
Australian Institute for Bioengineering and Nanotechnology
University of Queensland, Brisbane
Nanotechnology and Biomarkers: New approaches to preventative, personalised and 'at home' medicine 22/11/12

Prof Levon Khachigian
NHMRC Australia Fellow; Director, UNSW Centre for Vascular Research, University of NSW, Sydney
Growth regulatory networks in vascular pathobiology 29/11/12

Dr Paul Timpson
Head, Invasion and Metastasis Group
Garvan Institute and Kinghorn Cancer Centre, Sydney
Imaging the molecular dynamics of cancer cell behaviour in live tumour tissue using fluorescent biosensors 03/12/12

Dr Samantha Stebhens
Post-Doc, University of California, San Francisco, USA
Implications for Migration and Metastasis: The microtubule +TIP CLASP, mediates localized exocytosis to control extracellular matrix degradation and focal adhesion turnover 05/12/12

Invited Presentations 2012

Acute Leukaemia Laboratory

Prof Richard D'Andrea

Session Chair

Australian EpiAlliance Epigenetics 2012 Conference
Adelaide, Australia. May

Co-Chair

Organising and Scientific Committees
New Directions in Leukaemia Conference (NDLR2012)
Sunshine Coast, Australia. March

Haematopoiesis Session, Australasian Society
for Stem Cell Research, 5th Annual Meeting (ASSCR)
Adelaide, Australia. November

Assoc Prof Ian Lewis

Co-Chair

The Cellular Therapies Working Committee, Center for
International Blood and Marrow Transplant Research (CIBMTR)
San Diego USA February

Invited Speaker

36th Asia-Pacific Histocompatibility
and Immunogenetics Association Meeting
Adelaide, Australia. November

Dr Sarah Bray

Invited Speaker

12th Diamond Blackfan Anemia International
Consensus Conference (DBA ICC)
New York, USA. March

Dr Michelle Perugini

Invited Speaker

Centre for Personalized Cancer Medicine Annual Symposium
University of Adelaide, Adelaide, Australia. September

Cell Signalling Laboratory

Dr Yeesim Khew-Goodall

Invited Speaker

Garvan Signalling Meeting
Sydney, Australia. October

Hunter Cellular Biology Conference
Pokolbin, Australia. March

Phosphatases in Human Diseases (Satellite to Lorne Protein)
Melbourne, Australia. February

Cytokine Receptor Laboratory

Prof Angel Lopez

Invited Speaker

ASI Inflammation Conference, Melbourne, Victoria. December

Walter & Eliza Hall Institute Symposium
Melbourne, Australia. November

International Cytokine Society Annual Meeting
Geneva, Switzerland. September

ComBio 2012, Adelaide, Australia. September

Colloquium at University of Buenos Aires, Argentina. July

Gastroenterology Research Laboratory

Assoc Prof Andrew Ruszkiewicz

Invited Speaker

11th National Cancer Conference
Bangkok, Thailand. March

42nd Annual Scientific and Business Meeting
of Australian Society of Cytology
Adelaide, Australia. October

Australian Gastroenterology Week 2012
Adelaide, Australia. October

Gene Regulation Laboratory

Prof Greg Goodall

Invited Speaker

International Society of Nephrology Forefronts Symposium
Melbourne, Australia. October

Peter MacCallum Cancer Centre
Melbourne, Australia. October

ComBio 2012, Adelaide, Australia. September

Japanese Cancer Association, Sapporo, Japan. September

University of Adelaide School of Molecular and Biomedical
Science Research Symposium, Adelaide, Australia. July

Murdoch Children's Research Institute
Melbourne, Australia. April

NYU Langone Medical Center
New York, USA. March

Haematology Clinical Research Laboratory

Professor Luen Bik To

Invited Speaker

6th Australian Health and Medical Research Congress
Adelaide, Australia. November

Haematology Education Session for Adelaide Northern Division
of General Practice, Adelaide, Australia. September

2012 HSANZ Queensland State Meeting
Brisbane, Australia. March

Ms Elizabeth Duncan

Invited Speaker

Australian Society for Thrombosis and Haemostasis
Melbourne, Australia. October

Dr Simon McRae

Invited Speaker

Australian Society for Thrombosis and Haemostasis
Melbourne, Australia. October

Second ASEAN Federation of Haematology
Scientific Congress, Singapore. September

HAA 2012 Meeting, Melbourne, Australia. October

Session Chair

Master Class: Haemophilia Management, HAA 2012
Melbourne, Australia. October

Symposium: Haemophilia Update, HAA 2012
Melbourne, Australia. October

Leukaemia Biology Group

Prof Junia V. Melo

Keynote Speaker

Journal Clubs at the Royal North Shore Hospital,
Westmead Hospital and Royal Prince Alfred Hospital
Sydney, Australia. November

Nilotinib (Novartis) Investigator Meeting
Bordeaux, France. October

Leukaemia: new frontiers in therapeutic options
BMS Educational Symposium, Melbourne, Australia. October

The microRNA 2012 International Symposium
São Paulo, Brazil. March

Invited Speaker

54th Annual Meeting of the American Society of Hematology
Atlanta, USA. December

Novartis Italy Workshop on Chronic Myeloid Leukaemia at the
54th Annual Meeting of the American Society of Hematology
Atlanta, USA. December

CML Opinion Leader Training Programme (COLT)
Adelaide, Australia. October

44th Advances in Haematology Course, London, UK. October

Clinical Oncology Grand Rounds, Fred Hutchinson
Cancer Research Center, Seattle, USA. September

Highlights of ASH (American Society of Hematology)
in Latin America, Foz do Iguaçu, Brazil. May

4th Novartis R&D Symposium, Melbourne, Australia. May

Novartis Symposia, São Paulo, Belo Horizonte and
Rio de Janeiro, Brazil. March

Plenary Speaker

The 14th European Society of Haematology International
CML Conference, Baltimore, USA. September

The Mater Medical Research Institute (MMRI)
Stem Cell Symposium, Brisbane, Australia. May

Chairperson, Invited Speaker and Inaugural Lecturer

The Haematology Multidisciplinary Conference
Hopital Saint-Antoine, Paris, France. September

Leukaemia Unit, Genetics and Molecular Pathology

Assoc Prof Susan Branford

Invited Speaker and/or Session Chair

The American Society of Hematology. ASH CML
Education Session-Monitoring after successful therapy
Atlanta, Georgia, USA. December

Medical and scientific meetings, Meet the Expert sessions,
Shanghai and Beijing, China. November

European School of Haematology 14th International Conference
on CML: Biology and Therapy, Baltimore, USA. September

Asia Pacific Summit on CML, Kuala Lumpur, Malaysia. July

Speaking Tour of Canada, sponsored by Novartis Canada
Toronto, Hamilton, London, Ottawa and Montreal. June

Egyptian Stem Cell Transplantation and Hematological Disease
Association Conference (ESHA) and CML Experts meeting
Cairo, Egypt. May

Haematology Conference and Haematopathology Workshop
Ampang Hospital, Kuala Lumpur, Malaysia. March

European School of Oncology meeting: Lymphomas
and Leukaemias 2012, including Meet the Expert session
Mumbai, India. January.

Lymphatic Development Laboratory

Assoc Prof Natasha Harvey

Invited Speaker and/or Session Chair

42nd Annual Meeting of the Australasian Society for Immunology
Melbourne, Australia. December

Inaugural Meeting of the Australian Network of Cardiac
and Vascular Developmental Biologists
Sydney, Australia. December

Australian Health and Medical Research Congress
Adelaide, Australia. November

ComBio 2012, Adelaide, Australia. September

Suzhou International Symposium on Basic and Translational
Vascular Research, Suzhou, China. May

Gordon Research Conference: Molecular Mechanisms
in Lymphatic Function and Disease
Ventura, California, USA. March

Centenary Institute Colloquium 'Biology and Diseases
of the Endothelium', Sydney, Australia. February

Invited seminars

Brisbane Developmental Biology Seminar Series
Institute for Molecular Bioscience
Brisbane, Australia. November

Australian Regenerative Medicine Institute Seminar Series
Melbourne, Australia. September

UCLA, Department of Molecular, Cell and Development Biology
Special Seminar, Los Angeles, USA. March

Heart Research Institute Seminar Series
Sydney, Australia. February

Mast Cell Laboratory

Assoc Prof Michele Grimbaldeston

Invited Speaker and/or Session Chair

Australasian Society for Immunology, 42nd Annual Meeting
Melbourne, Australia. December

6th AH&MRC Congress, Molecular and Experimental Pathology Society of Australasia, Adelaide, Australia. November

Malaghan Institute, Wellington, New Zealand. November

Collegium Internationale Allergologicum 29th Symposium
Jeju Island, South Korea. October

Genentech Ltd, California, USA. October

ComBio 2012, Adelaide, Australia. September

Australasian Society for Immunology, SA/NT
8th Adelaide Immunology Retreat, Australia. September

NSW Immunology Retreat, Sydney, Australia. August

University of Sydney Dermatology, Sydney, Australia. August

University of Queensland Diamantina Institute
Brisbane, Australia. August

Australian Society for Medical Research SA Conference
Adelaide, Australia. June

3rd Co-Joint Meeting Australian Society for Dermatology and The Australasian Wound and Tissue Repair Society
Sydney, Australia. May

Bio21 CSL Ltd, Melbourne, Australia. May

'THING' Tasmanian Haematology, Immunology, Neoplasia Group Meeting, Hobart, Australia. April

Melissa White Memorial Laboratory

Professor Timothy Hughes

Invited Speaker

Brazilian Hematology Society. Sao Paulo, Brazil. November

Hematologic Malignancies 2012, Houston, USA. October

BMS Satellite Meeting, Haematology Society of Australia and New Zealand, Melbourne, Australia. October

Novartis Symposia / European Haematology Association, Amsterdam, Holland. June

CML GOLS 2012, Munich, Germany. March

New Directions in Leukaemia Research conference (NDLR), Sunshine Coast, Australia. March

Conference Organiser

ESH-iCMLf International Conference, Chronic Myeloid Leukemia: Biology and Therapy, Baltimore, USA. September

Associate Professor Deborah White

Invited Speaker

Lunchtime Research Seminar Duke NUS University
Singapore. November

Breakfast Research meeting, Peter MacCallum Cancer Research Institute, Melbourne, Australia. November

Lunchtime Research Meeting, Royal Melbourne Hospital
Melbourne, Australia. November

Special Breakfast Seminar on ALL subtypes
Austin Hospital, Melbourne, Australia. November

Special Lunchtime Seminar on ALL subtypes
Alfred Hospital, Melbourne, Australia. November

Lunchtime Meeting, Gold Coast Hospital Haematology Journal Club, Gold Coast, Australia. October

Research Spotlight Dinner Meeting, Royal Brisbane Hospital
Brisbane, Australia. October

Lunchtime Research Forum, Princess Alexandra Hospital
Brisbane, Australia. October

CML: ESH-iCMLf International Conference, Chronic Myeloid Leukemia: Biology and Therapy, Baltimore, USA. September

New Directions in Leukaemia Research conference (NDLR)
Sunshine Coast, Australia. March

CML: Molecular Workshop
Delhi, India. February

CML: Predictive Markers and Translation,
Jaipur, India. February

Organising Committee Member

New Directions in Leukaemia Research conference (NDLR)
Sunshine Coast, Australia. March

Molecular Pathology Research Laboratory

Professor Hamish Scott

Invited Speaker and/or Session Chair

PeterMac Institute Seminar, Melbourne, Australia. November

National Association of Research Fellows Symposium,
6th Australian Health and Medical Research Congress
Adelaide, Australia. November

HGSA SA Branch, Annual Meeting
Adelaide, Australia. October

ComBio 2012, Adelaide, Australia. September

Haematology Society of Australia and New Zealand
(SA Branch) Blood Club, Adelaide, Australia. June

Australian Institute of Medical Scientists
Cairns, Australia. June

Australian Institute of Medical Scientists
Barossa Valley, Australia. April

New Directions in Leukaemia Research (NDLR) Conference
Sunshine Coast, Australia. March

Lorne Genome 2012, Lorne, Australia. February

Molecular Regulation Laboratory

Prof Sharad Kumar

Invited Speaker and/or Session Chair

Institute of Molecular Cell Biology, Singapore. November

NARF Symposium, The Australian Health and Medical Research Congress, Adelaide, Australia. November

Biocenter, Innsbruck Medical University
Innsbruck, Austria. September

20th European Cell Death Organisation (ECDO) Meeting on Apoptosis, Rome, Italy. September

Lowy Cancer Research Centre Seminar Series,
Children's Cancer Institute Australia for Medical Research
Sydney, Australia. August

University of Rome Tor Vergata, Rome, Italy. July

Gordon Research Conference on Cell Death, Lucca, Italy. July

2012 Hunter Cell Biology Meeting, Pokolbin, Australia. March

Deputy Program Chair, Invited Chair
for a Plenary Session and Nominated Speaker

ComBio 2012, Adelaide, Australia. September

Dr Loretta Dorstyn

Invited Speaker

ComBio 2012, Adelaide, Australia. September

Dr Donna Denton

Invited Speaker

ComBio 2012, Adelaide, Australia. September

Molecular Signalling Laboratory

Assoc Prof Stuart Pitson

Invited Speaker

6th Garvan Meeting, Sydney, Australia. October

Baker IDI Heart and Diabetes Institute
Melbourne, Australia. August

3rd Australasian Wound and Tissue Repair Society Meeting
Sydney, Australia. May

Conference Convenor

ComBio 2012 Conference, Adelaide, Australia. September

Myeloma Research Laboratory

Professor Andrew Zannettino

Invited Speaker

ComBio 2012 Conference, Adelaide, Australia. September

AHMRC 2012, Adelaide, Australia. November

SA Multiple Myeloma Interest Group
Adelaide, Australia. September

St Vincent Research Institute Seminar Series
Melbourne, Australia. June

Public Lecture

Leukaemia Foundation Patient Information Day
AHMRC 2012, Adelaide. November

Neurovascular Research Laboratory

Dr Quenten Schwarz

Invited Speaker and/or Session Chair and/or Panel Member

Australian Society for Stem Cell Research
Junior Investigator Workshop, AHMRC Congress
Adelaide, Australia. November

4th Cell and Developmental Biology Meeting
Brisbane, Australia. October

Human Genetics Society of Australasia Annual Symposium
Adelaide, Australia. October

ComBio 2012 Conference, Adelaide, Australia. September

2nd ANZSCDB Cell and Developmental Biology Meeting
University of Adelaide, Australia. September

Department of Biochemistry, University of Adelaide, Australia. June

Department of Psychiatry, University of Adelaide, Australia. May

12th Hunter Cell Biology Meeting, Hunter Valley, Australia. March

Tumour Microenvironment Laboratory

Dr Michael Samuel

Invited Speaker

ANZSCDB, Adelaide Cell & Developmental Biology Symposium
Adelaide, Australia. November

Australian Health and Medical Research Congress
Adelaide, Australia. November

ANZSCDB, Brisbane Cell and Developmental Biology Symposium
Brisbane, Australia. October

Center for Bioengineering and Tissue Regeneration, UCSF
San Francisco, USA. October

ComBio 2012. Adelaide, Australia. September

Australian Society for Medical Research Annual Scientific Meeting
Adelaide, Australia. June

King's College London, London, UK. May

Vascular Biology and Cell Trafficking Laboratory

Dr Claudine Bonder

Invited Presentations

Women's and Children's Hospital, Delivery Suite Midwifery Group
Adelaide, Australia. October

Australian Vascular Biology Society, Gold Coast, Australia. September

South Australian Cardiovascular Research Forum
Adelaide, Australia. September

Adelaide Midwifery Meeting Group
Adelaide, Australia. July

Organising Committee

Australian Health and Medical Research Congress
Adelaide, Australia. November

Awards 2012

Acute Leukaemia Laboratory

Shahrin NH, Brown AL, Diakiw S and D'Andrea RJ
ASH Abstract Achievement Award
Blood (ASH Annual Meeting Abstracts), Nov 2012; 120: 2313

Cell Signalling Lab

Ms Leila Belle
PhD Thesis Research Excellence Award
Sponsor: Australian Society for Biochemistry and Molecular Biology

Cytokine Receptor Laboratory

Dr Hayley Ramshaw
Senior Research Fellowship
Peter Nelson Leukaemia Research Fund

Ms Nicole Christie
Best PhD Presentation
Adelaide Immunology Retreat (AIR) 2012

Overall Best Poster at ASI, Melbourne 2012

Gene Regulation Laboratory

Dr Simon Conn
Florey Fellowship, Royal Adelaide Hospital

Mr Yat Yuen Lim
Dean's Commendation for Doctoral Thesis Excellence

Mast Cell Laboratory

Assoc Prof Grimbaldeston
Collegium Internationale Allergologicum Alain de Weck Award

Dr Dave Yip
ASMR Early Career Research Award

Ms Natasha Kolesnikoff
McPhee Best Poster Award, 6th AHMRC, Adelaide, SA

Mr Houng Taing
Student Best Poster Award, ComBio, Adelaide, SA

Lymphatic Development Lab

Ms Kelly Betterman
PhD Thesis Research Excellence Award
Sponsor: Australasian Society for Immunology)

Melissa White Memorial Laboratory

Professor Timothy Hughes
NHMRC Practitioner Fellowship
Appointed to the Cancer Council SA Board
Special Orator, 2012 New Directions in Leukaemia Research Conference (NDLR), Sunshine Coast, Queensland

Dr Eva Nievergall
Non-member Travel Grant
2012 HAA Joint Scientific Meeting, Melbourne

Dr David Yeung
AR Clarkson PhD Scholarship, RAH Research Foundation

Ms Liu Lu
The University of Adelaide
International Postgraduate Research Scholarship

Mr Dale Watkins
Leukaemia Foundation Poster Prize, 2012 New Directions in Leukaemia Research (NDLR) Conference, Sunshine Coast, Queensland

School of Medicine Poster Prize
2012 University of Adelaide Faculty of Health Science Postgraduate Research Conference
Non-member Travel Grant, 2012 HAA, Melbourne

Ms Jackie Wong
Best Poster Presentation, Faculty of Health Sciences 2012 Postgraduate Research Conference, Adelaide

Molecular Pathology Laboratory

Dr Chris Hahn
Best Primary Research Publication
2012 Centre for Cancer Biology Research Prize
Sponsor: Miltenyi Biotec

Mr King-Hwa (Michael) Ling
PhD Thesis Research Excellence Award
Sponsor: Australian Society for Biochemistry and Molecular Biology

Dr Janice Fletcher, Professor David Vaux; Dr Chris Hahn accepting Mr Michael Ling's PhD Thesis Research Excellence Award from Dr Keith Shearwin, state representative for ASBMB, sponsors of the award

Left Ms Kelly Betterman, PhD Thesis Research Excellence Award
Centre Professor David Vaux; Dr Sally Martin, Early Career Investigator Award, 2012 Centre for Cancer Biology Prize
Right Ms Kate Vandyke, Mary Overton Fellowship, Royal Adelaide Hospital Research Foundation and PhD Thesis Research Excellence Award

Molecular Regulation Laboratory

Prof Sharad Kumar
Finalist, GSK Award for Research Excellence, 2012
Finalist, South Australian Scientist of Year, 2012

Mr Joey Puccini
Best Student Oral Presentation, ANZSCDB
Adelaide Cell and Developmental Biology Symposium

Ms Tianqi Xu
Best Student Poster Prize, ANZSCDB
Adelaide Cell and Developmental Biology Symposium

Molecular Signalling Laboratory

Ms Tamara Leclercq
Best Student Primary Research Publication
2012 Centre for Cancer Biology Prize
Sponsor: Qiagen

Assoc Prof Stuart Pitson
NHMRC Senior Research Fellowship

Dr Melissa Pitman
Royal Adelaide Hospital Research Foundation Fellowship

Myeloma Research Laboratory

Dr Kate Vandyke
Mary Overton Fellowship
Royal Adelaide Hospital Research Foundation

PhD Thesis Research Excellence Award
Sponsor: Life Technologies

Dr Jacqueline Noll
Veronika Sacco Postdoctoral
Clinical Cancer Research Fellowship
University of Adelaide Florey Foundation

Dr Sally Martin
Early Career Investigator Award
2012 Centre for Cancer Biology Prize
Sponsor: Qiagen

Vascular Biology and Cell Trafficking Laboratory

Ms Wai Sun
Australian Health and Medical Congress
'Best of the Best' Poster Prize

Faculty of Health Sciences
The University of Adelaide Poster Prize

Mr Nikhil Thyagarajan
Florey Medical Research Foundation Honours Scholarship

Research Staff and Students

Acute Leukaemia Laboratory
Professor Richard D'Andrea
Associate Professor Ian Lewis
Dr Sarah Bray
Dr Anna Brown
Dr Sonya Diakiw
Dr Chung Hoow Kok
Dr Michelle Perugini
Mr Grant Engler
Ms Diana Iarossi
Mr Nick Li
Ms Amilia Wee
Students
Mr Kyaw Ze Ya Maung (Hons)
Ms Nisha Rao (PhD)
Ms Teresa Sadras (PhD)
Ms Nur Hezrin Shahrin (PhD)
Students who completed
their degrees during 2012
Mr Kyaw Ze Ya Maung (Hons)

Cell Signalling Laboratory:
Dr Yeesim Khew-Goodall
Dr Leila Belle
Dr Xiaochun Li
Dr Ana Lonic
Dr Emily Paterson
Mrs Lesley Crocker
Ms Freya Gehling
Mr Nicholas Hauschild
Students
Mr Samuel Dyer (PhD)
Mr James Paltridge (PhD)

Cytokine Receptor Laboratory:
Professor Angel Lopez
Dr Sue Heatley
Dr Tim Hercus
Dr Winnie Kan
Dr Hayley Ramshaw
Dr Frank Stomski
Ms Emma Barry
Ms Mara Dottore
Ms Barbara McClure
Ms Melanie Pudney
Ms Rebecca Wright
Students
Ms Nicole Christie (PhD)
Ms Zarina Greenberg (Hons)
Students who completed
their degrees during 2012
Ms Zarina Greenberg
(Dux, School of Pharmacology
Honours Program, UniSA)

Gastroenterology Research Laboratory
Associate Professor
Andrew Ruskiewicz
Dr Maria Caruso
Dr Ross Hamilton
Ms Kay Taylor
Ms Teresa Tin

Gene Regulation Laboratory
Professor Greg Goodall
Dr Joanne Attema
Dr Cameron Bracken
Dr Philip Gregory
Dr Kimi Honma
Dr Katherine Pillman
Dr Anna Tsykin
Dr Josephine Wright
Mr Matthew Anderson
Mr Andrew Bert
Mrs Narrelle Mancini
Ms Suraya Roslan
Ms Marika Salmanidis
Ms Rosemary Sladic
Students
Ms Victoria Arnet (PhD)
Mr James Conway (Hons)
Mr Yat Yuen Lim (PhD)
Ms Corine Neilsen (PhD)
Mr Francisco Sadras (PhD)
Mr Daniel Thomson (PhD)
Students who completed
their degrees during 2012
Mr Yat Yuen Lim (PhD)

Haematology
Clinical Research Laboratory
Professor Luen Bik To
Associate Professor Ian Lewis
Dr Tony Cambareri
Dr Pratyush Giri
Dr Devendra Hiwase
Dr Smita Hiwase
Dr Noemi Horvath
Dr Sunayana Patel
Dr Simon McRae
Dr Naranie Shanmuganathan
Dr Agnes Yo
Ms Deborah Bennetta
Ms Carolyn Butcher
Ms Malgorzata (Gosia) Badowicz
Ms Pam Dyson
Mr Peter Harrison
Ms Monica Kutyna
Ms Kerry Munro
Mr Thanh Nguyen
Ms Silvana Niutta
Mr Trevor Rawling
Ms Susan Rodgers
Ms Judy Stevens
Mr Michael Vo
Students
Ms Elizabeth Duncan (PhD)

Hepatitis C Virus
Research Laboratory
Associate Professor Michael Beard
Dr Amanda Aloia
Dr Nicholas Eyre
Dr Karla Helbig
Dr Erin McCartney
Dr Kylie Van der Hoek
Ms Adriana Gaeguta
Students
Dr Edmund Tse MBBS (PhD)
Dr Kate Muller MBBS (PhD)
Mr Guillaume Fiches (PhD)
Ms Sumudu Narayana (PhD)

Leukaemia Biology Group
Professor Junia V. Melo
Dr Debora Casolari
Ms Annabel Good
Students
Mr Bradley Chereda (PhD)
Dr Stanley Cheung (PhD)

Leukaemia Unit,
Genetics and Molecular Pathology
Associate Professor Susan Branford
Dr Wendy Parker
Mr Sunil Abraham
Ms Emma Channon
Ms Chani Field
Ms Jasmina Georgievski
Ms Mary Leong
Mr Stuart Phillis
Mr Brad Sullivan
Students
Dr David Yeung (PhD)

Lymphatic Development Laboratory
Associate Professor Natasha Harvey
Dr Kelly Betterman
Dr Genevieve Secker
Dr Drew Sutton
Dr Sebastien Tabruyn
Ms Jan Kazenwadel

Mast Cell Laboratory
Associate Professor
Michele Grimbaldeston
Dr Kwok Ho Yip
Ms Natasha Kolesnikoff
Ms Alicia Chenoweth
Ms Svetlana Vassilieva
Students
Mr Houng Taing (PhD)
Ms Anastasia Yu (PhD)

Melissa White Memorial Laboratory
Clinical: Professor Timothy Hughes
Research: Associate Professor
Deborah White
Dr Devendra Hiwase
Dr Chung Hoow Kok
Dr Tamara Leclercq
Dr Eva Nievergall
Dr Carine Tang
Dr David Yeung
Ms Stephanie Arbon
Ms Bronwyn Cambareri
Ms Phuong Dang
Ms Amity Frede
Mr Jarrad Goyne
Mr Matthew Jarrett
Ms Jennifer McLean
Mr Kelvin Groot Obbink
Ms Verity Saunders
Ms Ljiljana Vidovic
Students
Ms Laura Eadie (PhD)
Dr Oi-Lin Lee (MSc)
Ms Liu Lu (PhD)
Ms Lisa Schafranek (PhD)
Mr Dale Watkins (PhD)
Ms Jackie Wong (PhD)

Molecular Pathology
Research Laboratory
Professor Hamish Scott
Dr Jinghua Feng
Dr Lucia Gagliardi
Dr Christopher Hahn
Dr Manuela Klingler-Hoffmann
Ms Milena Babic
Mr Peter Brautigan
Mr Chan Eng Chong
Ms Young Lee
Students
Ms Parvathy Venugopal (PhD)
Ms Nathalie Nataren (Undergraduate)

Molecular Regulation Laboratory
Professor Sharad Kumar
Dr May Aung-Htut
Dr Natasha Boase
Dr Hazel Dalton
Dr Donna Denton
Dr Loretta Dorstyn
Dr Natalie Foot
Dr Kimberly Mackenzie
Dr Jantina Manning
Dr Sonia Shalini
Dr Claire Wilson
Ms Alyshea Collaco
Ms Kathryn Mills
Ms Shannon Nicolson
Ms Earanee Niedzwiecki
Students
Mr Pranay Goel (PhD)
Mr Joey Puccini (PhD)
Ms Tianqi (Cindy) Xu (Honours)
Students who completed
their degrees during 2012
Ms Tianqi (Cindy) Xu (Honours)

Molecular Signalling Laboratory
Associate Professor Stuart Pitson
Dr Briony Gliddon
Dr Melissa Pitman
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Ms Catherine Gan (PhD)
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Ms Natalia Martin (PhD)
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Ms Lih Tan (Hons)
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