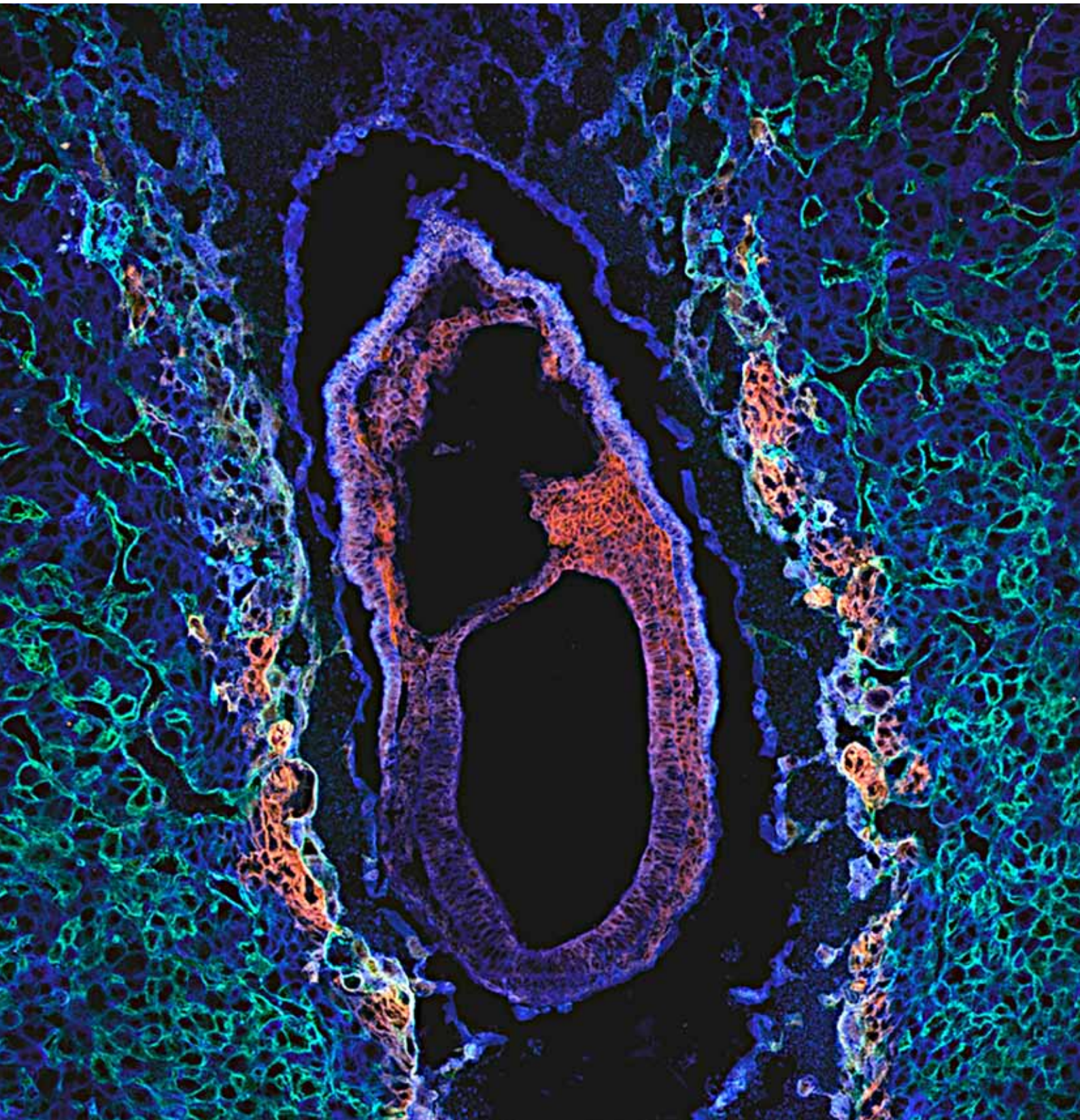
2014
Annual Report

Centre for Cancer Biology



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An alliance between
SA Pathology and the
University of South Australia

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cover image
Sagittal section of an E7.0 embryo surrounded by yolk sac and endometrial tissue immunostained to recognise Neuropilin 2 (red), E-cadherin (green) and DAPI (blue). Neuropilin 2 recognises primitive mesoderm that gives rise to the haematopoetic lineage of the embryo.

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Mr Ken Barr

Professor David G Lloyd

Alliance Partners Report

It gives me great pleasure to present the fifth Annual Report of the Centre for Cancer Biology (CCB) of SA Pathology and to reflect on its successes in 2014.

The CCB Alliance was formalised between SA Health and the University of South Australia coming in to full effect in 2014 to support and promote the growth of the CCB and its impressive ongoing research contributions to the health of the community. The CCB Alliance is an example of organisational synergy already delivering results and going from strength to strength, particularly in the dynamic genomics arena. For instance I am delighted to see the significant external competitive funding (NCRIS) that was obtained in 2014 to boost the ACRF Genomics Facility of the CCB.

The CCB Alliance is already leading to better patient care and the ACRF Cancer Genomics Facility of the CCB is a prime example of the direct patient benefits derived from a close integration of high performance research and acute pathology services with several new disease genes discovered during 2014 including those responsible for cancer predisposition syndromes. In addition, the close integration of research and services brings South Australia to the national forefront in gaining formal NATA accreditation to implement diagnostic testing using exome sequencing and related techniques.

I would also like to acknowledge the recognition of the CCB by the South Australian public as a high performing medical research institute which continues to attract philanthropic support. In particular, we are very grateful to the donors and the RAH Research Fund for their generosity and hard work not only on behalf of the CCB but on behalf of medical research generally.

In breaking news as this Annual Report goes to print, the latest exciting development is the admission of the CCB to the Australian Association of Medical Research Institutes (AAMRI). This national recognition of the CCB as a medical research institute enhances the growth and innovation opportunities for the CCB Alliance as new partnerships emerge in the evolving health and biomedical research precinct. In an Australian and global climate of constrained funding for health economies, we cannot underestimate the benefits and value that will derive from partnerships between health delivery units, Universities and medical research institutes. Together, these partnerships represent a new model of sustainability and growth, which will underpin high-quality medical research.

Mr Ken Barr
Executive Director, SA Pathology

My research career was in cancer drug discovery so I automatically had a soft spot for the Centre for Cancer Biology. Partnerships are at the heart of everything we do and when the opportunity came for the University of South Australia and the South Australian Department of Health, through SA Pathology, to form an alliance to give long-term support and appropriate infrastructure to the Centre for Cancer Biology, we jumped at it.

This is an opportunity not only to promote and support medical research, but by linking theory with practice, we are also able to maximise the resources and put the value of our discoveries directly into the delivery of quality health care services.

The University's health and biomedical research concentration, our education and research concerning the prevention, diagnosis and treatment of health problems, is a great fit for SA Health, and together with the CCB we can maximise our contributions to the health of the population.

Together UniSA and CCB enhance each other's efforts. The CCB is focused on a range of cancers, providing research and support for personalised DNA targeted treatments which are revolutionising cancer treatment and recovery. The alliance with CCB complements UniSA's expertise in the quality use of medicines, pharmaceutical science and pharmacokinetics research and also links with the University's advanced manufacturing capabilities in nanotechnology and coatings and with our technological leadership in the new CRC for Cell Therapy Manufacture.

Between our two organisations we embody a cancer research community of enormous depth and capacity. We're particularly proud of the two scientists who are driving the alliance. CCB Co-Directors Professors Angel Lopez and Sharad Kumar have contributed greatly to medical research throughout their careers. Both are Fellows of the Australian Academy of Science and, in 2014, were elected as Fellows to the Australian Academy of Health and Medical Sciences. This is a new organisation created to promote health and medical research and its translation to enable a healthy community in Australia and the world.

It is due recognition of their potential to make a significant contribution to better understanding cancer, improving its treatment and perhaps leading to a cure. We are especially proud to be part of that.

Professor David G Lloyd
Vice Chancellor and President
The University of South Australia

Professor Angel Lopez

Professor Sharad Kumar

Professor Jim McCluskey, keynote speaker at the CCB 2014 AGM

Professor Professor David Lloyd presents opening remarks
at the launch of CCB's alliance with SA Health and UniSA

Centre for Cancer Biology Directors Report

Professor Angel Lopez MBBS PhD FRCPA FAA FAHMS
Professor Sharad Kumar MSc PhD FAA FAHMS

We are pleased to present the 2014 Annual Report of the Centre for Cancer Biology: a year that is the first of the strategic alliance between the Department of Health's SA Pathology and the University of South Australia to strengthen and grow the CCB.

We are delighted and grateful for the strong support we are continuing to receive from SA Pathology while equally appreciative of the new and significant benefits that the University of South Australia brings to the CCB alliance.

In an era when medical research is under considerable budgetary pressures new partnerships such as this are incredibly important to maintain momentum and represent a valuable model for securing medical research excellence, sustainability and expansion.

A major contribution by the University of South Australia towards an effective and enduring CCB alliance is the provision of a new medical research facility in the western end of North Terrace. The design of this new building started in earnest in 2014 under the overall stewardship of Ms Christina Coleiro who brought together a team of architects and designers working in close consultation with the CCB membership under the tutelage of Professor Richard D'Andrea and the thoughtful and hard work of Ms Lagnado, Dr Nicholson, Mr Bert and Dr Ramshaw. The plans and design already look extremely attractive and practical to house and support the CCB staff and the cutting edge facilities that we will need.

In 2014, the CCB has continued to make significant inroads towards better cancer treatments through discovery. We published 106 scientific manuscripts in esteemed scientific journals, reporting our studies on leukaemia, lymphomas, breast, prostate, colon, skin and lung cancers. The contributions of each of the CCB's laboratories are listed in the annual report but here we would like to note a few of the highlights.

We reported in the EMBO Journal the identification of miR-200 targets and how they make a network that controls cancer cell invasion in breast and prostate cancers. In a paper published in Cell Reports with interstate colleagues we established how an antibody being developed against acute myeloid leukemia works, a finding that provides a road map for developing more effective antibodies as anti-cancer drugs. And in a paper in Oncotarget we showed how ovarian cancer can be targeted with a potent inhibitor. It was pleasing to see how many of our discoveries were the result of close collaboration amongst CCB members as well as with other colleagues locally and overseas.

A major catalyst for our cancer research continues to be our ACRF Cancer Genomics Facility. This is invaluable for enabling our discoveries and also helping with early and more precise diagnosis and tailored therapies for cancer patients. It is this symbiotic relationship between medical research and services that is making a major impact for patient care, with the CCB becoming a major player in the National Healthcare Genomics Initiative consortium. Being embedded in the health system our medical researchers and pathologists seamlessly interact to change the way we diagnose and treat individual cancer patients. We are now able to test for several mutations at a time, facilitating early treatment options and better patient-drug selection for clinical trials.

Underpinning our work in 2014 was the financial support of both SA Pathology and the University of South Australia and the extensive competitive funding obtained from national and international sources. Professors D'Andrea, Goodall, Pitson, Scott and Zannettino and Associate Professors Branford, Grimbaldeston, Harvey, Lewis, Khew-Goodall and Samuel were successful in the latest round of the highly competitive NHMRC project grants and Professor Kumar, an ARC project grant. A prestigious Department of State Development Fellowship was awarded to Professor Vinay Tergaonkar of the Institute of Molecular and Cell Biology (*ASTAR) in Singapore to establish a new laboratory at the CCB. We are very proud of this award that will facilitate significant collaborations between Singapore and South Australia and bring additional medical research expertise and 'new blood' into the state.

We are pleased to report that in 2014 both of us were elected as Fellows of the newly created Australian Academy of Health and Medical Science, an honor that reflects the high performance of the CCB and also represents an opportunity for us to promote and advance our younger CCB colleagues. In May the Program Grant led by Professors Lopez, Parker (St Vincent's Institute of Medical Research) and Hughes (SAHMRI and CCB) to seek better treatments in leukaemia was awarded the 'Best Program Grant' prize by the NHMRC.

In 2014 we welcomed Associate Professor Leanne Dibbens and Professor Paul Reynolds as new members to the CCB Faculty. Leanne has a recognized track record in genetic diseases and Paul is a specialist in translational and clinical lung research. We also welcome Mr Russell D'Costa as the inaugural CCB Operations Manager.

On 14 August the CCB held its 2014 Annual General Meeting. Professor Jim McCluskey, Deputy Vice-Chalcellor (Research) of Melbourne University, was the invited keynote speaker. In his address Jim described the Parkville Precinct in Melbourne where hospitals, universities and medical research institutes work in close proximity and highlighted the virtues of collaboration. He drew a parallel with the incipient Health and Medical Research Precinct in Adelaide and noted the important role that the CCB can play through its discovery and translation mission. Jim presented a number of research excellence awards to the staff and students of the CCB: 'Best Primary Research Publication from a CCB Researcher' to Drs Daniel Thomas and Jason Powell, 'Best Student Primary Research Publication Award' to Mr Joey Puccini and the 'CCB Early Career Investigator Award' to Dr Dave Yip.

In 2014 we continued our educational and professional development programs. An active weekly CCB Seminar program continues to feature some of the most eminent scientists as well as the rising stars in medical research to Adelaide, as listed at the back of this report. Our invited speakers spend a whole day with CCB members, young investigators and students to help with mentorship. In 2014 a new seminar series focused on 'Bioinformatics' was energized by Dr Andreas Schreiber of our ACRF Cancer Genomics Facility to bring together the major players in Adelaide of this essential discipline.

The CCB is conscious of the benefits of commercialisation as a way to facilitate the translation of our research into better health care. While already enjoying fruitful interactions with major pharmaceutical companies such as CSL Limited, Novartis, BMS, and Merck, in 2014 the CCB joined the Medical Research Commercialisation Fund with the view to attract investment to innovative projects and to accelerate the application of CCB discoveries. We also continue to be active participants in the Cooperative Research Centre for Cell Therapy Manufacturing in which the research led by Associate Professor Claudine Bonder is a major focus.

In advancing our vision, the CCB has a strong focus on women in leadership roles. CCB members support the improvement of career opportunities and Florey Fellow Dr Lisa Ebert exemplifies this as a mentor in the 'Women's Initiative' run by the Australasian Society for Immunology. Many of the CCB members actively participate in the 'Women in Science SA' scheme which facilitates a strong network for women in science in South Australia. Additionally, through the Adelaide Immunology Retreat, Associate Professors Claudine Bonder and Michele Grimbaldeston have provided annual mentoring opportunities for young women in science by inviting women scientists of outstanding calibre such as Professors Anne Kelso, Lynn Corcoran, Sarah Robertson and Carola Vinuesa to impart their wisdom and vision of the future.

We would like to use this opportunity to thank our Alliance partners SA Health and the University of South Australia for their support as well as the NHMRC, ARC, the Australian Cancer Research Foundation, CSL Limited, the Health Services Charitable Gift Board, eResearch SA, Cancer Council SA, Cancer Australia, Leukaemia Foundation, RAH Research Foundation, Channel 7 Foundation, Therapeutic Innovation Australia, The Kids' Cancer Project SA and Medvet. Their support of our infrastructure, Fellowships and projects are all essential for our cancer research.

We are also grateful for the support from the executive of SA Pathology Mr Ken Barr and Dr Janice Fletcher, and on operational matters from Dr Doreen Krumbiegel and Professor Robert Heddle. Similarly, we appreciate the support from the executive of the University of South Australia Professors David Lloyd (Vice-Chancellor), Tanya Monro (Deputy Vice-Chancellor Research and Innovation), Heddy Zola, Robert Vink and Dr Stephen Rodda. It is their strong support that makes the success of the CCB alliance possible now, and into the future. We are also very appreciative to our Advisory Committee of eminent local supporters and interstate colleagues who collegially and generously give their valuable time to advance the Centre for Cancer Biology.

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

Class of 2014
Robert Vink | Sharad Kumar | Richard Head | David Lloyd | Angel Lopez | Allan Evans | Staff and Students of the Centre for Cancer Biology

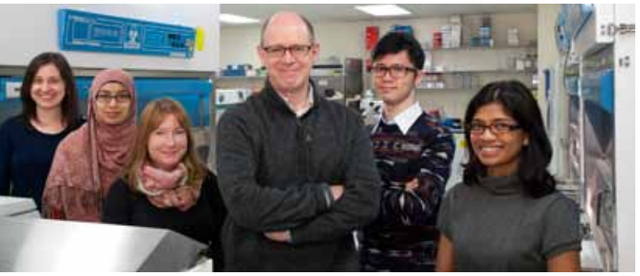
Mr Ken Barr with guest speaker the Hon Jack Snelling MP, Minister for Health

Professors Angel Lopez and David Lloyd presented opening remarks at the launch

Celebrating Our Strategic Alliance

On Friday 6 June 2014 we gathered in the UniSA Hawke Building's Bradley Forum to launch the Centre for Cancer Biology as an alliance between the Department of Health's SA Pathology and the University of South Australia

Photography courtesy UniSA. Photographer: Catherine Leo



Diana Iarossi | Nur Hezrin Shahrin | Sarah Bray | Richard D'Andrea
Nick Li | Saumya Samaraweera

Kyaw Ze Ya Maung | Tran Nguyen | Ljiljana Vidovic | Ian Lewis
Debora Casolari | Mahmoud Bassal

Acute Leukaemia Laboratory

Professor Richard D'Andrea PhD
Associate Professor Ian Lewis MBBS PhD FRACP FRCPA

The Acute Leukaemia Laboratory has a fundamental interest in Acute Myeloid Leukaemia (AML). This devastating disease is the most common form of acute leukaemia in adults and is responsible for one fifth of all childhood leukaemia cases. AML comprises several subtypes, characterised by different combinations of genetic aberrations and prognostic outcomes.

The genetic complexity of the disease has hampered progress in the field, with the molecular basis for some subtypes still largely unknown, and hence outcomes are still quite poor. Overall survival for adults with AML is still only 30–40%, and for some subtypes, prognosis is dismal, with a median overall survival of just 10 months. With the recent advances in genomics based applications, research in this field has been accelerated and we have been using some of these technologies to better understand the molecular aberrations responsible for this disease.

The research carried out by the Acute Leukaemia Laboratory strives to better understand the mechanisms underlying AML, with the ultimate goal of improving treatment outcomes. A significant research focus of the laboratory is the investigation of the mechanisms that control stem and progenitor cell growth and survival, and which are commonly deregulated in AML. We have used genetic and epigenetic approaches to identify novel genes and pathways important for AML pathogenesis and disease stratification, and to identify patients that may respond to novel, less toxic therapies. In addition, our research aims to understand the genetic changes that lead to the altered metabolism exhibited by AML cells. Finally, we are also interested in the role of the Epidermal Growth Factor Receptor (EGFR) in the Philadelphia Chromosome-negative Myeloproliferative Neoplasms (MPN), a group of chronic diseases associated with a predisposition for AML.

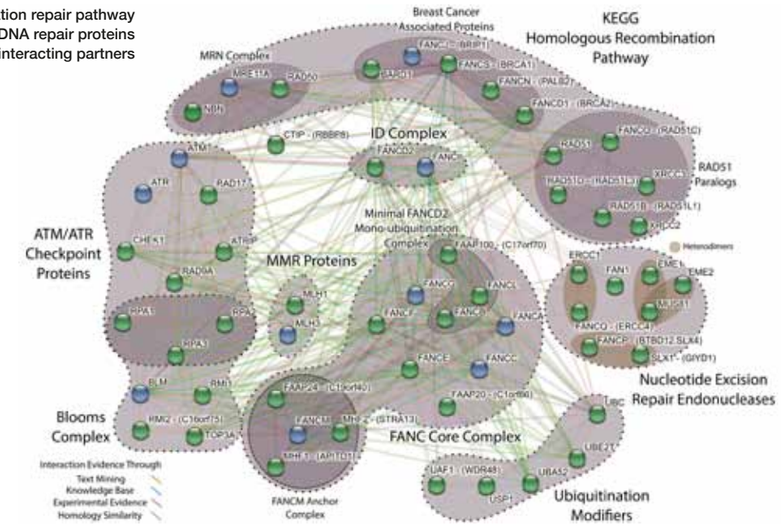
Clinical Trials in Acute Myeloid Leukaemia
Complementing the fundamental research being carried out in the Acute Leukaemia Laboratory, the Department of Haematology, at SA Pathology and the Royal Adelaide Hospital, participates in clinical trials testing new therapies in AML. This gives patients access to novel therapies and by studying the effects of these treatments on leukaemic cells in patients leads to improved understanding of the disease and may lead to better drugs. The commonest molecular mutation associated with an adverse outcome in AML is in the FLT3 gene. We are currently involved in clinical trials evaluating the role of two different inhibitors of FLT3, sorafenib and quizartinib, in different stages of AML. If these studies prove successful, it will open up new treatments in this high risk group of patients. Identification of other molecular mutations in AML is leading to the development of specific inhibitors targeting these genes. Of particular interest in our laboratory is the IDH2 mutation, found in 10 – 15% of AML patients and associated with GADD45A silencing. We will soon be involved in a clinical trial evaluating a specific inhibitor of IDH2 in patients with relapsed AML, the results of which should provide important findings in this subgroup of patients. By participating in clinical trials in AML, benefits accrue to patients and the community with the hope of better treatment success, and add to fundamental knowledge about the disease.

Outcomes for the Community

In solid cancers, defects affecting the HRR pathway confer sensitivity to selected anti-cancer therapies, thus raising the possibility that AML cases with mutations affecting this pathway may represent a group that can be targeted with tailored therapies. We are collaborating with a US group that is developing novel therapies allowing us to directly test this hypothesis. Our studies with the novel CDK inhibitor suggest that it represents a promising, less toxic, treatment for a selected AML subtype which has a dismal outcome with conventional chemotherapy. Since CDKI-73 is orally available and has shown limited effects on normal (non-leukaemic) cells (Walsby *et al*, 2013), we are now further investigating the anti-leukaemic activity of this compound in pre-clinical xenograft models of AML, and these experiments will form the basis for further translational studies.

Key discoveries 2014

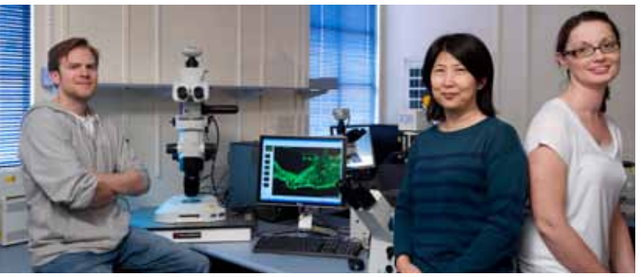
Extended homologous recombination repair pathway consisting of Fanconi Anemia DNA repair proteins and its direct interacting partners



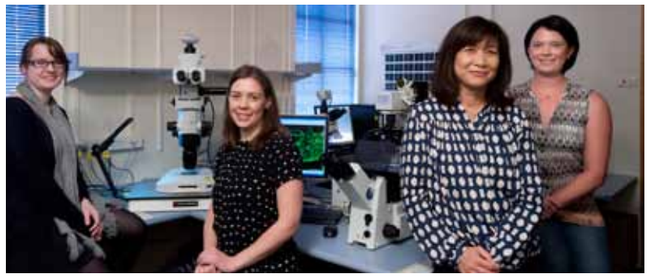
Whole exome sequencing of acute myeloid leukaemia patients identifies mutations in Fanconi Anaemia genes
As an approach for discovery of gene mutations in AML, we performed whole exome sequencing (WES) analysis of tumour DNA from 97 AML patients at diagnosis and disease relapse. Consistent with other AML genomics studies, we identified a number of aberrations specific to the leukaemic samples in genes that have previously been reported as recurrently mutated in AML. More interestingly however, we also identified an enrichment in the AML cohort of germline mutations in genes associated with the homologous recombination DNA repair (HRR) pathway (see figure). Patients with heterozygous mutations affecting selected genes within the HRR DNA repair pathway displayed distinct features, including an increased level of karyotypic abnormalities. Our findings suggest that heterozygous mutations affecting function of the HRR DNA repair pathway may confer increased risk for AML development and hence be a recurrent abnormality in AML patients.

Novel orally-available small molecule kinase inhibitors for treatment of poor prognosis AML
In 2014, we commenced a new collaboration with Professor Shudong Wang at the Centre for Drug Discovery and Development (University of South Australia). Professor Wang has developed a novel orally available inhibitor of cyclin dependent kinase 9 (CDK9) that has shown promising results in cells from Chronic Lymphocytic Leukaemia patients. As part of this collaboration, we have investigated the potential use of this drug (CDKI-73) as a treatment for selected AML subtypes. A panel of 7 AML cell lines showed significant growth inhibition at very low doses of the drug (GI50 = 47.5 – 606.8nM), with the three most sensitive AML cell lines (MOLM-13, MV4;11 and THP-1) representing a poor prognosis AML subtype. Further to this, we have shown that treatment with low dose CDKI-73 (200nM) results in a marked decrease in levels of the survival protein MCL1, and in apoptotic cell death of AML cell lines and primary AML patient samples of this subtype.

Significance of GADD45A promoter DNA hypermethylation in AML
We have previously shown that one target of DNA hyper-methylation in AML is the promoter of the tumour suppressor and stress-response mediator *Growth Arrest* and *DNA Damage inducible 45A* (*GADD45A*) (*GADD45A*me^{HI}; 42% of AML). Promoter hypermethylation of this gene defines a patient group with poor survival on standard therapy in two independent cohorts (Perugini *et al*, *Leukaemia* 2012 and unpublished data). Taken together with recent findings by Chen *et al*, (*Blood* 2014), our data suggests that the hypermethylation and silencing of the *GADD45A* gene in AML may play an important role in the altered properties of HSC, contributing to leukaemia initiation, progression and response to therapy.
To explore further the molecular basis of the *GADD45A*me^{HI} patient group we performed genetic profiling of AML diagnosis samples using a Sequenom multiplex mutation panel, or using whole exome sequencing (n=95 patients). This revealed a striking co-occurrence of the *GADD45A*me^{HI} phenotype with mutations in *IDH1*, *IDH2*, and *TET2* ($p<0.0001$, Fisher's exact test), suggesting silencing of GADD45A may be particularly important in AML patients with these common mutations (collectively these occur in 28% of AML (Network CGAR, *N Engl J Med*, 2013)).
We then showed that reactivation of *GADD45A* expression in the *GADD45A*me^{HI} AML cell lines MOLM13 and MV4;11, and three primary AML samples (*GADD45A*meHI) could be achieved through the use of the hypo-methylation agent, Decitabine (DAC). Further, this DAC pre-treatment resulted in an increased sensitivity to the chemotherapy drug daunorubicin (DNR). These *in vitro* drugs experiments suggest that a priming schedule of DAC followed by DNR may provide a successful tailored treatment strategy for *GADD45A*me^{HI} patients.



James Paltridge | Xiaochun Li | Ana Lonic



Sarah Bernhardt | Freya Gehling | Yeesim Khew-Goodall | Leila Belle

Cell Signalling Laboratory

Associate Professor Yeesim Khew-Goodall PhD

The interest of the Cell Signalling Laboratory is to understand how signals that are normally generated to maintain homeostasis, give rise to disease when dysregulated. Our primary research interest is to understand how a cancer cell progresses from a benign state, with good prognosis, to a malignant state resulting in metastatic disease. In solid cancers, which constitute 80% of human cancers, the vast majority of deaths are due to metastasis.

Our two main areas of research are:

Regulation of protein trafficking by tyrosine phosphorylation

Cells express a range of surface receptors and secrete a range of cytokines and growth factors that influence their growth and the activities of neighbouring cells. However, the spectrum of secreted proteins and cell surface receptors are often vastly altered in cancer cells relative to their cell of origin. These vast changes to the secretome and plasma membrane proteome of cancer cells which can make them grow better, more metastatic or chemoresistant are seemingly coordinated but how this occurs is not clear. We are interested in elucidating the signal transduction pathways that regulate trafficking of receptors and secreted proteins and how these are dysregulated in cancer cells to promote growth and metastasis.

Molecular regulation of cell invasion

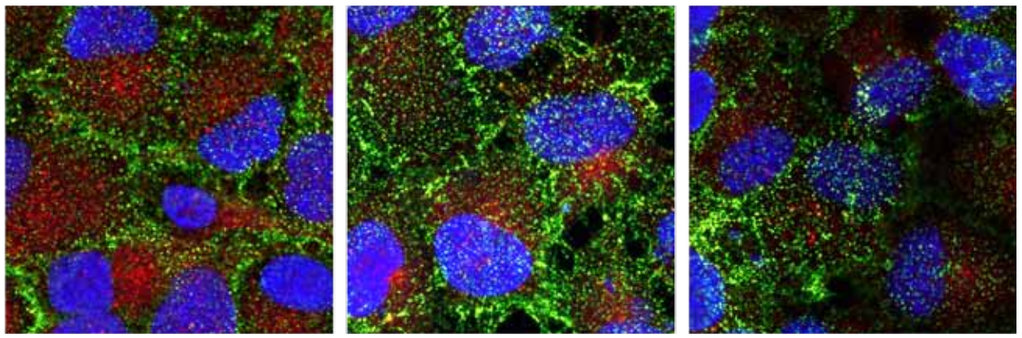
The ability of cancer cells to invade their surrounding tissue is critical for their spread to secondary organs. We are identifying molecules critical for assembly and regulation of the invasive machinery in breast cancer and in neuroblastoma, how they act to promote invasion and how they are regulated.

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 diseases. In addition to our studies on breast cancer, we are also exploring new ways to inhibit metastasis in neuroblastoma, the third most common type of childhood cancer and the leading cause of cancer deaths of children under 5, accounting for 15% of all childhood cancer deaths. Aggressive neuroblastoma has not seen a major change in the survival rate in the last ten years. Our studies aim to increase knowledge of the molecules driving metastasis using multiple strategies so that we may identify and open up avenues for new therapeutics to be developed.

Key discoveries 2014

This year we published works showing that the miR-200 family of microRNAs are critical regulators of cell invasion in breast cancer. We identified a key target of miR-200 that regulates metastasis *in vivo* which is not associated with its role in regulating epithelial-mesenchymal transition (Li *et al*, *Oncogene* 2014). We also published our study identifying one of the largest validated microRNA target network, that of the miR-200 family, and demonstrated a major function of this network is in regulating cell invasion, a driver and pre-requisite to cancer metastasis (Bracken *et al*, *EMBO J* 2014). We also identified a novel regulator of protein trafficking, the protein tyrosine phosphatase PTPN14, which coordinately regulates secretion of pro-metastatic factors and EGFR expression on breast cancer cells and which acts as a suppressor of breast cancer metastasis. This work was accepted in Science Signalling (Belle *et al*) to appear in print in 2015.



PTPN14 suppresses EGFR expression (green) on the cell surface of triple negative breast cancer cells while its substrate RIN1 opposes this effect

Frank Stomski | Angel Lopez | Barbara McClure | Nicole Wittwer | Denis Tvorogov

Tim Hercus | Emma Barry | Mara Dottore | Rebecca Wright | Anna Sapa
Hayley Ramshaw | Absent: Winnie Kan | Melanie Pudney | Bethan Jones

Cytokine Receptor Laboratory

Professor Angel Lopez MBBS PhD FRCPA FAA FAHMS

Cytokine receptors are critical membrane proteins that allow cells to sense changes in their immediate environment and to respond in an appropriate and coordinated manner. Cytokines are released into the extracellular space where they bind to specific receptors and initiate the assembly and activation of cytokine receptor complexes. Signals arising from these active receptor complexes have diverse consequences such as cell survival, growth or activation but ultimately they determine the fate of the target cell.

The production and action of cytokines is normally a tightly regulated process and when control of this process is lost diseases such as cancer and chronic inflammation arise. The focus of this laboratory is to understand how the receptors for a discrete family of cytokines, termed the βc cytokines, function in health and disease. Our work is particularly relevant in diseases such as leukaemia that exhibit abnormalities in expression of βc cytokine receptors and in asthma where excessive activation of βc cytokine receptors in myeloid cells in the lung causes chronic damage.

A major focus of our work has been to understand the mechanism of receptor signalling in the βc family of cytokines that includes IL-3, IL-5 and GM-CSF. Understanding the signalling of cytokines that utilise specific alpha receptor subunits and shared signalling subunits such as βc, is important for defining the molecular basis of many diseases. In collaboration with Professor Parker's group at St Vincent's Institute of Medical Research in Melbourne, we have ongoing projects to determine the 3-D structure of βc cytokine receptor complexes as well as structures of the individual components bound to blocking antibodies. We solved the structure of the purified extracellular portion of IL3Rα, that is responsible for specifically binding IL-3, bound to a Fab fragment of the IL-3 neutralising antibody, CSL362 which revealed its dual mechanism of action (Broughton *et al*, *ActaCrystallographica* F70, 2014; Broughton *et al*, *Cell Reports* 8, 2014). These studies will guide the development of therapeutic antibodies as well as novel, small molecule drug candidates that are able to modulate βc cytokine receptor function and potentially inhibit the growth and survival of myeloid leukaemias or diminish the activity of myeloid cells in inflammatory conditions such as asthma.

Activation of cytokine receptors on the cell surface triggers a multitude of biochemical responses within target cells that ultimately determine the nature of cellular responses to cytokine exposure. In collaboration with Professor Richard D'Andrea we investigated the role of IL-3 in the β catenin pathway in patients with acute myeloid leukaemia (AML). We found that β catenin is aberrantly activated in AML patients and correlates with poor prognosis and that blocking IL-3 with our neutralising antibody could reduce β catenin levels in AML (Sadras *et al*, *J Leukocyte Biology* 96, 2014).

The 14-3-3 adaptor proteins have previously been identified as part of the biochemical responses to βc cytokine receptor activation. We are finding that the exposure of cancer cells to compounds that target the 14-3-3 dimerization interface have dramatic consequences for cell survival. More recently, in collaboration with Professor Anthony Wynshaw-Boris (Ohio, USA) and Dr Quenten Schwarz, we have shown that the 14-3-3 family of proteins role in signalling extends to regulating neurogenesis and neuronal differentiation in the developing brain (Xu *et al*, *J Neuroscience* 34, 2014).

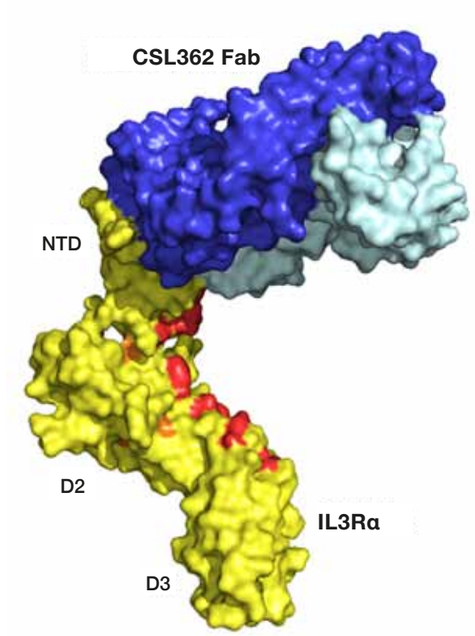
Our basic studies of βc cytokine receptor function are being translated into a number of human disease settings that explore the diverse actions of this important cytokine family. In auto-immune diseases we have an ongoing collaboration with Professor J Schrader (Vancouver) to characterise pathogenic autoantibodies against GM-CSF. In models of allergic inflammation we are collaborating with Associate Professor M Grimbaldeston and have determined that the βc cytokines are potent activators of mast cell function and that the pro-inflammatory activity of human mast cells can be inhibited by novel reagents that target the βc cytokine receptors. In collaboration with Professor T Hughes and CSL Limited we have demonstrated the functional utility of the antibody CSL362 that targets IL-3Rα (also known as CD123). CD123 is a key disease marker that is specifically overexpressed by the stem cells in human myeloid leukaemia. Blocking of CD123 with CSL362 elicits the killing of stem cells from AML patients by their own immune cells (Busfield *et al*, *Leukemia* 28, 2014) and in mouse models of chronic myeloid leukaemia (CML) reduces leukaemic burden (Nievergall *et al*, *Blood* 123, 2014).

In 2014 we welcomed two new Post-Doctoral researchers to the group; Dr Denis Tvorogov from the Alitalo Lab in Helsinki and Dr Bethan Jones from Cardiff, UK. In collaboration with Professor Parker (St Vincent's Institute of Medical Research, Melbourne) and Professor T Hughes (SAHMRI), Professor Lopez was the Chief Investigator of a Program Grant that received the 'Best Program 2014' award by the NHMRC. Funding for the five year grant entitled 'Abnormal Signalling in Leukaemia', commences in 2015.

Key discoveries 2014

Structure of the human IL-3 receptor
In collaboration with Professor Parker (St Vincent's Institute of Medical Research) and CSL Limited, we have worked to determine the structure of the IL-3 receptor complex and understand the mechanism of action for the IL-3 blocking antibody, CSL362. We solved the structure of a Fab fragment of CSL362 bound to IL3Rα. Our crystal structures identified alternative conformations of IL3Rα that point to unexpected dynamic properties of IL3Rα in IL-3 binding that may also be features of the IL-5 and GM-CSF receptors. These studies also revealed a dual mechanism of action of the antibody CSL362 and suggest ways to select and optimise anti-cytokine receptor blocking antibodies.

Anti-leukaemic activity of the anti-CD123 antibody CSL362
In collaboration with CSL Limited and Janssen Biotech Inc the antibody CSL362 progressed to Phase I Clinical Trial in the USA and Australia. Preliminary results have been promising with 60% of patients receiving all six injections outlined in the trial plan. At follow up, six months after treatment, half of the patients who could be evaluated remained in complete remission from their leukaemia and only a small number had relapsed. Of six patients who had residual disease when they started the trial, half had no sign of diseased cells after antibody treatment. The conclusion so far is that the antibody is safe and well tolerated in AML patients paving the way for its use in Phase 2 studies.

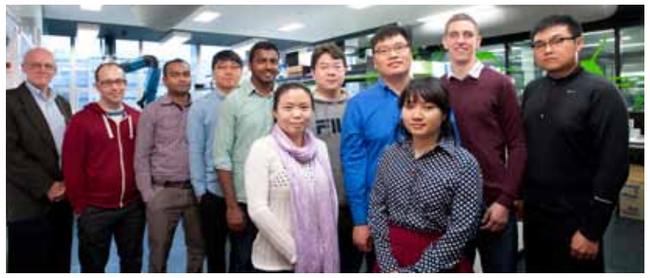


X-ray crystallography was used to determine the structure of IL3Rα (yellow) bound to a Fab fragment of the IL-3 blocking antibody, CSL362 (heavy chain in dark blue, light chain in cyan). The alpha subunit of the IL-3 receptor (IL3Rα) contains three distinct extracellular domains, NTD, D2 and D3, that are involved in IL-3 binding. Cytokine binding and functional studies have been used to identify specific residues in these domains that are directly involved in IL-3 binding (coloured red).

Outcomes for the Community

We are learning about the development of myeloid leukemias by studying critical survival, growth and activation signals transmitted into the cell through specific receptors on the cell surface. Through our research on one of these key receptor families, βc, we understand how these signals arise and are connected to cancer biology. These studies help us to identify new targets to modulate or block signalling pathways in cancer and contributes to the development of new and more specific anti-cancer drugs.

Malika Kumarasiri | Solomon Tadesse | Muhammed Rahaman | Hugo Albrecht, Vaskor Bala | Shudong Wang | Jingfeng Yu | Ahmed Abd El Aziz | Sunita KC Basnet



Bob Milne | Matt Sykes | Saiful Islam | Yi Long | Stephen Philip | Longjin Zhong Peng Li | Mingfeng Yu | Sapphire Le | Ben Noll | Frankie Lam

Drug Discovery and Development Laboratory

Professor Shudong Wang PhD FRSC

The Drug Discovery and Development Laboratory aims to develop new drug candidates for the clinic. We currently have three major programs at the different stages of drug development.

Cyclin-dependent kinase inhibitor drug program

Cyclin-dependent kinases (CDKs) are a family of protein kinases involved in cell cycle and transcription, and implicated in the progression of cancers. Aberrance of CDKs 4/6 cyclin D-INK4-pRb-E2F pathway is common in >80% of human cancers. CDKs 7/8/9 promote transcription of the genes encoding key apoptotic regulators such as anti-apoptotic Bcl-2 family, pro-survival XIAP, and onco-proteins such as c-Myc and HDM. As such, CDKs make prime targets for cancer therapy. We have identified several novel classes of small molecule inhibitors that are highly potent against individual CDKs, and demonstrated significant anti-cancer efficacy along with an impressive safety profile (Shao *et al*, *J Med Chem*, 2013; Lam *et al*, *Oncotarget*, 2014; Walsby *et al*, *Oncotarget*, 2013). The drug candidates have been developing towards clinical trials in patients with acute myeloid leukaemia, chronic lymphocytic leukaemia, advanced prostate, breast and ovarian cancers.

MAPK-Interacting kinase inhibitor drug program

Deregulation of protein synthesis is one of the common events in cancer. The key player in translational control is eukaryotic initiation factor 4E (eIF4E). Activity of the eIF4E is a key determinant of PI3K/Akt/mTOR- and Ras/Raf/MEK/ERK-mediated tumorigenic activity, and targeting eIF4E thus offers the possibility of influencing all of these pathways in cancer. MAPK-interacting kinases (Mnks) activate the eIF4E by phosphorylation and are responsible for eIF4E oncogenesis. Inhibition of the Mnk activity can effectively block the oncogenic transformation and development. Importantly, while Mnk activity is essential for tumourgenesis it is dispensable for normal development. As such, Mnk inhibitors offer an exciting opportunity for effectively treating cancer with low toxicity (Hou *et al*, *ACS Med Chem Lett*, 2013; Diab *et al*, *Chem & Biol*, 2014). We have recently identified several classes of heterocyclic compounds that potently inhibit Mnk activity with high specificity (Diab *et al*, *Chem & Biol*, 2014). We are optimising the current leads for drug development.

Mitotic inhibitor drug program

It has become apparent from clinical studies with some molecularly targeted therapy that cancers can 'escape' from a given state of oncogene addiction through mutations in other genes and pathways because of the frequent genomic instability of cancers. For this reason, as well as tumour heterogeneity, it is likely that the use of a single molecular targeted agent may not achieve long-lasting remissions or cures in cancers, especially for late-stage disease. Co-targeting the key components of signalling pathways has been proposed as an effective strategy for developing anti-cancer drugs. We have developed a novel class of orally deliverable compounds that are highly effective as anti-cancer agents (Lu *et al*, *J Med Chem*, 2014). This has been attributed to their mitotic inhibition through synergistically targeting key pathways essential to survival of cancer cells. A drug candidate has been nominated for pre-clinical and clinical development for potential treatment of myelodysplastic syndromes, acute myeloid leukaemia, ovarian and pancreatic cancers.

Key discoveries 2014

Highly selective Mnk inhibitors

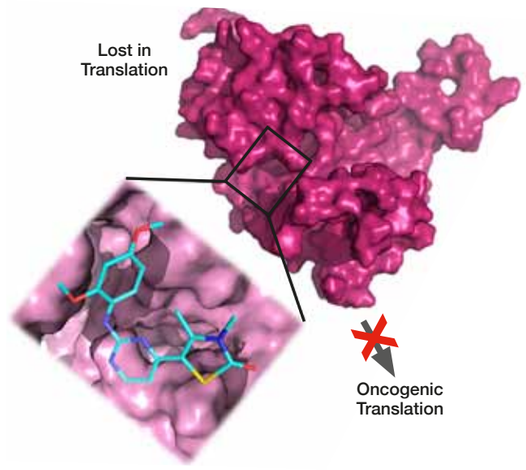
We have identified several classes of highly potent and selective Mnk inhibitors. The lead compounds suppress proliferation and block cell cycle progression in cancer cells.

A novel CDK9 inhibitor CDKI-73

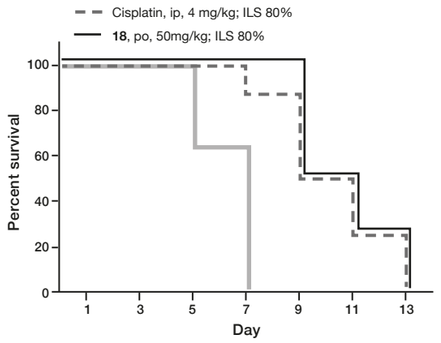
CDKI-73 is one of the most potent CDK9 inhibitors identified to date. It suppresses cancer survival genes ie Mcl-1, Bcl-2 and XIAP, and induces cancer cell apoptosis. CDKI-73 is highly cytotoxic with >200-fold selectivity against primary leukaemia cells when compared with normal CD34+ cells. Furthermore, CDKI-73 is equipotent in poor prognostic sub-groups of CLL patient samples and shows cytotoxic synergy with the chemotherapeutic agent fludarabine. Our data presents a strong rationale for the development of CDKI-73 as anti-leukemic therapeutic.

Preclinical drug candidate MKI-18

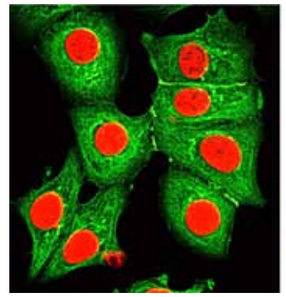
We have discovered a novel class of mitotic cell cycle inhibitors. The lead compound MKI-18 effectively stops cancer cell proliferation and induces apoptosis. Importantly, MKI-18 possesses favourable pharmaceutical and pharmacokinetic properties and demonstrates potent antitumor activity in animal models. MKI-18 is a suitable orally bioavailable anticancer agent to move forward in preclinical drug development.



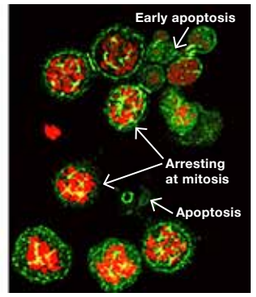
Computational model of our inhibitor 8e binding to Mnk protein which blocks oncogenic translation by targeting the Mnk-ATP active domain



Kaplan–Meier analysis of animal survival in an A2780 ovarian cancer xenograft treated with MKI-18 Groups of eight animals were administered vehicle or MKI-18 at 50 mg/kg by oral gavage (po) on every second day. The treatment with MKI-18 resulted in an increased animal life span (ILS) of 80% when compared to the vehicle-treated group.



Untreated human cervical tumor cells



Induction of spindle abnormalities and apoptosis by MKI-18 (50 nM, 24h) in human cervical tumor cells

Outcomes for the Community

Cancer remains the most common cause of human death. Our research leads directly to the development of novel, highly effective and low toxic anti-cancer agents for cancer patients.

Melissa Thompson | Andrew Ruszkiewicz

Maria Caruso | Vinh-An Phan | Teresa Tin

Gastroenterology Research Laboratory

Associate Professor Andrew Ruszkiewicz MD FRCPA

The main areas of interest of our laboratory are malignancies of the gastrointestinal tract, particularly colorectal cancer (CRC) and its precursor lesions, oesophageal neoplasms and pancreatic tumours. We are particularly interested in the underlying molecular alterations of sporadic and familial forms of CRC. Our main focus in pancreatic cancer is to improve techniques used for tissue diagnosis of this condition.

Most CRCs are sporadic and occur in people over 60 however around 20% occur in younger individuals with a family history of the disease. The most common familial colorectal cancer is Lynch syndrome (HNPCC) which is caused by germline mutation in a DNA mismatch repair gene. Our laboratory was the first in Australia to introduce an immunohistochemistry screening method in diagnostic setting. This test became a method of choice in selecting patients for further genetic studies and is widely used in today's routine pathology practice.

The underlying genetic basis for serrated polyposis syndrome, characterised by multiple serrated polyps occurring in the colorectum is unknown. However CRC developing in individuals with this syndrome display a familial history suggestive of inherited cause. Our research aims to identify these possible genetic markers.

Pancreatic adenocarcinoma is a cancer with one of the most unfavourable prognoses. The only curative treatment is surgery; however advanced disease at the time of diagnosis prevents this in most patients. Early and accurate diagnosis is usually difficult to achieve. Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) has emerged as the method of choice in the diagnosis of difficult to access pancreatic tumours and other extramural gastrointestinal lesions. The aspirated material obtained by EUS-FNA is usually examined as a cytological preparation, but often fails to provide adequate tissue samples for ancillary tests such as immunohistochemistry or molecular analyses. Alternative use of '*direct histology*' processing of aspirated material results in the preservation of the architectural integrity of the lesional tissue, which improves the diagnostic accuracy and reproducibility and can also provide tumour tissue for research.

Outcomes for the Community

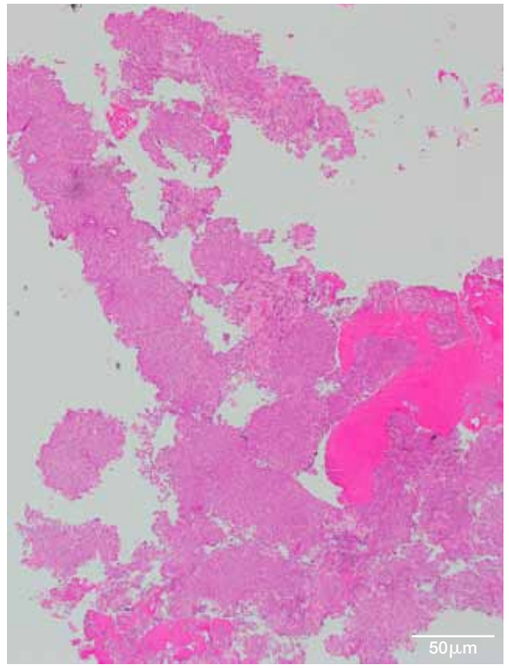
Our work towards better characterisation of colorectal and pancreatic cancer results in a better understanding of these diseases and subsequently facilitates their detection at an earlier stage, providing scope for more effective treatment options.

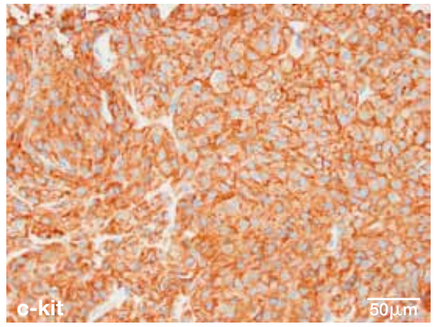
Key discoveries 2014

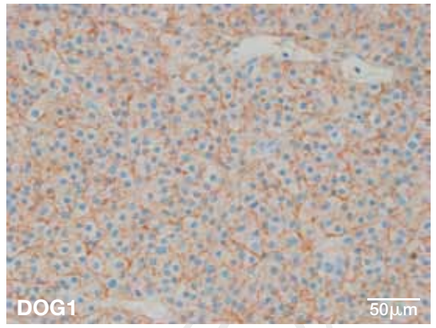
We have successfully modified methods of extraction and processing of aspirated material from ultrasound guided fine needle aspirations (EUS FNA) of pancreatic tumours and extramural lesions of the upper gastrointestinal tract. This method is now routinely used in diagnostic procedures providing a highly informative sample aiding in the accurate diagnosis of solid lesions. The diagnostic accuracy of our '*direct histology*' method is much higher compared with the more widely used conventional EUS FNA cytology method. This is due to the preservation of the tissue integrity and the greater amount of tissue material available for ancillary tests, including molecular studies required for the confident diagnosis of various primary tumours and metastatic malignancies.

This method has proven particularly effective in the diagnosis of autoimmune pancreatitis. This is a rare, chronic inflammatory disorder which is often mistaken for cancer but if diagnosed correctly responds to pharmacological treatment with steroids and does not require major surgery or chemotherapy treatment. In addition, '*direct histology*' provides abundant high quality tissue material for various research applications.

In collaboration with the ACRF Cancer Genomics Facility we have performed whole-exome sequencing on a series of patients with BRAF V600E mutated serrated pathway cancers and identified several gene variants potentially contributing to serrated neoplasia on a germ line level. While this work is still in progress, the initial results suggest that serrated pathway cancers, and serrated polyposis in particular, may have hereditary contributing factors.







Endoscopic Ultrasound guided Fine Needle Aspiration biopsy (EUS FNA) of gastric gastrointestinal stromal tumour (GIST)
The biopsy material was obtained using 25 gauge needle and used the '*direct histology*' method. Preservation of the tissue architecture and abundant tumour tissue facilitated the pathological diagnosis of this uncommon epitheliod variant of GIST providing excellent material for immunohistochemistry (c-kit and DOG1 stains) and molecular analysis which demonstrated a mutation in the PDGFRA gene. Previous attempts to obtain diagnostic tissue using conventional endoscopic biopsies were unsuccessful due to the deep and largely extramural location of this gastric tumour. The accurate diagnosis of GIST is critical as these tumours are now subject to targeted therapy with tyrosine-kinase inhibitors.

Kaitlin Scheer | Feng Yu | Klay Saunders | Greg Goodall | Katherine Pillman
John Toubia | Absent: Simon Conn | Francisco Sadras

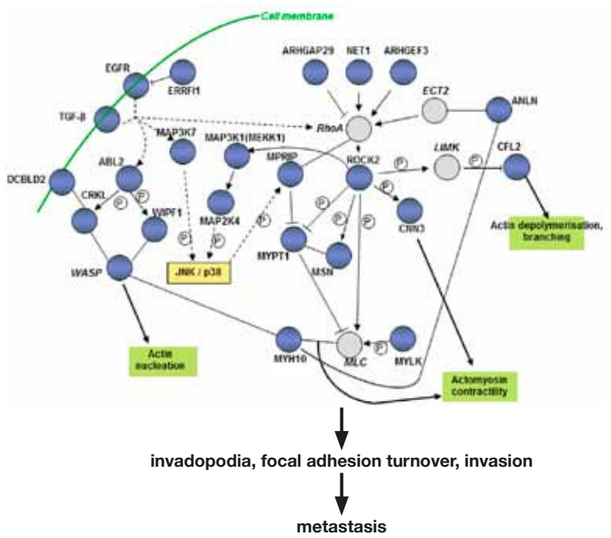
Philip Gregory | Caroline Phillips | Victoria Arnet | Rosemary Sladic
Suraya Roslan | Vanessa Conn | Absent: Andrew Bert | Cameron Bracken

Gene Regulation Laboratory

Professor Greg Goodall PhD

Cancer is not a single disease: it is a collection of many diseases with the common feature that cells grow in an uncontrolled manner. A common feature to many cancers though is the fact that it is usually not the initial tumour that is the dangerous aspect of the disease: it is the conversion of some of the cells in the cancer to a type of cancer cell that can spread to other tissues and establish secondary tumours — a process that is called metastasis.

This conversion of cancer cells to a spreading type of cell, called a mesenchymal cell, involves complex changes in the internal structures of the cell, and in the regulatory molecules that control cell activities. In the Gene Regulation Laboratory we study the control molecules that determine whether a cell will convert to the spreading (mesenchymal) cell type, and study how the cell's migration is achieved at the molecular level. We anticipate that understanding the molecular details of these processes will reveal ways of blocking the conversion of cells to the mesenchymal cell form and ways to block their spread. We are especially focussed on studying how a type of genetic regulator called microRNA controls the conversion of cells to the mesenchymal form in a process known as Epithelial to Mesenchymal Transition, commonly abbreviated to EMT.



The miR-200 family microRNAs target a network of regulators of the actin cytoskeleton, controlling filament nucleation, branching and actomyosin contractility
The figure shows relationships between direct miR-200 targets identified by the Ago/HITS/CLIP procedure and validated by luciferase reporter activity. Blue circles denote direct miR-200 targets. Grey circles denote network components not identified as miR-200 targets. (P) indicates phosphorylation.

Key discoveries 2014

Specificity Protein 1 (Sp1) maintains basal epithelial expression of the mir-200 family
EMT is required for the specification of tissues during embryonic development and is recapitulated in cancers that progress to spread to secondary sites, the process known as metastasis. The microRNA 'miR-200' plays a critical role in enforcing the epithelial state and is lost from cells undergoing EMT. EMT can be mediated by activation of the ZEB1 and ZEB2 transcription factors, which repress miR-200 expression via a self-reinforcing double negative feedback loop to promote the mesenchymal state. However, it was unclear what factors drive and maintain epithelial-specific expression of miR-200 in normal epithelium and in early stage cancers.

We expected to find that expression in epithelial cells is driven by one or more epithelial-specific transcription factors, but we found instead that the widely acting transcription factor, Sp1, is a major driver of the miR-200b/a/429 gene. In mesenchymal cells, Sp1 expression is maintained, but its ability to activate the miR-200 gene promoter is perturbed by ZEB-mediated repression. We found that inhibiting Sp1 expression caused a marked reduction in miR-200 expression and concommitant changes in EMT-associated markers in epithelial cells. On examining mouse embryonic tissues we observed co-expression of Sp1 and miR-200 during mouse embryonic development, and that miR-200 expression was lost in regions with high ZEB expression. Together, these findings indicate that miR-200 family members require Sp1 to drive basal expression and to maintain an epithelial state. This finding is consistent with the proposition that the epithelial state is a default state, while the mesenchymal state requires active intervention by inducible regulators. Such a situation has ramifications for understanding the mechanisms controlling early differentiation and for designing interventions to prevent cancer metastasis (Kolesnikoff N *et al*, *J Biol Chem*, 2014).

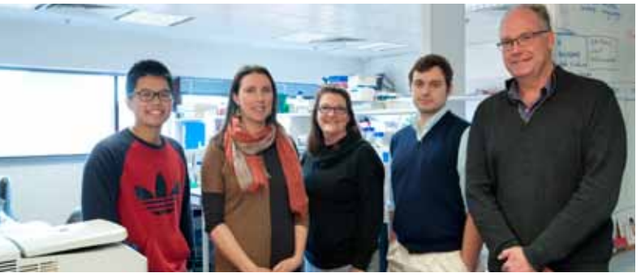
Genome-wide identification of miR-200 targets reveals a regulatory network controlling cell invasion
MicroRNAs and their targets are important components in the regulatory networks that maintain cell phenotype and control cell differentiation. Although microRNAs typically act as mild modulators of gene expression, exerting only a modest inhibitory effect on individual targets, conceivably they can broadly refine gene expression patterns because each microRNA may target several hundred different mRNAs. Thus, one microRNA can potentially influence a biological process by having a coordinated effect on multiple components of a network or pathway. However, due to the uncertainties in predicting or experimentally identifying the spectrum of targets of individual miRNAs, there are few confirmed examples of broad network regulation by a miRNA.

MicroRNAs function as the specificity component of the protein-RNA complex known as RISC (RNA-induced silencing complex). The microRNA provides sequence-specific binding of RISC to specific mRNA targets, resulting in decreased efficiency of translation and an increased rate of mRNA degradation. While miRNAs are now relatively easy to discover and measure, the key to understanding their functions remains the identification of their gene targets, which until recently has largely been achieved via computational prediction followed by individual experimental verification, one at a time.

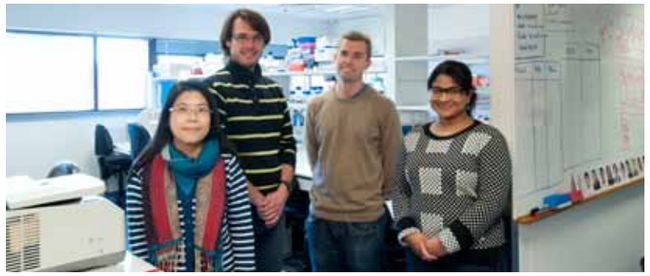
In silico target prediction is limited by our incomplete understanding of targeting 'rules' due largely to an inability to reliably model the influences of RNA secondary structure and RNA-binding proteins that interfere with potential target sites. A considerable methodological improvement has been the development of the Ago-HITS-CLIP (Argonaute High Throughput Sequencing after Cross-Linked Immunoprecipitation) procedure, in which RNA-protein complexes are stabilized by UV cross-linking in live cells, followed by direct immunoprecipitation and purification of miRNA-loaded RISC, enabling the identification of directly associated target transcripts on a global scale by massively parallel sequencing We have applied this procedure to identify many transcripts that interact with miR-200, including a number of non-canonical targets such as central-paired and seed-mismatch interactions, and also find novel target sites in previously misannotated transcripts. We find that regulators of actin cytoskeleton dynamics are strongly enriched among the targets of both miRNAs, indicating that the miR-200 family imposes coordinated control of functional networks that are central to cell shape and motility, and of crucial importance in cancer cell invasion and metastasis. In particular, we show that the formation of invadopodia, which relies on rearrangement of the actin cytoskeleton and provides a site for localized secretion of enzymes to degrade the extracellular matrix, is regulated by miR-200 at multiple points in the pathway (Bracken CP *et al*, *EMBO J*, 2014).

Outcomes for the Community

Our discoveries indicate potential avenues towards development of drugs that block cancer metastasis. They have influenced many labs around the world to take up the investigation of the role of miR-200 in cancer metastasis. In 2014 our publications received 1,397 citations.



Bryon Shue | Karla Kelbig | Kylie Van der Hoek | Colt Nash | Michael Beard



Onruedee Khantisitthiporn | Guillaume Fiches | Nicholas Eyre | Sumudu Narayana

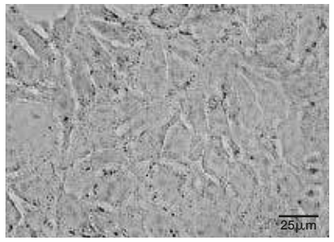
Hepatitis C Virus Research Laboratory

Associate Professor Michael R Beard PhD

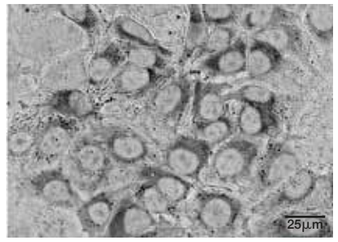
Infection of the cell with a virus results in a response in which the cell attempts to either remove the virus of control its replication. Our laboratory is interested in the genes and signaling pathways that are turned on in response to viral infection in particular hepatitis C virus (HCV) and Dengue virus infection.

Using a genomic approach we have identified hundreds of genes expressed following viral infection and interferon stimulation and we are now attempting to characterise their role in the antiviral process. Using cell culture based models of viral replication for HCV and Dengue we have identified a number of novel genes that control viral replication and the level of viral entry to the cell and replication of the RNA genome. I addition we are also interested in the viral host relationship and how viral proteins modify the cellular environment to their replication advantage. Using biochemical approaches coupled with live viral imaging and electron microscopy we are specifically investigating the role of the HCV protein NS5A in rearranging cellular membranes to establish viral replication factories.

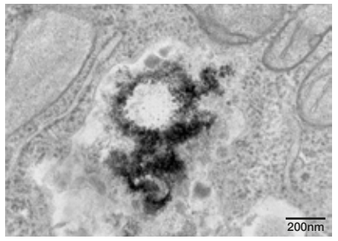
Light Microscopy
HCV (no tag) (+ H_2O_2/DAB)



Light Microscopy
HCV/5A-APEX (+ H_2O_2/DAB)



Electron Microscopy
HCV (no tag) (with H_2O_2/DAB)



Analysis of hepatitis C virus NS5A protein localization by APEX electron microscopy
To examine the localization of NS5A protein with respect to virus-induced membrane rearrangements during a productive infection, an 'APEX' peroxidase reporter protein was incorporated within the NS5A coding sequence in an infectious HCV chimera. This reporter enabled specific labeling of NS5A protein (with H_2O_2/DAB) (left and centre panels), and high resolution analysis of NS5A protein localization by electron microscopy while maintaining excellent ultrastructural preservation (right panel).

Key discoveries 2014

Control of the innate immune response
The early cellular innate response to a viral infection involves various signaling cascades that culminate in the expression of hundreds of interferon-stimulated genes (ISGs), most with unknown function. Work in our laboratory looks at defining which ISGs are important anti-viral effectors, and delineating their functional roles in the context of the early innate response to pathogens. Recent work on the interferon stimulated gene, viperin, has demonstrated that not only does this protein have a role in limiting multiple viral families (HCV, Dengue virus), but it also functions to positively augment both the dsDNA and the dsRNA sensing pathways within the host cell, resulting in an increased overall interferon response to both viral and bacterial infection. Furthermore, we have recently shown that this highly evolutionarily conserved protein, also plays a role in limiting intracellular bacteria, and believe that viperin may play a master regulatory role in the early innate response to both viral and bacterial pathogens.

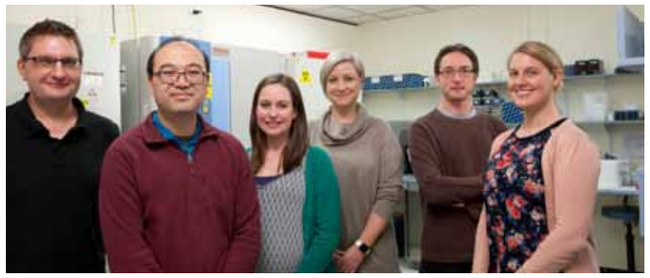
Regulation of HCV replication complex biogenesis and function
Like all positive strand RNA viruses, HCV infection induces cytoplasmic membrane rearrangements that support and compartmentalise the replication of its genome. Recent studies have indicated that the NS5A protein, a non-enzymatic phosphoprotein plays essential roles in replication compartment biogenesis and virus assembly. Through the use of genetically engineered viruses that encode reporter or epitope insertions within NS5A we have employed high resolution proteomics and imaging techniques to definitively identify NS5A phosphorylation sites and demonstrate that one of these phosphorylation sites (pSer235) is essential for HCV genome replication and may regulate replication compartment biogenesis. We are now using a combination of host kinase siRNA screening, and advanced imaging techniques, including 'APEX' electron microscopy and pulse-chase fluorescent imaging of NS5A biosynthesis, to determine which host kinases mediate essential NS5A phosphorylation events and replication compartment biogenesis and virus assembly.

The pathogenesis of non-alcoholic steatohepatitis (NASH)
Non-alcoholic steatohepatitis (NASH) is primarily an immune driven disease of the liver characterised by fat accumulation in hepatocytes and inflammation. Its prevalence is increasing in the Western world as a result of a high fat diet, however we know little about the pathogenesis of this disease. NASH is often encountered with hepatitis C virus infection that exacerbates liver disease and furthermore impacts antiviral therapies. We have shown in an *in vitro* model of steatosis that lipid loading of Huh-7 cells leads to increased expression of classical interferon stimulated genes (ISGs) and NF-κb dependent pro-inflammatory genes in a Toll-like-receptor (TLR) 2 signalling dependent manner. A number of these genes (CXCL10, CXCL8) are classical chemokines involved in attracting immune cells to the liver and suggests that fat accumulation in the liver drives a gene expression profile that is pro-inflammatory. Furthermore, this profile is further increased in the presence of HCV infection that explains the increase in liver disease in the context of fatty liver and HCV infection.

Outcomes for the Community

Understanding the host response to viral infection is essential if we are to develop novel therapeutic strategies to combat the emerging threat of viral pathogens. Furthermore the increasing incidence of fatty liver in the community is a concern as chronic fat accumulation can lead to inflammation and serious liver disease such as fibrosis and cirrhosis. Our work has identified a mechanism(s) that underpins the inflammatory process in fatty liver disease that may provide a possible therapeutic target to alleviate the inflammation associated with this disease.

Zoe Donaldson | Sue Branford | Alex Yeoman | Jodi Braley | Stuart Phillis



Adrain Purin | David Yeung | Haley Altamura | Jasmina Georgievski
Bradley Chereda | Justine Marum

Leukaemia Unit, Department of Molecular Pathology

Associate Professor Susan Branford PhD, FFSc (RCPA)

Chronic myeloid leukaemia (CML) is a fatal disease within three to five years of diagnosis if left untreated. However, drugs that target the leukaemic cells are extremely effective at reducing the leukaemic cells and the majority of patients now have a normal life expectancy.

However, most patients will need to take their medication every day for the rest of their lives to avoid the leukaemia rapidly re-emerging. Unfortunately, drug resistance can occur in some patients, which is associated with disease relapse.

Our laboratory investigates the molecular response to therapy by an examination of the BCR-ABL1 oncogene. The protein product of this abnormal gene causes the leukaemia and all of the pathological features of the disease. A panel of experts recommend that molecular monitoring of BCR-ABL1 is incorporated into patient management and clinical decisions are now focused on the initial molecular response to therapy. The early response can determine whether a patient has failed therapy and allow rapid treatment intervention if required to limit the risk of disease progression to an acute leukaemia and death.

We investigate factors associated with clinical response and resistance to the targeted therapy. The rate of leukaemic cell death may be an important factor for response and could predict outcome. We are investigating the rate of BCR-ABL1 decline in more than 500 patients that we have monitored in clinical trials. Those with a very rapid initial response have been identified as having the best long term prospects, whereas those with a slow response may need a change of therapy to avoid treatment failure. We are also investigating biological factors, such as a patient's inherited genetic makeup, to determine their association with the kinetics of response for individual patients. Our aim is to identify biomarkers at the time of diagnosis that will predict response and to guide the most appropriate type of drug the patient should receive. Our research continues to offer guidance to haematologists for appropriate monitoring of treatment response and the early prediction of drug resistance.

Outcomes for the Community

Our research has benefited patients with CML by identifying the poorest risk patients at a very early time after commencing therapy. Some recommendations suggest changing therapy based on a single BCR-ABL1 measurement but our data suggest this may not be necessary in certain cases. Some drugs have a greater toxicity profile and are more expensive, thus our research contributes to potential reduced harm to patients and has cost saving benefits.

Key discoveries 2014

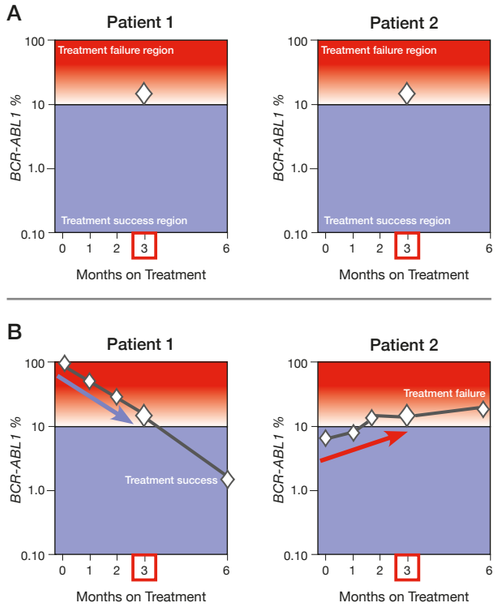
The initial kinetics of response to treatment is a better predictor of outcome than assessing a single BCR-ABL1 measurement

The molecular response at three months of tyrosine kinase inhibitor therapy for patients with CML has prognostic significance and has been confirmed by many groups. One group claims that measuring BCR-ABL1 at three months is the only requirement to predict long term outcome and decisions to change treatment based on a single BCR-ABL1 measurement are reliable. However, we have challenged this claim. Although we agree that measuring BCR-ABL1 at three months is a very strong predictor of response, the poorest risk patients can be more reliably identified by assessing the trend of response from the pre-treatment level. We assessed the kinetics of response by calculating the number of days over which BCR-ABL1 halved, termed the halving time. A longer halving time distinguished the patients with the poorest outcomes. Those with a more rapid rate of BCR-ABL1 decline may not require treatment intervention. This finding was confirmed by another study from Germany.

Many compound mutations reported in patients with CML identified as technical errors

The main mechanism of drug resistance is the acquisition of a mutation within the BCR-ABL1 gene. More than 100 different mutations can interfere with drug binding. Most resistant patients only have one mutation but a proportion have more than one. A change of therapy restores drug sensitivity for most of the mutations. Ponatinib is a third generation drug, which overcomes resistance to all types of single mutations. When two mutations occur on the same BCR-ABL1 molecule, termed a compound mutation, resistance to ponatinib can occur. Therefore, it is important to determine whether multiple mutations are compound in order to select appropriate treatment. However, identifying compound mutations using standard techniques is problematic and groups have used alternative techniques to determine the compound mutation status.

These studies have consistently revealed a high prevalence of compound mutants, and a surprisingly complex structure of mutant clones. The reported BCR-ABL1 mutation complexity is unprecedented and has rarely been described, and never to the extent reported in CML. The anomaly prompted us to investigate whether artificial DNA recombination events occurred during the analysis processes. We showed that this was indeed the case, which suggests that the compound mutation frequency may have been markedly overestimated in the previous clinical studies. Our study highlighted that thorough clinical investigation of the efficacy of ponatinib according to mutation status has been hampered because methods to robustly and sensitively detect compound mutations is currently lacking.



Redefining early treatment response

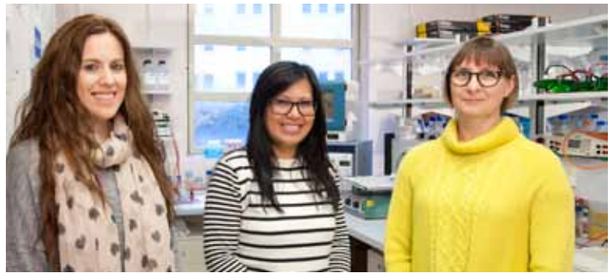
Some clinical experts suggest that an isolated BCR-ABLI measurement is all that is required to determine clinical outcome. Some guidelines mandate a therapy change if BCR-ABLI values are >10% after three months of treatment since these values are associated with high failure rates.

(A) Patient 1 and 2 both had BCR-ABLI values in the failure range, but treatment was not changed.

(B) We determined that assessing the trend of response from the pretreatment value can more precisely identify patients destined for a poor response (*Blood* 2014; 124:511–518).

Patients with a constant downward trend of BCR-ABLI are more likely to have treatment success than patients where there is very little, or no change at three months from the pre-treatment level.

Natasha Harvey | Drew Sutton | Kelly Betterman



Genevieve Secker | Melinda Tea | Jan Kazenwadel

Lymphatic Development Laboratory

Associate Professor Natasha Harvey PhD

Lymphatic vessels are an integral component of the cardiovascular system. These specialised vessels maintain fluid homeostasis, absorb fats from the digestive tract and are an important highway for immune cell transport. Defects in the growth and development of lymphatic vessels underlie human disorders including lymphoedema, vascular malformations and lymphangiectasia.

Cancer cells exploit the lymphatic vasculature as a route for metastasis and in some cases, promote the growth of new lymphatic vessels within the tumour environment in order to gain entry to this vascular highway and spread throughout the body. The focus of our laboratory is to understand how the lymphatic vascular network is constructed during development. We are interested in identifying and characterising genes that are important for lymphatic vessel growth, patterning and maturation.

Once we understand how lymphatic vessel growth and development is normally controlled, we will gain new insight into how this process 'goes wrong' in human disease and moreover, will be afforded the opportunity to rationally design novel therapeutics able to block or promote lymphatic vessel growth and/or function and thereby treat human lymphatic vascular disorders.

Outcomes for the **Community**

Lymphatic vessels are of major importance to cancer patients. Cancer cells exploit lymphatic vessels as a 'highway' for metastasis and can enter pre-existing lymphatic vessels, or promote the growth of new lymphatic vessels in order to gain access to the lymphatic vascular network. Lymphatic vessel damage following lymph node resection results in secondary lymphoedema, a disabling condition for a substantial proportion of 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 lymphatic vessel growth. Blocking agents should prove valuable for the inhibition of tumour metastasis, while growth promoting agents could provide novel therapeutics for the treatment of secondary lymphoedema.

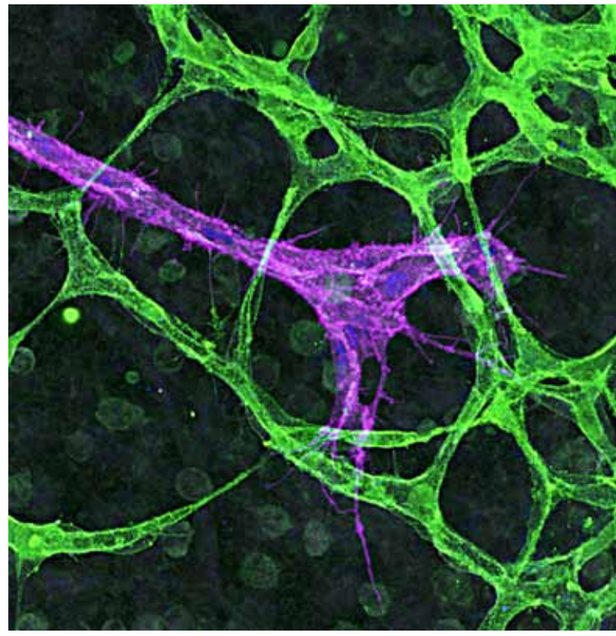
Key discoveries 2014

GATA2 is important for the development and maintenance of lymphatic vessel valves

In collaboration with Professor Hamish Scott's team at the Centre for Cancer Biology, we recently discovered that heritable mutations in the transcription factor GATA2 predispose carriers to lymphoedema and myelodysplasia syndrome (MDS)-acute myeloid leukaemia (AML) (Kazenwadel *et al Blood*, 2012). This discovery revealed a key role for GATA2 in lymphatic vessels. We subsequently demonstrated that GATA2 is present at high levels in lymphatic vessel valves and that GATA2 regulates the expression of genes required for valve development. Our recent work has established that GATA2 is required both to initiate the process of lymphatic vessel valve development and maintain the architecture of lymphatic vessel valves once they have formed. Currently, we aim to define precisely how GATA2 regulates gene transcription in the lymphatic vasculature to control valve development. Ultimately, our goal is to identify new therapeutic targets to which effective therapeutics for the treatment of lymphoedema could be designed.

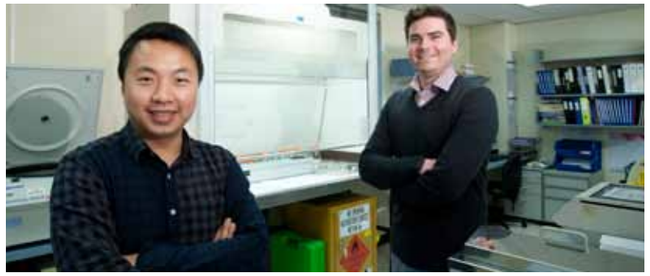
Regulation of vascular development by the ubiquitin ligase Nedd4

Ubiquitination is a highly conserved process of protein modification that leads to the tagging of target proteins by one or more ubiquitin molecules. Ubiquitination can 'flag' proteins for degradation, dictate their subcellular localisation and/or regulate protein trafficking through cellular compartments. As such, ubiquitination has crucial roles in regulating many signalling pathways and mis-regulation of this process is associated with numerous human pathologies. We have found that the ubiquitin ligase Nedd4 plays key roles in the growth and development of both blood vessels and lymphatic vessels. Our current work aims to dissect the endothelial cell autonomous versus non-autonomous roles of Nedd4 during vascular development and to define the signalling pathways regulated by Nedd4 that are important for vessel growth and remodelling.



Sprouting lymphatic vessel (violet) and blood vessels (green) in developing skin

Houng Taing | Michele Grimbaldeston | Natasha Kolesnikoff



Dave Yip | Nicholas Hauschild

Mast Cell Laboratory

Associate Professor Michele Grimbaldeston PhD

Mast cells are unique immunocytes that normally reside in peripheral 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 immunoglobulin E (IgE)-associated allergic disorders and considered the first responders to opportunistic pathogens. 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 skin cancer development, stroke and allergy. In collaboration with Dr Michael Samuel (CCB), Dr Thomas Gebhardt (University of Melbourne, Vic), Professor Gunnar Pejler (Uppsala, Sweden) and Associate Professor Natasha Harvey (CCB), 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. In other collaborative studies with Professor Ian Frazer (Diamantina Institute, Qld), we discovered that human papillomavirus (HPV) 16 E7 protein expression in squamous epithelium creates a local immune suppressive environment via secretion of CCL-2 and CCL-5 chemokine-mediated recruitment of mast cells to the epidermal/dermal interface (Bergot *et al*, *Plos Pathogens* 10, 2014).

The contribution of mast cells to innate immune responses against pathogens or in the course of IgE driven inflammation can be dependent on anatomical-specific differences in the composition and localisation of mast cells and their interaction with other immune cell subsets. In our on-going collaboration with Professor Wolfgang Weninger (Centenary Institute, NSW), we have shown using 3D analysis by multiphoton microscopy that mast cell localisation and density varies in defined skin sites and that such site-specific disparities are functionally relevant in the experimental setting of IgE-mediated passive cutaneous anaphylaxis (Tong *et al*, *J Invest Dermatol* 135, 2014).

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. Mast cells have long been causally linked to the pathogenesis of IgE-dependent allergic inflammation. 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. Allergic foci contain an array of cytokines, including elevated levels of the β common cytokines IL-3, IL-5 and GM-CSF. These cytokines can amplify activity of resident mast cells, and thereby drive certain aspects of allergic pathology during multiple cycles of allergen-induced mast cell activation. In partnership with Professor Angel Lopez (CCB) and CSL Limited we are developing therapeutics that can specifically target such overactivity of mast cells without causing loss of their viability.

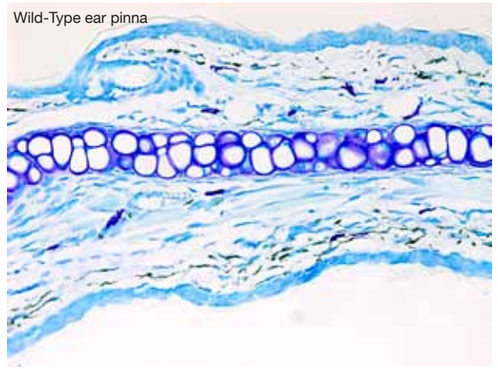
Key discoveries 2014

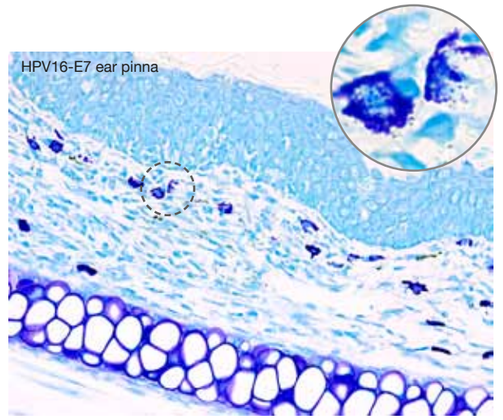
Vitamin D_3 metabolites repress IgE-mediated mast cell activation

The pro-inflammatory properties of mast cells in certain IgE-dependent immune settings can be reduced upon vitamin D_3 metabolite 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 biologically active ($1\alpha,25(OH)_2D_3$) or inactive ($25OHD_3$) 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 and CYP27B1 for the hydroxylation of $25OHD_3$ to bioactive vitamin D_3 (Yip *et al*, *J Allergy Clin Immunol* 133, 2014).

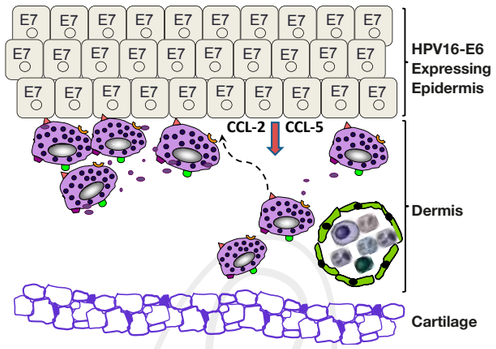
Meningeal mast cells worsen stroke pathology

In collaboration with Professor Gary Steinberg and Dr Tonya Bliss (Dept Neurosurgery, Stanford University, USA), we identified with the use of genetic and cell transfer approaches in mice that meningeal mast cells importantly contribute to key features of stroke pathology, including infiltration of granulocytes and activated macrophages, brain swelling and infarct size. The extent of each of these parameters depended on the expression of mast cell-derived interleukin 6 and, to a lesser degree, the chemokine CCL7. This study supports the notion that mast cells in the meninges, the membranes that envelope the brain, are potential gatekeepers for modulating brain inflammation and pathology after stroke (Arac *et al*, *Am J Pathol* 184, 2014).





Mast cells (purple granulated cells) are recruited to the epidermal/dermal interface of human papillomavirus (HPV) 16 E7 squamous epithelium via a mechanism involving the chemokines, CCL-2 and CCL-5
(Bergot *et al*, *PLOS Pathogens*, 2014)



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 overarching aim is to understand the underlying molecular mechanisms of mast cell function in a range of disease settings where they contribute to the pathology. This will enable us to identify potential druggable targets to alter mast cell activity in a specific disease setting. Such endeavours will be of paramount importance, for example, to people who suffer with allergic disease or stroke, settings where mast cells can exacerbate the extent of the pathology.

Young Lee | Anna Brown | Luke Weinel | Milena Babic | Hamish Scott

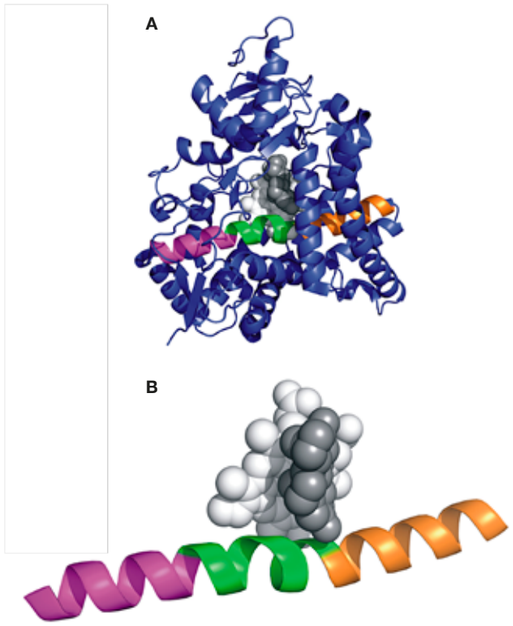
Parvathy Venugopal | Chan Eng Chong | Alicia Byrne | Peter Brautigan
Bradley Chereda | Chris Hahn

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.



A) Crystallographic structure of human wild-type aromatase in complex with the cofactor protoporphyrin IX and the substrate androstenedione. The segment of an α-helix in green shows where the duplication occurred. N- and C-terminuses of the α-helix are in orange and magenta, respectively. The rest of aromatase is shown in blue, protoporphyrin IX, white, and androstenedione, grey.
B) A close-up showing the α-helix providing binding sites of protoporphyrin IX (white) and androstenedione (grey).

Outcomes for the Community

We have found a 'druggable' pathway altered in Down syndrome brain development in an animal model. This finding may eventually result in a therapeutic option to improve cognition in these patients. We report a case of the very rare condition, aromatase deficiency. Our case is unique because it is the first reported case of aromatase deficiency in a female not treated until adulthood, and it depicts, for the first time, the natural history of aromatase deficiency in females extending the clinical spectrum of this disorder to include osteopaenia, tall stature, metabolic syndrome, and streak ovaries. Finally, we reviewed how to implement Next Generation Sequencing as a diagnostic tool and have successfully implemented it in South Australia to the immediate benefit of many patients with rare diseases ending their diagnostic odysseys and improving treatments.

Key discoveries 2014

A case of aromatase deficiency due to a novel CYP19A1 mutation

Aromatase deficiency is a rare, autosomal recessive disorder of which there are approximately twenty four case reports. The aromatase enzyme is crucial in the biosynthesis of oestrogens from androgens. The phenotype of aromatase deficiency therefore is the result of androgen excess and oestrogen deficiency in the absence of normal aromatase activity. We reported the first case of aromatase deficiency diagnosed in a female adult, at the age of 32 years, due to a novel duplication in the aromatase gene. A 32 year old Indian woman presented with a history of gender assignment difficulties at birth, lack of pubertal development, osteopaenia with fracture and tall stature. She had central obesity, impaired fasting glucose and borderline hypertension. Past examinations had revealed partial fusion of urethra and vagina, hypoplastic uterus and streak ovaries. The ovaries had been excised due to malignant risk after an initial clinical diagnosis of Turner's syndrome with Y mosaicism. Oestrogen replacement commenced shortly after her fracture, in adulthood. After reassessment, aromatase deficiency was diagnosed.
Sequencing of the coding exons of the aromatase (CYP19A1; OMIM 109710) gene revealed a novel 27-base duplication in exon 8 (p.Ala306_Ser314dup). This duplication, occurring within the aromatase alpha-helix, would be likely to disrupt substrate (androgen) and cofactor (protoporphyrin IX) binding, resulting in a lack of oestrogen synthesis. We have reported a female with a phenotype compatible with aromatase deficiency which was unrecognised until adulthood and found she had a novel duplication in CYP19A1. Previous case reports have described polycystic ovarian morphology, especially in childhood and adolescence, but never streak ovaries. This may reflect the few adult cases reported, that aromatase deficiency in females is generally diagnosed at birth and oestrogen treatment commences decades earlier than occurred in our patient. Streak ovaries are consistent with the phenotype of the aromatase knockout mouse followed through adulthood. The observed clinical features of obesity, dysglycaemia and hypertension, are compatible with the observation that lack of a counterbalancing effect of oestrogen on tissue androgens until adulthood may lead to a metabolic syndrome phenotype. This report broadens the spectra of phenotype and genetic mutations underlying this rare disorder. See figure, left.

Functional transcriptome analysis of the postnatal brain of the Ts1Cje mouse model for Down syndrome reveals global disruption of interferon-related molecular networks

The Ts1Cje mouse model of Down syndrome (DS) has partial triplication of mouse chromosome 16 (MMU16), which is partially homologous to human chromosome 21. These mice develop various neuropathological features identified in DS individuals. We analysed the effect of partial triplication of the MMU16 segment on global gene expression in the cerebral cortex, cerebellum and hippocampus of Ts1Cje mice at 4 time-points: postnatal day (P)1, P15, P30 and P84. Gene expression profiling identified a total of 317 differentially expressed genes (DEGs), selected from various spatiotemporal comparisons, between Ts1Cje and disomic mice. A total of 201 DEGs were identified from the cerebellum, 129 from the hippocampus and 40 from the cerebral cortex. Of these, only 18 DEGs were identified as common to all three brain regions and 15 were located in the triplicated segment. We validated 8 selected DEGs from the cerebral cortex (Brwd1, Donson, Erdr1, Ifnar1, Itgb8, Itsn1, Mrps6 and Tmem50b), 18 DEGs from the cerebellum (Atp5o, Brwd1, Donson, Dopey2, Erdr1, Hmgn1, Ifnar1, Ifnar2, Ifngr2, Itgb8, Itsn1, Mrps6, Paxbp1, Son, Stat1, Tbata, Tmem50b and Wrb) and 11 DEGs from the hippocampus (Atp5o, Brwd1, Cbr1, Donson, Erdr1, Itgb8, Itsn1, Morc3, Son, Tmem50b and Wrb). Functional clustering analysis of the 317 DEGs identified interferon-related signal transduction as the most significantly dysregulated pathway in Ts1Cje postnatal brain development. RT-qPCR and western blotting analysis showed both Ifnar1 and Stat1 were over-expressed in P84 Ts1Cje cerebral cortex and cerebellum as compared to wild type littermates. These findings suggest over-expression of interferon receptor may lead to over-stimulation of Jak-Stat signaling pathway which may contribute to the neuropathology in Ts1Cje or DS brain. The role of interferon mediated activation or inhibition of signal transduction including Jak-Stat signaling pathway has been well characterised in various biological processes and disease models including DS but information pertaining to the role of this pathway in the development and function of the Ts1Cje or DS brain remains scarce and warrants further investigation.

Integrating Next Generation Sequencing into diagnostic workflows and managing the annotation and clinical interpretation challenge

Next Generation Sequencing has become a powerful tool for the clinical management of patients with applications in diagnosis, guidance of treatment, prediction of drug response, and carrier screening. A considerable challenge for the clinical implementation of these technologies is the management of the vast amount of sequence data generated, in particular the annotation and clinical interpretation of genomic variants. Here, we described annotation steps that can be automated and common strategies employed for variant prioritization. The definition of best practice standards for variant annotation and prioritization is still ongoing; at present, there is limited consensus regarding an optimal clinical sequencing pipeline. We provide considerations to help define these. For the first time, clinical genetics and genomics is not limited by our ability to sequence, but our ability to clinically interpret and use genomic information in health management. We argue that the development of standardized variant annotation and interpretation approaches and software tools implementing these warrants further support. As we gain a better understanding of the significance of genomic variation through research, patients will be able to benefit from the full scope that these technologies offer.

Ian Nicholson | Omri Alfassy | Claire Wilson | Sharad Kumar
Kimberly Mackenzie | Donna Denton | Sonia Shalini | Loretta Dorstyn

Pranay Goel | Tianqi (Cindy) Xu | Swati Dawar | Andrej Nikolic | Natalie Foot
Sonia Dayan | Shannon Nicolson

Molecular Regulation Laboratory

Professor Sharad Kumar MSc PhD FAA FAHMS

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

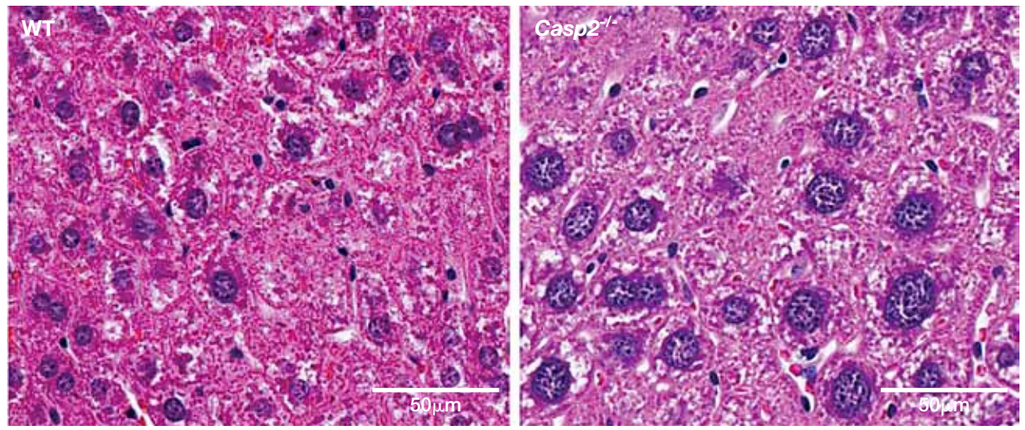
Millions of cells in the human body die every minute in a precise and coordinated process of programmed cell death. Programmed cell death, mediated by specific cellular pathways such as apoptosis, necrosis or autophagy, plays a fundamental role in development and in cell and tissue homeostasis, and too little or too much cell death can lead to many human diseases including cancer. Given the essential role of cell death in normal development and functioning in the human body, deciphering the mechanisms that mediate cell death is essential for understanding disease processes and to design effective treatments for pathologies which arise due to inappropriate cell death. We study the mechanisms and regulation of cell death in normal homeostasis, during animal development and disease, 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 involved in the regulation of protein stability, degradation, localisation and trafficking. Ubiquitination is a major regulator of many ion channels, membrane receptors and transporter proteins. We are studying the physiological and pathological functions of a group of ubiquitin-protein ligating enzymes (Nedd4 family of ubiquitin ligases) which we have shown to be involved in the ubiquitination of a number of membrane proteins. We use a variety of molecular, cellular, physiological and gene knockout approaches to study the physiological function of these enzymens and establish their roles in human diseases.

Key discoveries 2014

An unexpected role for caspase-2 in neuroblastoma
Caspases are proteases that function as important regulators of apoptosis and inflammation. Our previous studies have shown a novel role for caspase-2 in both apoptotic and non-apoptotic signalling pathways including tumour suppression, genomic stability, and the regulation of oxidative stress pathways associated with premature ageing. In a recent publication (*Cell Death & Disease*, 5: e1383. 2014), we unexpectedly found that *caspase-2* gene deficiency (*Casp2*$^{-/-}$) in mice can delay tumour onset and progression in neuroblastoma indicating it does not act as a tumour suppressor in this model. Importantly, we demonstrated that high caspase-2 levels are associated with poor outcome in human neuroblastoma. Our work has highlighted an important a tissue and context specific function for caspase-2 in both tumour suppression and tumour progression, and has provided a potential biomarker for neuroblastoma prognosis.

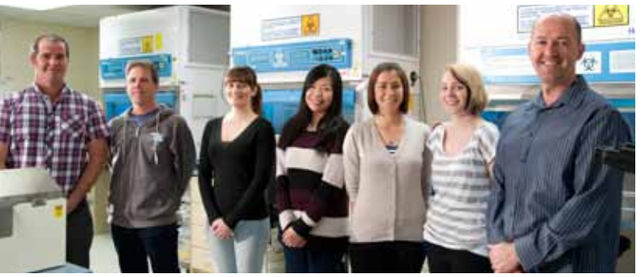
Caspase-2 is required to prevent excessive oxidative stress
In a paper published in *Oncogene* (Dec 22. doi: 10.1038/onc.2014.413), we demonstrated that *caspase-2* deficiency exacerbates cellular stress in mice following low dose challenge with the potent reactive oxygen species (ROS) generator, paraquat (PQ). This was due to an increased inflammatory response (IL-1β and IL-6) and impaired response to oxidative stress, including failure to upregulate the antioxidant defence mechanism in animals lacking caspase-2. Interestingly, we found that *Casp2*$^{-/-}$ mice exhibited more severe lung and liver lesions with extensive karyomegaly (see Figure), a feature commonly associated with ageing and genomic instability. Thus, our work indicates that caspase-2 is critical in regulating the oxidative stress response and in preventing cellular stress and pre-mature ageing.



***Caspase-2* deficiency exacerbates cellular damage and promotes karyomegaly following paraquat induced oxidative stress.** Images of haematoxylin and eosin stained liver sections from treated control (WT) and *Casp2*$^{-/-}$ mice, showing abnormal cell morphology and size in tissues from *caspase-2*-deficient mice.

Outcomes
for the **Community**

Our research provides a greater understanding of the biology of cancer and diseases associated with disruption of normal cellular repair, cell death and oxidative stress. Our current work has discovered a role for caspase-2 as a marker of poor outcome and prognosis in neuroblastoma. In addition, caspase-2 is required for a normal cellular stress response to prevent excessive build up of oxidative stress that could lead to genomic instability and pathologies such as cancer and ageing. We are currently investigating the biological pathways involved in these processes to understand how they can potentially be used for development of new disease markers and therapeutic targets.



Jason Powell | Paul Moretti | Heidi Neubauer | Wenying (Layla) Zhu
Elferaan Quatermass | Melissa Bennett | Stuart Pitson

Alex Lewis | Maurizio Costabile | Briony Gliddon | Melissa Pitman | Lorena Davies
Carl Coolen | Joanna Woodcock

Molecular Signalling Laboratory

Professor Stuart Pitson PhD

The Molecular Signaling Laboratory examines cell signalling pathways regulated by sphingolipids. In particular, our work focuses on understanding the regulation of these pathways, how they are dysregulated in cancer and other conditions, and the development of novel small molecules as potential therapies to target these pathways.

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 cell surface receptors. Sphingosine kinase is a key enzyme controlling the cellular abundance of these lipids, and through this action can regulate central processes such as cell survival and proliferation. Indeed, we and others have shown that high levels of sphingosine kinase can lead to neoplastic cell transformation. This indicates an oncogenic role for sphingosine kinase, which is further supported by findings of 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 regulation of leukocyte migration, enhancing blood vessel formation, and enhancing constriction of airway smooth muscle cells. Thus, sphingosine kinase is also a potential target for therapeutic intervention in inflammation, atherosclerosis, hypertension and asthma.

Recent work in the Molecular Signalling Laboratory has concentrated on identifying the mechanisms regulating sphingosine kinase, the cellular functions controlled by this enzyme, and in developing small molecule inhibitors as potential 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 and other diseases.

Outcomes
for the **Community**

Cancer has 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 progression and chemotherapeutic resistance of some cancers, but also identified new targets for therapeutic intervention in the treatment of these cancers.

Key discoveries 2014

Exploiting the sphingolipid pathway for the development of anti-cancer agents

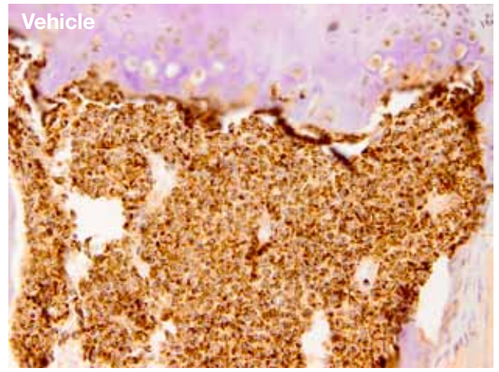
The importance of the sphingolipid pathway in the development of many cancers has provided impetus for the development of small molecule modulators of this pathway as potential anti-cancer agents. To this end we have employed a structure-based approach to develop first-in-class sphingosine kinase inhibitors that show considerable promise as anti-cancer agents. These inhibitors are highly specific, and in pre-clinical studies show efficacy in blocking the progression of a range of different human cancers *in vivo*, with few side-effects. We have also identified that sphingosine is a key regulator of the pro-survival 14-3-3 proteins, and using this knowledge, developed small molecule sphingosine-mimetics to target the 14-3-3 proteins as an anti-cancer strategy. Again, we have shown these agents block the growth of some human cancers *in vivo*, and are therefore attractive candidates for further development.

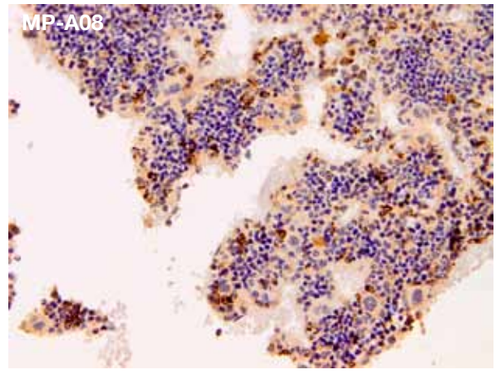
Sphingosine kinase contributes to cancer progression through transferrin receptor 1

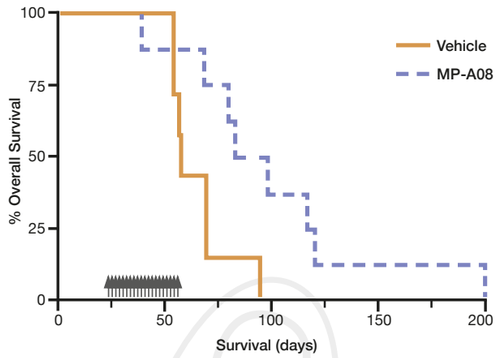
The mechanisms whereby sphingosine kinase enhances cancer progression have not been well understood. Using a gene expression array approach, we have demonstrated a novel mechanism whereby sphingosine kinase regulates cell survival, proliferation and neoplastic transformation through enhancing expression of transferrin receptor 1. Importantly, these findings, published in Oncogene, identify a novel means of targeting the oncogenic signalling of sphingosine kinase via blocking transferrin receptor 1 function.

Sphingosine kinase 2 regulates hepatitis C virus replication

In collaborative work with Professor Stanley Lemon of the University of North Carolina, USA, we have shown that sphingosine kinase 2 plays an important role in hepatitis C virus replication. This work, published in Nature Medicine, demonstrates that sphingosine kinase 2 activity promotes lipid peroxidation that, in turn, inhibits the viral replication machinery. These findings may provide a mechanism for long-term viral persistence, as well as potential therapeutic targets for control of this virus.

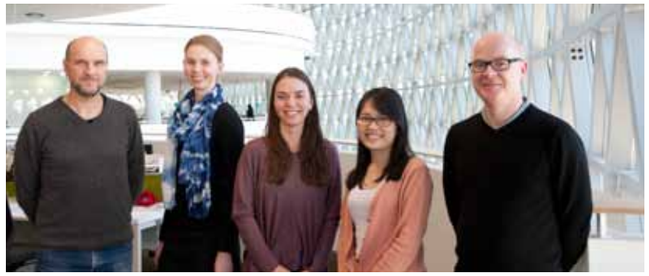






Sphingosine kinase inhibition reduces leukaemic burden and enhances survival of mice with human leukaemia. Upper panels show bone marrow from sphingosine kinase inhibitor (MP-A08) treated or control mice stained for human leukaemia cells (brown). Bottom panel shows enhanced survival of mice with human leukaemia after a short series of treatments with MP-A08 (arrows).

Krzysztof Mrozik | Vicki Wilczek | Ankit Dutta | Kate Vandyke | Andrew Zannettino



Stephen Fitter | Natasha Friend | Kimberley Evans
Chee Man Cheong | Duncan Hewett

Myeloma Research Laboratory

Professor Andrew Zannettino PhD

Myeloma is a haematological malignancy characterised by the clonal proliferation of plasma cells, an immune cell type that normally protects us against infection. Myeloma is the second most common blood cancer and more than 100,000 people are diagnosed each year worldwide.

Despite recent advances in treatment, myeloma remains almost universally fatal and has a ten year survival rate of approximately 17%. The main clinical manifestations of myeloma are the development of osteolytic bone lesions, bone pain, hypercalcaemia, renal insufficiency, suppressed immunoglobulin production and increased bone marrow angiogenesis (blood vessel formation). Myeloma is preceded by a premalignant (asymptomatic) monoclonal gammopathy of uncertain significance (MGUS) stage. The factors that trigger the progression from MGUS to myeloma remain to be determined; however, our studies show that both intrinsic genetic changes and extrinsic factors play a role in disease progression. Our laboratory's research is focussed on detecting the key signalling pathways that are deregulated during disease development and determining what microenvironmental changes occur during disease pathogenesis. We believe that these approaches will enable us to identify new molecular markers of disease risk and to design drugs against novel therapeutic targets.

Current projects are focused on:

- Identifying the genetic, transcriptional and epigenetic changes that trigger the progression from asymptomatic MGUS to myeloma.
- Determining why the bone marrow is a 'hot-spot' for myeloma plasma cell metastasis.
- Identifying the mechanisms governing dissemination and relapse in multiple myeloma.
- Identifying the role played by the newly described tumour suppressor genes *GLIPR1* and *SAMSN1* in multiple myeloma development.
- Determining the effects of myeloma plasma cells on mesenchymal stem cell differentiation.
- Assessing the effectiveness of targeting class IIa histone deacetylases (HDAC) to treat myeloma and myeloma-associated bone disease.
- Identifying the role of the mTOR pathway in mesenchymal stem cell biology and bone formation.
- Assessing the effectiveness of targeting skeletal mTORC1 as a novel approach to treat diet-induced insulin resistance.

Outcomes for the Community

In addition to discovery research, aimed at identifying new treatment targets, the Myeloma Research Laboratory supports patient outcomes by contributing to clinical practice guidelines for the management of myeloma patients and patients with systemic light chain amyloidosis.

Key discoveries 2014

N-cadherin is a therapeutic target in t(4;14)-positive multiple myeloma

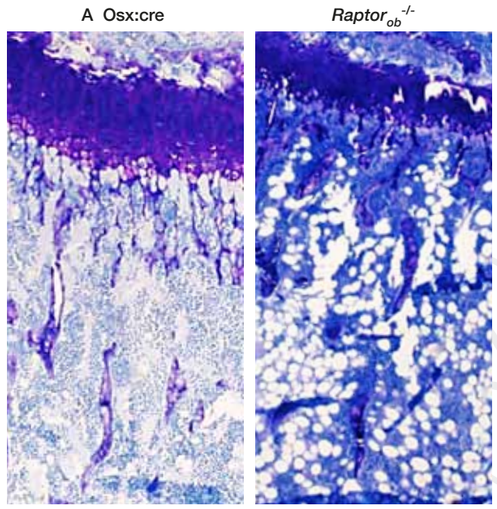
The t(4;14) multiple myeloma (MM) subgroup, characterised by expression of the histone methyltransferase MMSET, has a poor prognosis. We have identified that an epithelial-to-mesenchymal transition (EMT)-like process plays a critical role in t(4;14)-positive MM disease pathogenesis. This EMT-like phenotype is, in part, characterised by increased expression of the cell adhesion molecule N-cadherin. We have previously shown that circulating N-cadherin levels are a prognostic marker for high-risk myeloma patients (Vandyke *et al, Br J Haematol.* 2013 May;161(4):499-507). In 2014, we extended these initial findings by investigating whether N-cadherin represented a good therapeutic target in t(4;14)-positive MM. Using the well established C57BL/KaLwRijHsd mouse model of MM, we showed that the N-cadherin antagonist ADH-1 (100mg/kg/day) commencing at the time of tumour inoculation significantly decreased tumour burden after 4 weeks compared with PBS-treated mice. In contrast, ADH-1 had no effect on tumour burden in the established disease setting. Our findings demonstrate a potential role for N-cadherin in MM plasma cells extravasation and bone marrow homing. Furthermore, these studies suggest that N-cadherin represents a novel therapeutic target to prevent the dissemination of MM plasma cells and delay MM disease progression in MM patients with high N-cadherin expression.

SAMSN1 is a tumor suppressor gene in multiple myeloma

Several genetic abnormalities have been identified as critical for the development of multiple myeloma (MM); however, a number of these abnormalities are also found in patients with the asymptomatic, benign precursor, monoclonal gammopathy of uncertain significance (MGUS), indicating that there are other, as yet unidentified, factors that contribute to the onset of MM disease. We have identified that the *Samsn1* gene is deleted in the C57BL/KaLwRij mouse line, which is pre-disposed to developing MM. Furthermore, we showed that SAMSN1 expression is reduced in the malignant plasma cells of patients with MM and identified promoter methylation as a potential mechanism through which SAMSN1 expression is modulated in human myeloma cell lines. Notably, re-expression of SAMSN1 in the C57BL/KaLwRij mouse line resulted in complete inhibition of MM disease development *in vivo* and decreased proliferation in stromal cell-plasma cell co-cultures *in vitro*. This is the first study to identify deletion of a key gene in C57BL/KaLwRij mice that also displays reduced gene expression in patients with MM and is therefore likely to play an integral role in MM disease development.

mTORC1 plays an important role in post-natal skeletal development by controlling osteoblast differentiation and function

Extracellular factors that control intramembranous and endochondral ossification, the two developmental programs required for the formation of the mammalian skeleton, activate the mammalian target of rapamycin (mTOR) pathway. mTOR, a serine/threonine kinase, forms two functionally and elementally distinct multi-protein complexes termed mTORC1 and mTORC2. mTORC1 plays an essential role in coordinating anabolic and catabolic processes in mammalian cells to control cellular growth. To date, data describing a direct role of this complex in skeletal biology is limited. To investigate the role of mTORC1 in skeletal development, we used genetically modified mouse strains to disrupt mTORC1 function in pre-osteoblasts by targeted deletion of raptor (*Rptor*), a unique component of mTORC1, in Osterix-expressing cells. Deletion of *Rptor* led to reduced limb length at birth that was associated with smaller epiphyseal growth plates in the postnatal skeleton. *Rptor* deletion also caused a marked reduction in pre- and post-natal bone acquisition, which was evident in skeletal elements derived from both intramembranous and endochondral ossification, leading to skeletal fragility. A marked increase in intramedullary adiposity was also observed in the long bones of knockout animals. The decrease in bone formation was not due to a reduction in osteoblast numbers but a reduction in osteoblast function. *In vitro*, primary osteoblasts from knockout animals failed to respond to insulin or BMP-2, extracellular factors that promote bone formation. Direct assessment of bone developmental markers in *Rptor* knockout osteoblasts revealed a transcriptional profile consistent with an immature osteoblast phenotype suggesting that differentiation is stalled early in osteogenesis. These findings demonstrate that mTORC1 plays an important role in skeletal development by regulating osteoblast differentiation and, hence, function.



Elevated levels of intramedullary adipose in $Raptor_{ob}^{-/-}$ mice.
(A) Tolulene blue stained tibial sections of Osx:cre (cre) and $Raptor_{ob}^{-/-}$ (hom) mice. Adipocytes appear as cleared circles.

Sophie Wiszniak | Rachael Lumb | Quenten Schwarz

Zarina Greenberg | Peter McCarthy | Eiman Saleh

Neurovascular Research Laboratory

Dr Quenten Schwarz PhD

The vision of the neurovascular research laboratory is to identify the cell and molecular mechanisms controlling neuronal, vascular and neural crest cell development with the intent of providing novel insight toward the origins and treatments of these highly prevalent neurocrestopathies and neurodevelopmental disorders.

Almost three out of every 100 children suffer from a congenital disorder that necessitates ongoing medical treatment throughout life. A significant proportion of these disorders arise from aberrant neuronal, neural crest and vascular development which alone affect over 2% of all births.

Understanding how and why multiple cell types functionally integrate during embryonic development presents a major challenge to developmental biologists worldwide. Taking advantage of multiple *in vivo* model systems, including mouse, zebrafish and chick, recent advances from our laboratory have uncovered previously unrecognised co-dependencies of these three cell types during embryonic development. Excitingly, our research further demonstrates that each cell type uses similar molecular pathways to communicate with each other to control their development.

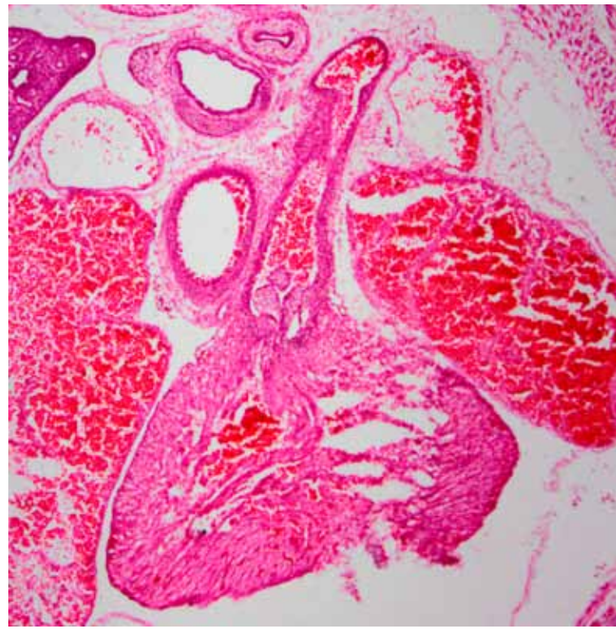
Our current research projects are fusing high throughput proteomics and genomics approaches with novel animal models to identify the signalling pathways through which: 1) neurons position themselves in appropriate locations of the brain to form functional and complex connections that are essential for cognition and other behaviours, 2) blood vessels sense their environment to form functional networks, 3) neural crest cells sense their environment to position themselves in appropriate locations to form a functional nervous system, 4) neural crest cells differentiate in to bone and cartilage to control craniofacial morphogenesis, and 5) neural crest cells communicate with blood vessels and cardiac precursors to control formation of the heart.

Key discoveries 2014

In 2014 the Neurovascular Research Laboratory had several key discoveries that provide novel insight to embryonic development and the origins of congenital birth disorders.

Over the past 5 years our laboratory has generated a large body of work into the involvement of vascular growth factor receptors in neural crest cell development. Using a string of KO and conditional KO mouse models we identified that the vascular growth factor receptors Nrp1 and Nrp2 are expressed in neural crest cells and required cell-autonomously for their migration. On the basis that Nrp1 and Nrp2 KO mice had non-overlapping defects in different neural crest cell derivatives we postulated that Nrp1 and Nrp2 control migration of only a subset of neural crest cells. This finding lead to a significant conceptual advance in the neural crest cell field as it answered the fundamental question of which molecules coordinate the choice of migration path with correct positioning of neural crest cell-derivatives. Recent work from our own laboratory using a novel mouse model in which we lineage traced Nrp2 expressing neural crest cells provided definitive support to this notion that the Nrp receptors coordinate cell migration with specification.

Our previous work in mouse models identified an essential role for the protein 14-3-3ζ in neuronal development. Moreover, we also defined a causal relationship between deficiencies of the protein 14-3-3ζ and neurodevelopmental disorders such as schizophrenia and autism. How 14-3-3ζ plays a role in neuronal development and how deficiencies give rise to neuronal pathologies has been an ongoing line of investigation in our laboratory. Our recent publication in collaboration with Anthony Wynshaw-Boris in the USA demonstrates that 14-3-3ζ promotes neuronal migration and neural stem cell dynamics by interacting with several classical signalling proteins. These findings provide exciting avenues toward future studies and toward possible targets for innovative therapies.



Normal septation of the cardiac out-fow tract section of embryo heart stained with eosin

Outcomes for the **Community**

Our findings provide novel insight to the aetiology of a large number of congenital birth defects, including neuronodevelopmental disorders and craniofacial defects. Aberrant developmental processes sit at the centre of these disorders and our findings offer hope of innovating new diagnostic and prognostic tests, and for the generation of new therapies tacking advantage of directed differentiation of stems cells in to distinct derivatives. Our advances in understanding how 14-3-3ζ functions in development also take us closer toward identifying the origins of disorders of the mind and toward novel therapies.

Michael Brown | Stanley Yu

Tessa Gargett | Yan Chan

Translational Oncology Laboratory

Professor Michael P Brown MBBS, PhD, FRACP, FRCPA

The Translational Oncology Laboratory is associated with the Royal Adelaide Hospital Cancer Clinical Trials Unit, which has a tumour subtype focus of melanoma and lung cancer.

Melanoma projects include the CARPETS study, which is a NHMRC-funded phase 1 clinical trial of autologous chimeric antigen receptor (CAR) gene-modified T cells in patients with advanced melanoma. The CAR is directed toward the glycolipid, GD2, which is expressed in most metastatic melanoma samples and which may be associated with a resistant, invasive, mesenchymal phenotype of melanoma.

Two patients, who have been recruited at the first dose level of this study, have received gene-modified cells without any adverse events. Human Research Ethics Committee approval has been received to continue recruitment at the next highest dose level. In up to a half of advanced melanoma cases, BRAF inhibitor therapy provides short to medium term tumour control. However, this therapy eventually fails in most cases because of mutational and non-mutational mechanisms. In collaboration with Professor Stuart Pitson, Associate Professor Claudine Bonder and Dr Lisa Ebert we are investigating genotype/phenotype correlations of BRAF inhibitor-resistant melanoma. In addition to studying molecular mechanisms of BRAF inhibitor resistance in melanoma cell lines, we are also investigating the role of vasculogenic mimicry in the phenotype of BRAF inhibitor-resistant melanoma cells. The findings are likely to be of direct therapeutic relevance.

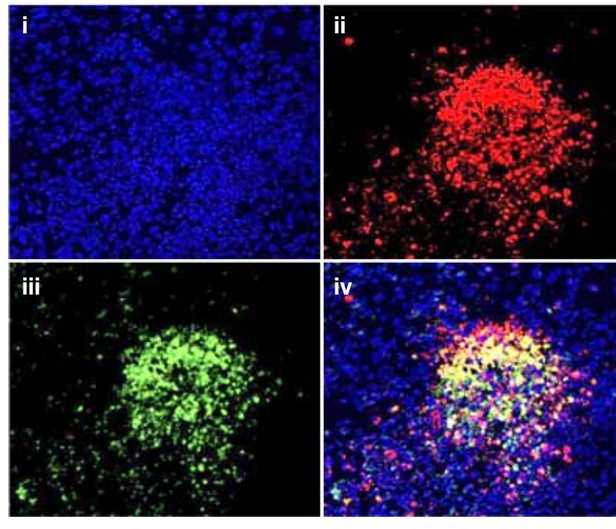
Front-line therapy for lung cancer typically involves cytotoxic chemotherapy, which is DNA-damaging and causes cancer cell death. We have pre-clinical proof of concept for a novel method of detecting cancer cell death based on the APOMAB® monoclonal antibody that is specific for a ribonucleo-protein overexpressed in malignancy. Non-invasive methods for the detection of cancer cell death are useful both for prognostication (where necrotic tumours have a worse prognosis) and prediction of therapeutic response (where increased rates of tumour apoptosis and necrosis are associated with improved patient outcomes). Using the long-lived positron emitter, Zirconium-89, we are adapting APOMAB for immuno-positron emission tomography (immunoPET). In an extension of this project, we are investigating the anti-tumour activity of APOMAB antibody-drug conjugates (ADCs) in pre-clinical lung tumour models. We have shown that the activity depends solely on bystander killing effects mediated by cleavable linkers and cell-permeant, diffusible cytotoxins. Meanwhile a chimeric version of APOMAB has been made and a batch of the antibody will be qualified in readiness for a first-in-human clinical trial as a medical imaging agent.

Key discoveries 2014

In the highly ranked *Journal of Nuclear Medicine*, we showed that post-chemotherapy and tumour-selective targeting with the La-specific DAB4 monoclonal antibody (APOMAB) is influenced by the extent of intratumoral apoptotic cell clearance. Specifically, we show that defective clearance of dead cells produces selective tumour accumulation of radiolabelled APOMAB, helping to explain its bystander-killing effects (Al-Ejeh *et al*, *J Nucl Med*, 2014).

We demonstrated that the La antigen is over-expressed in lung cancer and is a selective dead cancer cell target for radioimmunotherapy using the La-specific antibody APOMAB. Furthermore, we demonstrated that bystander beta-radioimmunotherapy significantly delayed tumour growth, particularly as concurrent PARP inhibition increased dead tumour cell targets of APOMAB (Staudacher *et al*, *EJNMMI Res*, 2014).

We demonstrated that targeted alpha-therapy using 227Th-APOMAB had crossfire anti-tumour effects *in vivo*. Importantly, this extension of our work with beta-radioimmunotherapy showed that even the shorter path length of APOMAB alpha-radioimmunotherapy induces significant bystander effects (Staudacher *et al*, *Nucl Med Commun*, 2014).



Treatment of lung tumour-bearing mice with a PARP inhibitor and chemotherapy increases both tumour cell death and tumour uptake of APOMAB. Biotinylated APOMAB was injected IV 24 hours after the treatment. (i) Tumour section is counterstained with DAPI with detection of (ii) cell death (ApopTag+), and (iii) biotinylated APOMAB. (iv) images (i–iii) were pseudo-coloured and merged. DAPI = blue, red = dead cells, green = APOMAB, yellow = co-localisation of APOMAB and dead cells.
photomicrographs courtesy of Dr Alex Staudacher

Outcomes for the Community

Melanoma and lung cancer are two common types of cancer that require new therapies to improve patient outcomes. We are testing genetic modification of the patient's own T cells as a new way of fighting melanoma in the body. We are also developing a new way of targeting lung cancer based on a technology called antibody drug conjugates.

Michael Samuel | Kaitlin Scheer

Natasha Pyne | Jasreen Kular

Tumour Microenvironment Laboratory

Dr Michael Samuel PhD

It is well known that the biochemical and biomechanical properties of the tumour microenvironment strongly influence the progression of cancers and thereby the disease prognosis. While the mechanisms by which tumour biochemistry influences tumour progression are becoming increasingly well elucidated, the mechanisms underlying the role of biomechanics in tumour progression are less well understood.

Nevertheless, it is well accepted that increasing stiffness of the extra-cellular matrix (ECM) and the polarisation of cells within the microenvironment (including fibroblasts and macrophages) are potent tumour promoters by enhancing mechano-reciprocity. Enhanced mechano-reciprocity is a cycle of increasing tissue stiffness set up by the reciprocal induction of specific signalling pathways within parenchymal and stromal cells during tumour progression. Our laboratory uses genetic tools and animal models to understand how the microenvironment is remodelled at both the biophysical and biochemical levels during tumour initiation and progression, to identify novel targets that would be useful in therapeutic normalisation of the tumour microenvironment.

In collaboration with Associate Professor Michele Grimbaldeston we have demonstrated that ROCK is hyper-activated within fibroblasts, macrophages and mast cells populating the tumour microenvironment. Using murine models in which the Rho signalling pathway can be conditionally activated in any cell type of interest, we are working to determine the mechanisms by which this pathway modifies the ECM and the cellular component of the microenvironment.

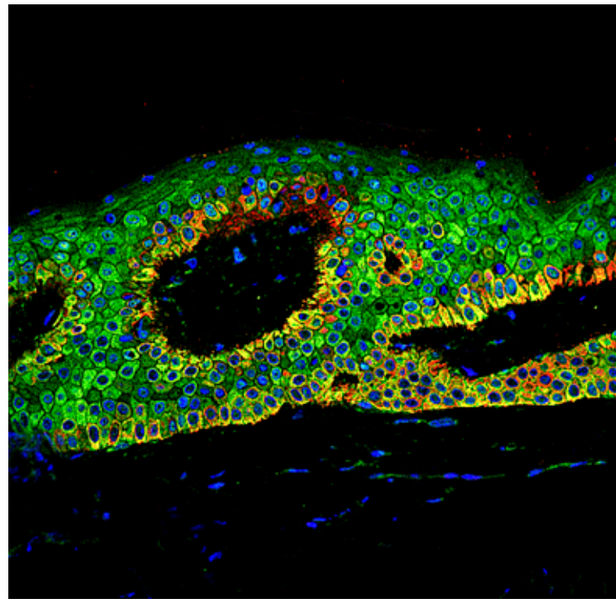
Key discoveries 2014

ROCK activation accelerates tumour progression in mechano-responsive tissues

The Rho signalling pathway is well-known to promote tumour cell invasion by regulating the synthesis and contractility of the actomyosin cytoskeleton. We have previously demonstrated that activation within the skin of Rho kinase (ROCK), a major effector protein of the Rho-signalling pathway, causes increased production of 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). Crucially, we have shown that these mechanisms are active in the progression of human SCCs and identified a novel therapeutic approach to target this disease (*Am J Patho*l 183:930–7). More recently, we have found that activating ROCK in a tissue specific manner within mechano-responsive tissues such as the mouse mammary (in collaboration with Dr Marina Kochetkova, University of Adelaide) and intestinal epithelia enhances tumour progression.

Hyperactivating Rho signalling via a druggable molecular adaptor protein enhances wound healing

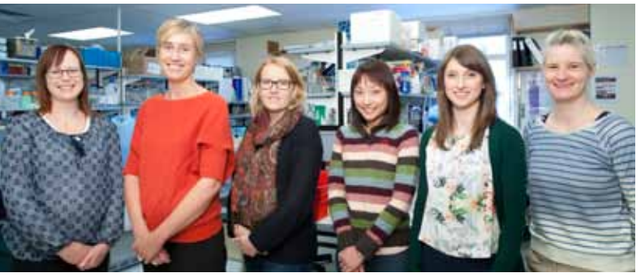
The Rho signalling pathway is known to be upregulated at wound margins to permit the establishment of an actomyosin ring that facilitates wound closure. We have established for the first time that Rho signalling at wound margins is also crucial for the production and remodelling of the ECM components that make up the new dermal tissue at the wound site and re-establish normal mechano-reciprocity. We have shown that the ζ isoform of the 14-3-3 family of molecular adaptor proteins acts to restrain Rho signalling at this location, providing temporal control of the production and remodelling of the ECM and through this the speed of re-epithelialisation, enhancing the quality of the resulting healed skin. In collaboration with Dr Jo Woodcock and Professor Stuart Pitson (Molecular Signalling laboratory) and Dr Hayley Ramshaw and Professor Angel Lopez (Cytokine Receptor Laboratory), we have shown that pharmacological inhibition of 14-3-3 activity enhances ROCK activation at wound margins and enhances wound healing. Slow healing wounds, such as those exhibited by diabetics, frequently exhibit high levels of 14-3-3ζ expression. Our observations suggest that enhancing Rho-ROCK signalling at wound margins by inhibiting 14-3-3ζ may have therapeutic utility in enhancing wound healing.



A section of human hypertrophic scar tissue, showing a high level of 14-3-3ζ (green) expression within keratinocytes (red) Nuclei are blue

Outcomes for the Community

Epithelial tumours and chronic wounds exhibit altered microenvironments associated with aberrant signalling via the Rho pathway. We are working to identify the mechanisms by which this pathway acts and to discover new approaches to normalise this pathway that could lead to new therapies to treat both conditions.



Lisa Ebert | Claudine Bonder | Kate Parham | Wai (Kiwi) Sun
Emma Thompson | Natasha Pyne

Eli Moore | Michaelia Cockshell | Zahied Joha | Lih Tan | Kay Khine
Myo Min | David Dimasi

Vascular Biology and Cell Trafficking Laboratory

Associate Professor Claudine Bonder PhD

With a focus on human disease we study the intricate network of blood vessels that carry blood cells throughout the body. Blood vessels contribute to life threatening diseases such as cancer and heart disease but are also essential for fighting infection and wound repair.

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, vascular tone, permeability, and vessel growth.

A major focus of our group is to (i) investigate blood vasculature in normal and disease states and (ii) better define blood vessel progenitor cells for clinical application. Our work may provide new opportunities to (i) treat debilitating diseases such as allergy, (ii) assist blood vessel repair in patients with cardiovascular disease and (iii) block blood vessel development in cancer patients. 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.

Outcomes
for the **Community**

With a focus on health and well-being we study the intricate network of blood vessels that carry blood cells throughout our body. Blood vessels contribute to life threatening diseases but are also essential for tissue regeneration and repair. Associate Professor Bonder's work may provide new opportunities to enhance blood vessel development following organ transplantation and control their levels of activation during allergic inflammation. A better understanding of blood vessels in disease will provide new treatment options for many debilitating diseases.

Key discoveries 2014

Blood vessels are critical for pancreatic islet function

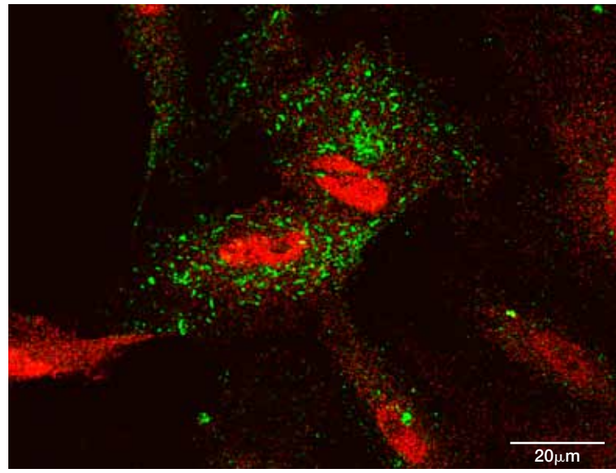
Pancreatic islet transplantation is an emerging cure for Type 1 Diabetes but success is limited by death of insulin producing beta cells post transplantation. Vasculogenic endothelial progenitor cells (EPCs) have the potential to improve islet engraftment, and may also improve islet graft function. In collaboration with Dr Claire Jessup and Associate Professor Toby Coates of the Royal Adelaide Hospital 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:EPC clusters can form successfully and glucose stimulation index function was superior to clusters comprised of islet cells only (Penko *Islets* 3:1, 2011). More importantly, in 2013 we demonstrated that co-transplantation of islets and EPCs into diabetic mice significantly increased the cure rate when compared to islets alone (Penko D *et al*, *Cell Transplantation*, 2013). This work has formed a leading project in the six year $59M Cell Therapy Manufacturing CRC wherein smart surface biomaterials will be generated to bind both islets and EPCs for therapeutic application.

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. We recently identified that (i) histamine-induced P-selectin expression on human umbilical vein ECs is sphingosine kinase (SK)-1 dependent and (ii) histamine-induced neutrophil rolling along the vasculature *in vitro* and *in vivo* is SK-1 dependent (Sun W *et al*, *Am J Pathol*, 2012). In 2013 we revealed that administration of Fingolimod (approved pro-drug for treatment of multiple sclerosis) attenuates histamine-induced neutrophil recruitment in multiple animal models of allergic inflammation and have initiated human clinical trials to investigate this additional indication for Fingolimod.

Development of EPCs for therapeutic use

We recently identified a new population of immature, non-adherent endothelial progenitor cells (naEPCs) (Appleby S *et al, PLoS ONE*, 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 (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 and we have executed *in vivo* models to validate their application.



Human endothelial cells which line blood vessels respond to an allergic stimulus with increased surface expression of P-selectin (green) and production of sphingosine kinase (red)

Rosalie Kenyon | Wendy Parker | Ming Lin | Joel Geoghegan

John Toubia | Kat Pillman | Andreas Schreiber | Liam McIntyre | Anna Tsykin
Klay Saunders | Dave Lawrence | Jinghua Feng

The Australian Cancer Research Foundation Cancer Genomics Facility

Professor Greg Goodall Director Professor Hamish Scott Director
Joel Geoghegan Bsc, MSc Facility Manager Dr Andreas Schreiber PhD Head of Bioinformatics

The ACRF Cancer Genomics Facility is an integral part of the cutting edge research carried out at the CCB. With an emphasis on translating innovative research into tangible results for patients the CCB's partnership with SA Pathology has enabled the efficient implementation of genomic technologies for diagnostics.

Over the course of 2014, working in close collaboration with the Karin Kassahn, Head of the Advanced Technology Unit in the Genetics and Molecular Pathology directorate of SA Pathology, the ACRF Cancer Genomics Facility received National Association of Testing Authorities (NATA) accreditation for a number of genomic clinical tests that include the following:

- Constitutional and cancer cytogenetic screens using microarrays
- Next-generation sequencing (NGS) targeted panels for detecting mutations in familial cancers, cardiomyopathy and other inherited diseases
- We are the first laboratory in Australia to receive accreditation for clinical whole exomes.

This was a huge undertaking and a great accomplishment that required research, diagnostics and bioinformatics staff working together as a single unit. These tests will reduce the time it takes to get results to patients, improve clinical yields and provide definitive diagnoses to complex cases that have previously gone unanswered.

In addition to working with diagnostics, the Genomics Facility has processed over 2000 research samples throughout the year across a range of next-genetation sequencing (NGS) applications (RNAseq, ChIPseq, DNAseq) from a number of institutions across South Australia. These projects have encompassed understanding the fundamentals of cancer, but also include the study of ancient DNA, economically important agricultural crops, as well as bacterial and viral genomes. Bridging the gap between research and diagnostics is an exciting development for the Genomics Facility.

Bioinformatics Group

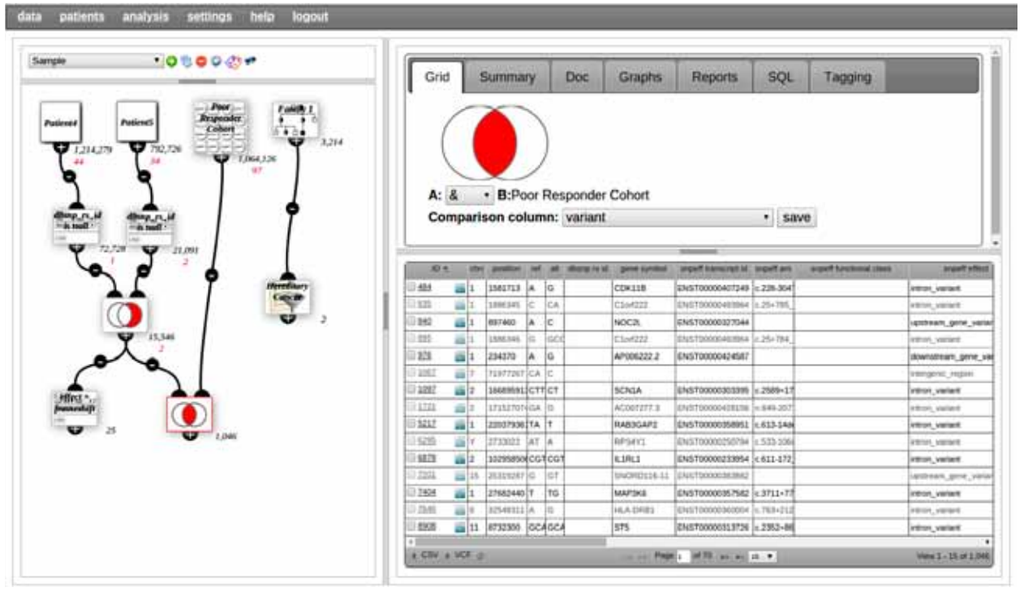
In 2014 the Bioinformatics Group consisted of seven members: three employed by the ACRF Cancer Genomics Facility and two each through the Immunology and Molecular Pathology directorates of SA Pathology. In addition, two bioinformaticians on short-term contracts worked on projects together with the Molecular Signalling and Gastroenterology Laboratories.

The HiSeq, MiSeq and Ion Torrent Proton sequencers produced data for around 160 sequencing projects in 2014. For about half of these projects mapping of raw sequencing reads to the reference genome was carried out by the Facility and for about 70 projects additional bioinformatics analysis was necessary. Frequently occurring analyses, such as quantification of RNA transcript levels and differential expression, or DNA mutation discovery and annotation, are performed using computational pipelines that have been developed by our group and are constantly being improved and updated. Other less frequent analyses, such as detection of structural mutations in whole-genome data, are first done on a one-off basis and only developed into general-purpose pipelines if the need arises.

While most bioinformatics projects carried out by the group arise directly from biological research projects and are described elsewhere is this report, some members of the group also carry out direct developmental bioinformatics work. Examples of this include automation of base-calling, QC and subsequent data management for the HiSeq sequencer and the development of a very useful tool that compares mapped sequencing data, at genomic positions known to be frequently mutated, in order to detect sample mix-ups that inevitably occur at a low but unfortunately non-zero rate, particularly in large sequencing projects with many samples.

Key discoveries 2014

A project worked on throughout 2014 and to which considerable resources continue to be devoted is the development of VariantGrid, a variant database combined with an intuitive graphical web-based interface that enables researchers to carry out complicated mutation analyses on large families and cohorts that in the past had to be carried out by bioinformaticians. This project formed the basis of a patent application with our partners at ITEK, the commercialization arm of UniSA. VariantGrid is also part of the Genomic Facility's ongoing efforts to facilitate and aid the uptake of next generation sequencing technology by our diagnostic laboratories.



The VariantGrid is a variant database combined with an intuitive graphical web-based interface that enables researchers to carry out complicated mutation analyses on large families and cohorts

Outcomes for the Community

With National Association of Testing Authorities (NATA) accreditation and the subsequent implementation of cytogenetic microarrays, next-generation sequencing panels and clinical whole exome sequencing, we are ensuring new technologies improve the standard of healthcare for South Australians. These new tests cost less, are more informative and for some patients may even suggest new treatment options. This personalised approach will give patients and their doctors alternative therapeutic options when conventional therapies have failed. Looking forward to 2015, we will continue to support both researchers and clinicians in basic research, translational research and diagnostics

Bioinformatics analyses performed in our group are an essential component of the Centre for Cancer Biology's leading role in developing high throughput sequencing capabilities for South Australia, providing researchers an ever-more comprehensive tool for studying the workings of human cells and the mechanistic origins of disease. Increasingly, these capabilities promise to directly impact diagnostic tests performed by SA Pathology, promising to ultimately decrease costs while improving patient outcomes.

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Publications continued

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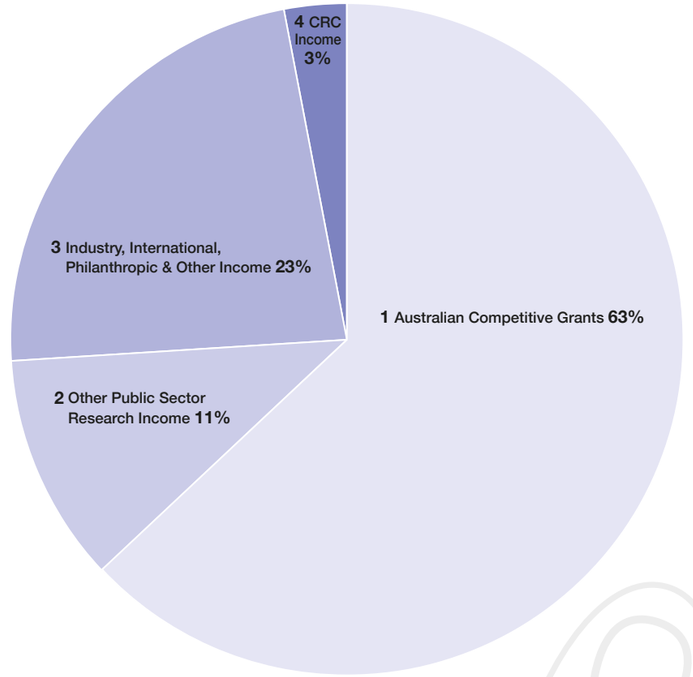
Financial Highlights

Research Income 2014

1	Australian Competitive Grants		8,120,996
2	Other Public Sector Research Income		1,461,955
3	Industry, International, Philanthropic & Other Income		2,871,351
4	Cooperative Research Centre (CRC) Income		355,885
	Total	AUD	12,810,187

Note: Total 2014 Research Income includes $1,730,000 in 2013 brought forward balances due to the CCB transition of grants to UniSA



New Grants and Fellowships

Investigator	Title	Granting Body
Bonder CS, Heddle RJ	Fingolimod, a new treatment for allergy	Royal Adelaide Hospital
Bonder CS, Lopez A	Endothelial progenitor cell (EPC) expansion surfaces	Cell Therapy Manufacturing CRC
Bonder CS, Lopez A	Targeting interleukin-3 to prevent vascular development in breast cancer progression	Royal Adelaide Hospital
Brown MP	Research Infrastructure Block Grant	Royal Adelaide Hospital
Carr J, Pitson SM, Bonder CS	Endothelial progenitor cells (EPC) and sphingosine-1-phosphate (S1P) as modulators and therapeutic targets during Dengue virus infection	Australia-India Strategic Research Fund
Cheung KC, Yeung D, Lee C, Scott H, Zannettino A, To LB, Horvath N	Minimal residual disease (MRD) detection in Multiple Myeloma patients in complete remission post-autograft: correlation with risk of relapse?	HSCGB
D'Andrea RJ, Lewis ID, Wang S, Ekert P, Brown AL	Identification and mechanism of action of new drugs for treatment of MLL-AML	Royal Adelaide Hospital Research Fund; NHMRC Near Miss Grants
Gagliardi L	Postdoctoral Award	Endocrine Society of Australia
Goodall G, Conn S, D'Andrea R	Formation and function of circular RNAs in human cells	NHMRC
Goodall GJ, Khew-Goodall Y	Control of the actin cytoskeleton by miR-200 family microRNAs in neuroblastoma	Kids Cancer Project
Goodall GJ, Khew-Goodall Y	miR-200 and its targets as inhibitors of neuroblastoma growth and metastasis	Channel 7 Children's Research Foundation
Grimbaldeston MA, Lopez A	Commercial in Confidence	CSL Limited
Grimbaldeston MA, Lopez A	Modulating mast cell function in allergic inflammation.	RAH NHMRC Near Miss Project Grant
Gronthos S, Zannettino A, Arthur A	Osteogenic cell differentiation and function are mediated by ephrinB1 reverse signaling during skeletal development and following the onset of osteoporosis	NHMRC
Harvey N	Regulation of VEGFR trafficking and signal transduction by the ubiquitin ligase Nedd4	NHMRC
Harvey N, Schwarz Q	Regulation of neuro-vascular patterning and morphogenesis by semaphorin/neuropilin signalling	SAHMRI Beat Cancer Project
Helbig KJ, Beard MR, Revill P, Thomas P	Targeting HBV cccDNA using the CRISPR/Cas system	Australian Center for HIV and Hepatitis Virology (ACH2)
Hiwase DK, Scott HS, Hahn CN, Moore S, Schreiber AW	Comprehensive mutational screening to differentiate between hypoplastic MDS and aplastic anaemia.	RAH Research Foundation
Hogan B, Harvey N	Defining the earliest events in lymphatic vasculature formation from the veins	ARC Discovery Project
Hogarth M, Wines B, Grimbaldeston M, O'Hehir R	Structure and function of human Fc receptors	NHMRC
Hughes T, White D, Branford S, Mullighan C, Yong A, Ross D	Determining the prerequisites for the achievement of treatment-free remission in chronic myeloid leukaemia to facilitate the development of new therapies	NHMRC
Khew-Goodall Y	New signalling pathways regulating receptor tyrosine kinase trafficking	Royal Adelaide Hospital
Khew-Goodall Y	Regulating EGFR in breast cancer.	SAHMRI Beat Cancer Project Grant
Lewis ID, D'Andrea RJ	Investigation and development of novel orally-available small molecule kinase inhibitors as therapeutic treatments for relapse AML patients	Ray and Shirl Norman Cancer Research Trust
Lewis ID, D'Andrea RJ, Wang S, Brown AL	Establishment of xenograft models for the testing of new therapeutics	Royal Adelaide Hospital Contributing Haematologists' Committee
Lopez A, Geoghegan J, Scott HS	Translating Health Discovery Project	Therapeutic Innovation Australia
Parker WT, Yeung DT, Branford S, Scott HS	Investigating the clinical significance of BCR-ABL1 compound mutants in tyrosine kinase inhibitor resistant patients with chronic myeloid leukaemia	RAH Research Foundation
Pitman MR, Oehler M, Pitson SM	Role of CIB2 as potential tumour suppressor with prognostic significance in ovarian cancer	Royal Adelaide Hospital
Pitson SM	Defining the role of a palmitoylated variant of sphingosine kinase 1 in cancer	NHMRC
Pitson SM, Cowin AJ	Enhancing wound healing via modulation of the sphingosine kinase/sphingosine 1-phosphate pathway	Royal Adelaide Hospital
Pitson SM, Powell JA	Targeting sphingosine kinase 1c degradation to enhance cancer chemotherapeutic sensitivity	Cancer Council South Australia
Samuel MS, Grimbaldeston MA, Ruszkiewicz A	Defining the function of ROCK in establishing a tumour-promoting microenvironment	Cancer Council South Australia
Scott HS, Barnett CP, Moore L, Khong TY, Kassahn KS, Adelson DL	Genetic autopsy of perinatal death: diagnosis and discovery by whole genome sequencing	RAH Research Foundation
Scott HS, D'Andrea RJ	Diamond Blackfan Anaemia and bone marrow failure.	Captain Courageous Foundation
Scott HS, D'Andrea RJ, Hahn CN, Brown AL, Lewis ID.	Co-operation between GATA2 mutation or expression and RAS signalling in AML	NHMRC
Staudacher AH, Selva-Nayagam S, Moore J, Manavis J, Ruszkiewicz A, Brown MP	Investigation of markers of DNA damage in rectal cancer tissues after DNA-damaging anti-cancer treatment: correlation with pathological and clinical outcomes	Royal Adelaide Hospital
Wang S	Development of CDK4/6 inhibitors for treatment of cancer	ITEK Catalyst Fund
Wang S	Discovery of CDK inhibitors for treatment of childhood medulloblastoma	Channel 7 Children's Research Foundation
Wang S, Fan H	CDK inhibitors for the treatment of breast and prostate cancers	China–Australia Centre for Health Sciences Research
Wang S, Marshall G, Ziegler D	Targeting CDK6 for treatment of childhood medulloblastoma	The Foundation of Children
Wang S, Tilley W, Raj G	CDK9 Inhibitors for the treatment of castration resistant prostate cancer	Cancer Council
Wang S, Wang W	Evaluation of CDK9 inhibitors for treatment of acute mylogenous leukaemia (AML)	China–Australia Centre for Health Sciences Research
Wilhelm D, Kumar S	Post-translational control of cell fate decision	Australian Research Council
Woodcock J, Lopez AF, Hughes T	Targeting dimeric 14-3-3 proteins as therapy for Ph+ leukemia	Royal Adelaide Hospital
Yip KH	Mary Overton Early Career Research Fellowship	Royal Adelaide Hospital
Zannettino A, Revesz T	Bone Marrow Recovery in Acute Lymphoblastic Leukaemia	Women's and Children's Hospital Foundation
Zannettino A, To LB	Cooperating genetic changes that drive MM development: the role of SAMSN1 and GLIPR1 tumour suppressor gene	Beat Cancer Cancer Council South Australia

Seminar Program

Dr Jane Holland
Scientist, Signal Transduction in Development and Cancer, Max-Delbrück Centre for Molecular Medicine (MDC), Berlin, Germany
Molecular therapy of basal breast cancer 27/02/14

Professor Alex Brown
Aboriginal Research Program Leader, and Deputy Director, South Australian Health and Medical Research Institute (SAHMRI)
Building a research program in Aboriginal health 13/03/14

Dr Julie Secombe
Assistant Professor, Albert Einstein College of Medicine, Jack & Pearl Resnick Campus, Bronx, New York, USA
Myc oncoprotein function in cell growth and aging 20/03/14

Dr Lisa Butler
Acting Head, Dame Roma Mitchell Cancer Research Laboratories (DRMCRL), University of Adelaide
Leveraging ex vivo culture of human tumours for prostate cancer drug development 27/03/14

Dr Michael Murray
Research Fellow, Department of Genetics, University of Melbourne
New roles for a chemoattractant: Regulation of epithelial mesenchymal plasticity in Drosophila by Netrin 03/04/14

Dr Nicole Verrills
Cancer Institute NSW ECR Fellow, School of Biomedical Sciences and Pharmacy, University of Newcastle
Targeting a tumour suppressor phosphatase, PP2A, in haematological and solid cancers 10/04/14

Associate Professor Peter Anderson
Visiting Research Fellow, Centre for Orofacial Research and Learning, Faculty of Health Sciences, University of Adelaide
Clinical update on hemifacial microsomia 17/04/14

Professor Timothy Cox
Research Professor, Pediatrics, Center for Developmental Biology and Regenerative Medicine, University of Washington, Seattle, USA
Genetic and epigenetic contributions to common facial anomalies 24/04/14

Professor Michelle Haber
Director, Children's Cancer Institute Australia, Sydney
Molecular targeted therapy for childhood cancer 05/05/14

Professor Michael Parker FAA
Deputy Director, Biota Structural Biology Lab, ACRF Rational Drug Discovery Centre, St Vincent's Institute of Medical Research, Melbourne
Approaches to combating Alzheimer's disease: before you grow old! 08/05/14

Dr Alex Swarbrick
Head, Tumour Progression Laboratory, Garvan Institute, Sydney
ID4 controls mammary stem cells and marks breast cancers with a stem cell-like phenotype 15/05/14

Dr Jenny Wang
Group Leader, Cancer and Stem Cell Biology Group, Children's Cancer Institute Australia, University of NSW, Sydney
Targeting leukaemia stem cells: genetics, epigenetics and microenvironment 29/05/14

Associate Professor Ingrid Winkler
Senior Research Fellow, Team Leader, Stem Cells and Cancer Laboratory, Mater Research, TRI, Brisbane
Stem cells and the bad seeds 05/06/14

Associate Professor Susie Nilsson
Principal Research Scientist, CSIRO Molecular and Health Technologies, Australian Stem Cell Centre, Clayton, Victoria
Regulators of hemopoietic stem cells, the players and their roles 19/06/14

SAHMRI Inaugural Scientific Launch
26/06/14

Professor Katharina Gaus
Deputy Director, Centre for Advanced Molecular Imaging, University of NSW, Sydney
Insight into the regulation of T cell signalling with single molecule imaging 03/07/14

Professor Mark Davis
Warren and Katharine Schlinger Professor of Chemical Engineering, California Institute of Technology, Pasadena CA, USA
Nanoparticle therapeutics for treating solid tumors 15/07/14

Dr John Bruning
Lecturer, School of Molecular and Biomedical Science, University of Adelaide
Determining the mechanism of PPARgamma partial agonism 17/07/14

Associate Professor Matthew Simpson
Senior Lecturer in Mathematics, Science and Engineering Faculty, and Institute of Health Biomedical Innovation (IHBI), Queensland University of Technology, Brisbane
Quantifying mechanisms driving collective cell spreading using mathematical models 24/07/14

Dr Melissa Davis
Senior Research Fellow, Cancer Systems Biology, Systems Biology Laboratory, School of Engineering, University of Melbourne
Knowledge-based modelling and network analysis methods in biological systems analysis 31/07/14

Associate Professor Michael Beard
Head, Hepatitis C Virus Pathogenesis Laboratory, Centre for Cancer Biology, and School of Molecular and Biomedical Science, University of Adelaide
Interferon stimulated gene expression and control of viral replication and the host innate response 07/08/14

CCB Annual General Meeting
14/08/14

Professor Nico Voelcker
Deputy Director, Mawson Institute, University of South Australia, Adelaide *Nanostructured Silicon in Nanomedicine* 28/08/14

Professor Jane Visvader
Breast Cancer Laboratory, Stem Cells and Cancer Division, Walter & Eliza Hall Institute, Melbourne
Tracking mammary stem and progenitor cells in vivo 04/09/14

Dr Tracy Putoczki
Laboratory Head, Inflammation Division, Walter & Eliza Hall Institute, Melbourne
Therapeutic targeting of cytokine signalling in gastrointestinal cancers 11/09/14

Professor Geoffrey Greene
Co-Director, Signaling, Stem Cells, University of Chicago Center, Chicago, USA
Estrogen receptor as an evolving target in breast cancer prevention and treatment 18/09/14

Professor Merlin Crossley
Dean of Science, University of NSW, Sydney
Regulatory single nucleotide polymorphisms (SNPs) and genomic editing 25/09/14

Professor Sarah A Robertson
Director, Robinson Research Institute, School of Paediatrics and Reproductive Health, University of Adelaide
The immune response to conception: new insights and implications 09/10/14

Professor Alan Cowman FAA FRS
Head, Division of Infection and Immunity, Walter & Eliza Hall Institute, Melbourne
Moving in and renovating: invasion and remodeling of the human erythrocyte by the malaria parasite 16/10/14

Professor Patrick Tam
Deputy Director and Head, Embryology Unit, Children's Medical Research Institute, Sydney
Head formation in the mouse: input of transcription factor activity to WNT signalling pathway 23/10/14

Associate Professor Jody Jonathan Haigh
Division of Blood Cancers, Australian Centre for Blood Diseases (ACBD), Head, Mammalian Functional Genetics Laboratory, Monash University, Melbourne
Novel roles for the Zeb and Snai family of transcription factors in haematopoiesis and leukaemia? 30/10/14

Professor Brandon Wainwright
Director, Institute for Molecular Bioscience, University of Queensland, Brisbane
Hedgehog signalling controlling stem cells and common human cancer 13/11/14

Professor Philip Hansbro
Deputy Director, Centre for Asthma and Respiratory Disease, Hunter Medical Research Institute, The University of Newcastle, Newcastle NSW
Investigating the pathogenesis and developing new therapies for respiratory diseases 20/11/14

Associate Professor Veronique Angeli
Department of Microbiology, National University of Singapore, Singapore
Origin and function of LYVE-1 expressing tissue macrophage 25/11/14

Professor David Bowtell
Head, Cancer Genomics and Genetics Program, Peter MacCallum Cancer Centre, Melbourne
Mutational landscape of primary and acquired resistance in high grade serous ovarian cancer 27/11/14

Professor Myles Axton
Chief Editor, Nature Genetics (UK)
Publishing your work in Nature Journals 3/12/14

Professor Daniel Speiser
Head, Clinical Tumor Biology and Immunotherapy Group, Ludwig Center for Cancer Research, University of Lausanne, Switzerland
with
Dr Steven J O'Day (present to answer questions)
Medical Oncologist, Director, Clinical Research Beverley Hills Cancer Center, California USA
Basic and translational considerations for checkpoint blockade therapy for cancer 4/12/14

Invited Presentations

Acute Leukaemia Laboratory

Professor Richard D'Andrea

Invited Speaker

5th New Directions in Leukaemia Research (NDLR) Meeting. Noosa, Australia. April

Lowy Cancer Research Centre. Sydney, NSW. August

Dr Sarah Bray

Invited Speaker

The University of the Third Age (Flinders) Inc. Adelaide, Australia. September

Dr Anna Brown

Invited Speaker

Human Genetics Society of Australasia Adelaide Branch Seminar. Adelaide, Australia. May

Session Chair

Australian Society for Medical Research, Annual Research Day. Adelaide, Australia. June

Cell Signalling Laboratory

Assoc Professor Yeesim Khew-Goodall

Session Chair

ComBio 2014. Canberra, Australia. September

Cytokine Receptor Laboratory

Professor Angel Lopez

Invited Speaker

Gordon Research Conference. Girona, Spain. July

2014 Annual Meeting of the International Cytokine and Interferon Society. Melbourne, October

Drug Discovery and Development Laboratory

Professor Shudong Wang

Invited Speaker

Congress of International Drug Discovery Science & Technology (IDDST-2014). Suzhou, China. November

China-Australia Centre for Health Science and Research. Shandong University, China. November

Faculty of Pharmacy and Pharmaceutical Sciences, Monash University. Melbourne, Australia. July

Zhejiang University. Zhejiang, China. May

University of New South Wales. Sydney, NSW. April

Gastroenterology Research Laboratory

Assoc Professor Andrew Ruszkiewicz

Invited Speaker

South Australian Gut Club. Adelaide, Australia. March

Gene Regulation Laboratory

Professor Greg Goodall

Invited Speaker

Centenary Institute. Sydney, Australia. June

Garvan Signalling Symposium. Sydney, Australia. May

14th Hunter Meeting. Hunter Valley, Australia. March

Symposium Chair and Plenary Lecture Chair

ComBio 2014. Canberra, Australia. September

Dr Phil Gregory

Invited Speaker

ComBio 2014. Canberra, Australia. September

Dr Simon Conn

Invited Speaker

4th Australia and New Zealand Society for Cell and Developmental Biology (ANZSCDB) Meeting. Adelaide, Australia. November

Life Technologies Innovations in Cell Engineering Symposium. Adelaide, Australia. November

50th FEBS-EMBO Meeting. Paris, France. September

SACE Research Project Student Expo. Adelaide, Australia. August

Adelaide RNA Special Interest Group Meeting. Adelaide, Australia. May

Hepatitis C Virus Research Laboratory

Associate Professor Michael Beard

Invited Speaker

Asia Pacific Association for the Study of the Liver (APASL), Brisbane, Australia. April

International Congress of Medical Virology. Thailand. November

Dr Karla Helbig

Invited Speaker

Adelaide Infection and Immunity Group Meeting, SAHMRI, Adelaide, Australia. June

Leukaemia Unit, Genetics and Molecular Pathology

Associate Professor Susan Branford

Invited Speaker

Annual Meeting of the Japanese Society of Hematology. Osaka, Japan. November

16th Annual John Goldman on CML: Biology and Therapy. Philadelphia, USA. September

China CML Global Opinion Leaders Summit (GOLS). Qingdao, China. July

3rd International Conference Leukemia 2014. Santa Margherita Ligure, Italy. May

CML Global Opinion Leaders Summit (GOLS). Amsterdam, The Netherlands. March

Co-Chair

ASMR Ross Wishart Award Session, ASMR Meeting. Adelaide, Australia. September

Lymphatic Development Laboratory

Associate Professor Natasha Harvey

Invited Speaker and/or Session Chair

3rd Meeting of the Australian Network of Cardiac and Vascular Developmental Biologists. Melbourne, Australia. December

NAVBO Vascular Biology 2014. Asilomar, USA. October

St Jude Children's Research Hospital. Memphis, USA. October

Cardiovascular Research Institute, UCSF. San Francisco, USA. October

International Vascular Biology Meeting. Kyoto, Japan. April

Gordon Research Conference: Molecular Mechanisms in Lymphatic Function and Disease. Il Ciocco, Italy. March

14th Hunter Cell and Developmental Biology Meeting. Hunter Valley, Australia. March

Mast Cell Laboratory

Assoc Professor Michele Grimbaldeston

Co-Chair

Vitamin D Symposium, 7th Australian Health and Medical Research Congress. Melbourne, Vic. November

Australasian Society for Immunology, SA/NT 10th Adelaide Immunology Retreat. Adelaide, Australia. August

Invited Speaker

44th Australasian Society for Immunology Annual Meeting. Wollongong, Australia. December

7th Australian Health and Medical Research Congress. Melbourne, Australia. November

Walter and Eliza Hall Institute Postgraduate Seminar Program. Melbourne, Australia. April

Dr Kwok Ho (Dave) Yip

Invited Speaker

Centre for Cancer Biology Annual General Meeting. Adelaide, Australia. August

Molecular Pathology Research Laboratory

Professor Hamish Scott

AML Workshop Presenter

Australasian Leukaemia & Lymphoma Group 2014 Scientific Meeting. Sydney, Australia. November

Invited Speaker and Workshop Presenter

Australasian Genomic Technologies Association (AGTA). Melbourne, Australia. October

Invited Speaker

Familial Aspects of Cancer 2014 Research and Practice. Tweed Heads, Australia. September

2nd National Translational Health Capability Symposium. Brisbane, Australia. July

Conference Committee

The Seventh Barossa Meeting 'Cell Signalling in Cancer Biology and Therapy.' Barossa Valley, Australia. November

Molecular Regulation Laboratory

Professor Sharad Kumar

Invited Speaker

Ozophagy Meeting. Melbourne, Australia. February

39th Lorne Conference on Protein Structure and Function. Lorne, Australia. February

Perkins Institute. Perth, Australia. April

EMBO Conference on Cellular Signalling and Cancer Therapy. Cavtat, Croatia. May

Gordon Conference on Cell Death. West Dover, VT, USA. June

Cold Spring Harbor Asia Conference: Protein Modification and Homeostasis. Suzhou, China. June

Australian Fly Meeting. Warburton, Australia. September

ComBio 2014. Canberra, ACT. September

The 5th Cell Death and Disease Symposium on Cancer and Stem Cells. Changzhou, China. October

International Proteostasis and Disease Symposium. Wollongong, Australia. November

Session Chair

ComBio 2014. Canberra, Australia. September

Dr Donna Denton

Invited Speaker

ComBio 2014. Canberra, Australia, September.

Australian Fly Meeting. Warburton, Australia. September

Co-Convenor

Ozophagy Meeting. Melbourne, Australia. February

4th Adelaide Cell and Developmental Biology Meeting. Adelaide, Australia. November

Dr Joey Puccini

Invited Speaker

Australian Society for Medical Research (ASMR). Adelaide, Australia. June

Dr Claire Wilson

Invited Speaker

4th Adelaide Cell and Developmental Biology Meeting. Adelaide, Australia. November

Molecular Signalling Laboratory

Professor Stuart Pitson

Session Co-Chair

ComBio2014 Conference. Canberra, Australia. September

Dr Joanna Woodcock

Invited Speaker

2nd International Workshop on Molecular Medicine of Sphingolipids. Kloster Banz, Germany. October

Dr Jason Powell

Session Chair

ASMR SA Conference. Adelaide, Australia. June

Myeloma Research Laboratory

Professor Andrew Zannettino

Invited Speaker

Sydney Cancer and Bone Meeting, Myeloma and Bone, ANZAC Institute. Sydney, Australia. November

Garvan Institute, Bone Group Meeting. Sydney, Australia. November

Dr Kate Vandyke

Invited Speaker / Oral Presentation:

Multiple Myeloma Research Foundation Symposium. San Francisco, USA. December

American Society for Hematology 56th Annual Meeting. San Francisco, USA. December

South Australian Blood Club Translational Research Meeting. Adelaide, Australia. November

Mr Krzysztof Mrozik

Speaker

Haematology Society of Australia and New Zealand Annual Scientific Meeting. Perth, Australia. October

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

Dr Melissa Cantley

Invited Speaker

ACMM23 & ICONN 2014 Conference. Adelaide, Australia. February

Group of Eight (G08) supported Fellowship, 64th Lindau Nobel Laureate Meeting. June–July

Neurovascular Research Laboratory

Dr Quenten Schwarz

Chair

Post-Doctoral Short Talks session, South Australian ANZSCDB State Meeting, UniSA. Adelaide, Australia. November

Invited Speaker

11th World Congress of Society for Brain Mapping and Therapeutics. Sydney, Australia. April

10th Asia Pacific Craniofacial Conference. Adelaide, Australia. October

3rd Meeting of the Australian Network of Cardiac and Vascular Developmental Biologists. Melbourne, Australia. December

Dr Sophie Wiszniak

Invited Speaker

3rd ANCVDB Meeting. Melbourne, Australia. December

Adelaide Protein Group Early Career Researcher Early Bird Award Finalist. Adelaide, Australia. June

Ms Rachael Lumb

4th Cell and Developmental Biology State Meeting of the ANZSCDB. Adelaide, Australia. November

Translational Oncology Laboratory

Professor Michael P Brown

Chair

GSK Melanoma Launch Meeting. Adelaide, Australia. April

Chair, Independent Steering Committee and Session Chair

GSK Melanoma Masterclass. Melbourne, Australia. July

Dr Tessa Gargett

Invited Speaker

Australasian Society for Immunology Annual Scientific Meeting. Perth, Australia. December

Tumour Microenvironment Laboratory

Dr Michael Samuel

Invited Speaker

Cancer Research Network, University of Sydney. Sydney, Australia. March

Biotech Research and Innovation Centre (BRIC), University of Copenhagen. Denmark. August

2014 Cutaneous Biology Meeting, Australian Society for Dermatology Research. North Stradbroke Island, Australia. September

ComBio 2014, Signalling Enzymes Symposium. Canberra, Australia. September

Conference Organisation and Session Chair

ComBio 2014, Co-chaired the Matrix, Migration & Mechanobiology Symposium. Canberra, Australia. September

Co-Organiser and Session Chair

4th Adelaide Cell and Developmental Biology Meeting. Adelaide, Australia. November

Vascular Biology and Cell Trafficking Laboratory

Associate Professor Claudine Bonder

Invited Speaker

Australasian Society of Clinical Immunology and Allergy (SA Branch Meeting). March

Walter and Eliza Hall Institute, Division of Immunology. Melbourne, Australia. July

4th Proteomics and Bioinformatics Conference. Chicago, USA. August

SA Breast Cancer Study Group. Adelaide, Australia. September

Cancer Council SA. Adelaide, Australia. October

Australasian Society for Immunology. Wollongong, Australia. December

Session Chair

Australian Vascular Biology Society. Adelaide, SA. September

Dr Lisa Ebert

Invited Speaker

Basil Hetzel Institute. Adelaide, Australia. August

Society for Melanoma Research Annual Congress. Zurich, Switzerland. November

Dermatology Department, University Hospital Zurich. Zurich, Switzerland. November

Awards

Acute Leukaemia Laboratory

Dr Saumya Samaraweera

Leukaemia Foundation Poster Prize, 5th New Directions in Leukaemia Research (NDLR) Meeting, Noosa, Queensland

Dr Michelle Perugini

ASH Abstract Achievement Award

Cytokine Receptor Laboratory

Professor Angel Lopez

Elected a Fellow of the Australian Academy of Health and Medical Sciences (FAHMS)

Drug Discovery and Development Laboratory

Mr Vaskor Bala

Best Poster Award, Pharmaceutical Sciences World Congress 2014, Melbourne, Victoria

Ms Theodosia Teo

Best Poster Award, UniSA Division of Health Sciences Postgraduate Expo 2014, Adelaide, South Australia

Ms Sarah Al Haj Diab

Third place, Health Division Three Minute Thesis, University of South Australia, Adelaide, South Australia

Gene Regulation Laboratory

Dr Simon Conn

Best Oral Presentation, 4th ANZSCDB Meeting, Adelaide, South Australia

Ms Caroline Phillips

The University of Adelaide Medal for Honours Year, Adelaide, South Australia

Lymphatic Development Laboratory

Dr Genevieve Secker

Best Postdoctoral Poster Presentation, 4th Adelaide Cell and Developmental Biology Meeting, Adelaide, South Australia

Dr Drew Sutton

Best Postdoctoral Poster Presentation, 3rd Meeting of the Australian Network of Cardiac and Vascular Developmental Biologists, Melbourne, Australia

Mast Cell Laboratory

Dr Kwok Ho (Dave) Yip

CCB Early Career Research Award, Adelaide, South Australia

Dr Natasha Kolesnikoff

Finalist, Ross Wishart Memorial Award, ASMR SA Annual Scientific Meeting, Adelaide, South Australia

Mr Houng Taing

PhD Student Presentation Award, ASMR SA Annual Scientific Meeting, Adelaide, South Australia

PhD Student Presentation Award, ANZSCDB Scientific Meeting, Adelaide, South Australia

Ms Viera Stanekova

Ian Gould Experimental Science Grant Scholarship, University of South Australia

Chancellor's Letter of Commendation for Honours Degree, University of South Australia

University of South Australia Honours Medal

Molecular Pathology Research Laboratory

Ms Alicia Byrne

Karen Snow-Bailey Award for Best Oral Presentation by an MGSA member, Human Genetics Society of Australasia, 38th Annual Scientific Meeting, Adelaide, South Australia

Molecular Regulation Laboratory

Professor Sharad Kumar

Elected a Fellow of the Australian Academy of Health and Medical Sciences (FAHMS)

Dr Joey Puccini

Centre for Cancer Biology Best Student Primary Research Publication

Australian Society for Medical Research Ross Wishart Memorial Award

PhD (University of Adelaide)

Mr Pranay Goel

Medical Staff Society Travel Award

EMBL Australia PhD Student Travel Grant

Ms Tianqi (Cindy) Xu

Student Poster Award, ANZSCDB, Adelaide

EMBL Australia Student Travel Grant

Molecular Signalling Laboratory

Ms Heidi Neubauer

Most Outstanding Poster Award, Adelaide Protein Group, Adelaide, South Australia

Winner, University of Adelaide Faculty of Sciences Three Minute Thesis Competition, Adelaide, South Australia

Dr Jason Powell

Best Primary Research Publication from a CCB Researcher

Myeloma Research Laboratory

Ms Kimberley Evans

APA Postgraduate Award

New Colombo Grant for Study Tour of Japan Award

State Dinner in Canberra in honour of the Japanese Prime Minister, His Excellency Mr Shinzo Abe

Dr Natasha Friend

APA Postgraduate Award

Dr Ankit Dutta

Leukaemia Foundation of Australia Research Award, PhD Scholarship

Dr Melissa Cantley

University of Adelaide Fellowship to attend Science in the Dome Event May 2014

2014 ASMR SA Branch Annual Scientific Meeting Ross Wishart Finalist

2014 ASMR Domestic Research Award

Mr Krzysztof Mrozik

School of Medical Sciences HDR Travel Award, University of Adelaide

Neurovascular Research Laboratory

Dr Quenten Schwarz

Australasian Neuroscience Society AW Campbell Award for Early Career Research Excellence

Ms Rachael Lumb

International Society of Differentiation Best Poster Award, London, UK

Vascular Biology and Cell Trafficking Laboratory

Associate Professor Claudine Bonder

Australasian Society of Clinical Immunology and Allergy: Paul Clarke Poster Award

Dr David Dimasi

Australian Vascular Biology Society at State of the Heart Congress: Early Career Researcher Poster Prize

Ms Kate Parham

Australian Vascular Biology Society at State of the Heart Congress: Best PhD Oral Presentation Award

Australasian Society for Immunology, Student Retreat: Best PhD Oral Presentation Award

Ms Wai Yan Sun

Australian Vascular Biology Society, student travel bursary to attend the International Vascular Biology Meeting, Kyoto, Japan

Ms Emma Thompson

Australian Vascular Biology Society at State of the Heart Congress: Student Poster Award

CCB Early Career Research Award
Ms Fabienne Payen (Miltenyi Biotec), Dr David Yip (recipient) and Ms Briony Forbes (Australian Society of Biochemistry and Molecular Biology)
Sponsors: Miltenyi Biotec and **Australian Society of Biochemistry and Molecular Biology**

CCB Best Student Primary Research Publication
Professor James McCluskey (guest speaker), Joseph Puccini (recipient), Ms Cara Fraser (Australasian Society for Immunology) and Mr Peter Harpas (Life Technologies)
Sponsors: Thermo Fisher Scientific representing Life Technologies, Genesearch and **Australasian Society for Immunology**

Best Primary Research Publication from a CCB Researcher
Professor James McCluskey (guest speaker), Dr Jason Powell (recipient)
Sponsors: Promega Corporation, Roche and **Millennium Science**

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Dr Christopher N Hahn
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Ms Parvathy Venugopal (PhD)
Dr David Yeung (with Leukemia Unit)
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Mr Alexander Lewis (Hons)

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Thank you

Notes