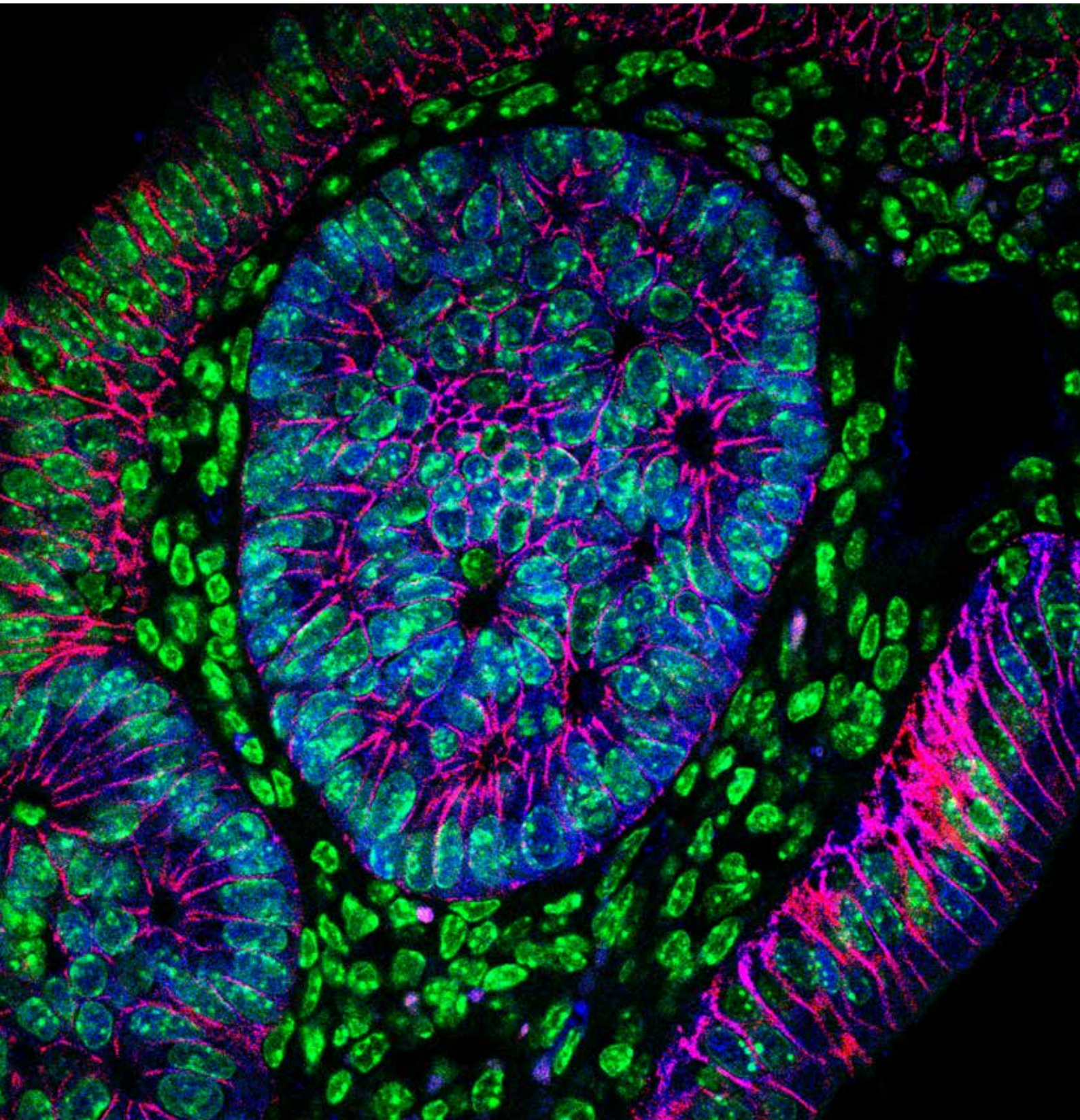
2015
Annual Report

Centre for Cancer Biology



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Centre for Cancer Biology

Centre for Cancer Biology
An alliance between
SA Pathology and the
University of South Australia

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cover image
Section through an incipient intestinal tumour, showing early stabilisation of β-catenin (blue), well before significant reduction in cell-cell contacts (magenta). Tumour and stromal nuclei are in green.

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Professor David G Lloyd

Alliance Partners Report

It gives me great pleasure to present the sixth Annual Report of the Centre for Cancer Biology (CCB) of SA Pathology and to reflect on its successes in 2015.

The CCB Alliance was formalised between SA Health and the University of South Australia 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. As a Medical Research Institute (MRI) with the largest concentration of cancer research in South Australia the CCB is also working closely with SAHMRI in complementary projects aimed at attracting funds into South Australia. Close collaborations between MRIs are important for success in grant funding and to bring to Australian patients better health outcomes. A key success in 2015 was the CCB participation in the Australian Genomics Health Alliance, a $25M commitment by the NHMRC to support the integration of genomic medicine into health care across Australia. Partnerships and alliances between the different MRIs are emerging as preferred structures by government into which future major funding such as that provided by the Medical Research Future Fund may be allocated.

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 2015 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.

The CCB continues to be strongly supported by both SA Pathology, SA Health and UniSA and a key benefit from being embedded in SA Pathology has been the ability to dramatically increase the speed and number of diagnostic tests for patients and families affected by genetic diseases at a reduced cost to the health care system. In October 2015 the CCB's genomics facility became the first Australian laboratory to receive official accreditation to test the coding regions of all 20,000 human genes in a single test, illustrating SA Pathology's national leadership in innovative patient care. For this achievement the CCB ACRF Genomics facility was presented with the SA Health Excellence Award. Also, with the support of UniSA and the South Australian Department of State Development (DSD), the CCB was able to establish a Joint Laboratory with the Institute of Molecular and Cell Biology of A*STAR in Singapore. The Joint Laboratory, headed by Professor Vinay Tergaonkar, will study the role of inflammation in cancer and brings much needed new expertise to South Australia as well as access to state of the art infrastructure. This new 'medical research highway' between Adelaide and Singapore will facilitate innovation in the whole of the new South Australian Health and Biomedical precinct.

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.

The admission of the CCB to the Australian Association of Medical Research Institutes (AAMRI) confirms the national recognition of the CCB as a Medical Research Institute that 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. Through the CCB, with its major new findings and inventions of new genomics tests and new forms of drugs, immunotherapies and personalised medicine (covered by patents), SA Pathology is actively contributing to a better and more effective patient care in South Australia.

Dr Janice Fletcher
Acting Executive Director
SA Pathology

When UniSA and SA Pathology joined forces to create the CCB Alliance we knew that this was a partnership that would make a huge difference to cancer and the way it is treated. In 2015 we celebrated the second year of this partnership which has gone from strength to strength as we promote and support medical research and put the value of our discoveries into delivering high quality health care services.

Together UniSA and CCB enhance each other's efforts. The CCB concentrates on research excellence and support for personalised DNA targeted treatments for cancer, and other UniSA research concentrations work in the quality use of medicines, pharmaceutical science and pharma-cokinetics research. The partnership 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. The value of this collaboration has been proven with some remarkable success stories that were widely acknowledged during the year.

The year began with Professor Angel Lopez and Professor Sharad Kumar both being elected Fellows of the Australian Academy of Health and Medical Sciences. It concluded with the CCB and the University's aligned research in Biochemistry and Cell Biology, Clinical Sciences and Pharmacology and Pharmaceutical Sciences all earning the highest possible world-class rating in the 2015 Excellence in Research for Australia (ERA) results.

That rating places research work at the CCB and research concentrations across the University's Division of Health Sciences and Sansom Institute in an elite field of world-class research in the vital area of cancer, including a wide range of specific cancers such as leukaemia and bone cancer and also a range of other serious diseases such as diabetes and epilepsy.

Other successes notched up during the year include the award of a $2M grant to establish the world-class ACRF Cancer Discovery Accelerator facility in Adelaide and the head of the CCB's Neurovascular Research Laboratory, Dr Quenten Schwarz being awarded a four-year Future Leader Fellowship from the Heart Foundation to further his research. Professor Sharad Kumar, who has contributed to many significant discoveries with broad implications in biomedicine, was awarded the highest level (SPRF) of NHMRC fellowship.

I congratulate all of the brilliant minds at the Centre for Cancer Biology and the University's Health Sciences Division for the valuable work they are doing to improve the health of all Australians.

In 2018, of course, we'll all move together into a building befitting the 21st century nature of our research. The $230M Health Innovation Building will support a collaborative and holistic approach to health research and will be an integral part of the South Australian Health and Biomedical Precinct on North Terrace. It will open up a number of new health research, teaching and community engagement opportunities and I for one can't wait to get started.

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

Professor Angel Lopez

Professor Sharad Kumar

The CCB team after the ACRF interview

Advisory Board: Front: Profs Angel Lopez, Ian Frazer AC, Sharad Kumar
Back: Profs Brendan Crabb AC, Christina Mitchell, Michelle Haber AM, Joe Trapani

Directors Report

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

2015 saw a strong performance by the Centre for Cancer Biology and we are pleased to record the major highlights.

We are delighted to report that in March the Centre for Cancer Biology was recognised as a Medical Research Institute and admitted to the Australian Association of Medical Research Institutes (AAMRI), the peak body of medical research in Australia. This is a great accolade to our critical mass and excellence in discovery and translation of medical research, as much as a significant responsibility to continue to improve people's health and work with our Australian colleagues to strengthen medical research in Australia. In this pursuit we are privileged to count on distinguished colleagues who kindly agreed to give their time and expertise in being part of the CCB Scientific Advisory Board: Professor Ian Frazer AC (Chair, University of Queensland). Professor Michelle Haber AM (Children's Cancer Institute, NSW), Professor Brendan Crabb AC (Burnet Institute, Victoria), Professor Christina Mitchell (Monash University, Victoria) and Professor Joseph Trapani (Peter MacCallum Cancer Centre, Victoria). The advisory board met with us and gave us invaluable advice on scientific directions and our strategic framework.

Later in the year we also saw the establishment and first meeting of the Strategic Liaison Committee that brings us together with the executive of both alliance partners to support and grow the CCB. We are pleased to report that John Hill (former SA Minister for Health) was selected as the independent chair. His strong support for medical research in SA and his vast knowledge in all matters related to health gives us enormous optimism for the future. It is worth noting that both Ian Frazer and John Hill jointly launched the CCB in 2009. It is wonderful to see the faith they maintain in us and continue to be our champions.

In 2015 we continued our two-pronged approach to conquer cancer. We made significant discoveries on the basic mechanisms that underpin cancer and, on the translational front, several candidate drugs are progressing to clinical trials. The work at the CCB is also leading the way for new molecular diagnostics and prognostic tests to help with early cancer detection and better tailored treatments of the future. The research at the CCB continues to provide unique insights into fundamental understanding of how the human body works while also bringing more immediate and tangible benefits to the healthcare of patients. Our work was published in 154 scientific articles and the intellectual property protected through patents. Details of publications by each laboratory can be seen at the end of this report but we would like to highlight the work by Professor Greg Goodall and his group who made a major discovery on a new mechanism by which our genetic information is processed in health and disease. This was published in arguably the most prestigious journal, *Cell*, a wonderful achievement that has gained the attention of the international scientific community.

We are pleased to highlight the strong performance by our Australian Cancer Research Foundation (ACRF) Genomics Facility. Its molecular diagnostic service provides the information required by Royal Adelaide Hospital (RAH) and other oncologists to decide on specific cancer treatments. The method it uses provides additional benefits for RAH cancer patients by diagnosing other cancer mutations that can allow entry to clinical trials of new anti-cancer drugs. In 2015, the ACRF Genomics Facility developed new methods for the early detection of cancer and genetic defects. Its exome sequencing platform that now allows us to test for 50 genes simultaneously is already making a difference to SA patients being NATA accredited for routine diagnostic services, a first in Australia. We congratulate the team led by Professor Hamish Scott which received the SA Award for Excellence in Non-Clinical Research at the SA awards night in August.

We continue to bring new technologies into SA through the help of several charities and philanthropic support. In 2015 we were delighted to be selected to receive $2M in infrastructure funding from ACRF to establish the ACRF Discovery Accelerator Facility.

A magnificent team effort ably led by Professor Greg Goodall and boosted by the participation of our new State Australian Research Fellow, Professor Vinay Tergaonkar. The additional contributions from UniSA, the Beat Cancer Project and Therapeutic Innovation Australia will further enhance this unique facility for the benefit of the new Health and Biomedical Precinct as a whole.

A major endeavour of the CCB is to build capacity in medical research by partnering with the best. We were therefore delighted when after protracted negotiations we formalised the establishment of the CCB-IMCB Joint Laboratory, a partnership between the CCB and the Institute of Molecular and Cell Biology (IMCB) of A*STAR in Singapore, to study the role of inflammation in cancer. We are very grateful to the Department of State Development, particularly Professor Andy Dunbar, and Drs Jenny Carter and Ross McLennan of UniSA, for underpinning this effort. The 'Joint Lab' is being led by Professor Vinay Tergaonkar, a world expert in cell signalling in cancer, and strongly supported by the IMCB and its Executive Director Professor Wanjin Hong. We are indebted to Professor Hong for his friendship and support to enable this partnership to happen. This new medical research link between Adelaide and Singapore should bring tangible benefits to both in terms of close scientific interactions, student training and development, and promises to be an attractive new model for Australia to collaborate with like-minded medical research institutes in the region.

As one of the biggest assets of the CCB is its culture and its people we were delighted to see the recognition and success in 2015 of many faculty members. Professors Greg Goodall and Hamish Scott were both admitted as Fellows of the Australian Academy of Health and Medical Sciences. A number of new highly competitive fellowships were awarded, including an NHMRC SPRF to Professor Sharad Kumar, a Peter Nelson Leukaemia Research Fund Senior Fellowship to Dr Hayley Ramshaw, a Mary Overton Fellowship to Dr Dave Yip and a National Heart Foundation Fellowship to Dr Quenten Schwarz. Dr Schwarz also won the 2015 South Australian Leading Light Award for his achievements in developmental biology. Several CCB members won competitive NHMRC project grants: Professors Kumar and Lopez; Associate Professors Bonder and Grimbaldeston, and Drs Ramshaw and Samuel. Dr Michael Samuel's success with two NHMRC grants was soon followed in December with a landmark article in Developmental Cell detailing the fundamental mechanism of skin healing and pioneering a candidate drug that shortens the time needed for healing in half.

CCB staff both contribute to and benefit from close interactions with the RAH. CCB members have been awarded RAH research fellowships including the Florey and Mary Overton, and CCB laboratory heads serve on clinical project grant, PhD scholarship and research fellowship committees of RAH. CCB members continue to build and maintain collaborations with RAH clinicians that help to establish the clinical relevance of research work with the additional benefit of enhancing the prospects for future funding in an increasingly competitive funding environment.

In July we held our Annual General Meeting with Professor Brendan Crabb AC, Executive Director of the Burnet Institute, as our keynote speaker. Brendan played a major role in the establishment of the Medical Research Future Fund (MRFF) so it was fascinating to hear about how the process unfolded, the persistent efforts by him and Doug Hilton, ably supported by the political lobbyist Ian Smith, and the fantastic opportunity that the MRFF represents for the future of medical research in Australia. As is customary at our AGM, Brendan presented several prizes and awards to CCB staff. Best Primary Research Publication from a CCB Researcher went to Dr Dave Yip and colleagues for their paper *Mechanisms of vitamin D3 metabolite repression of IgE-dependent mast cell activation*. Best Student Primary Research Publication Award went to Duyen Pham for her paper *Enhanced expression of transferrin receptor 1 contributes to oncogenic signalling by sphingosine kinase 1*. The CCB Early Career Researcher Award went to Dr Claire Wilson.

In November, under the leadership of Professor Stuart Pitson, we hosted our biennial Science Amongst the Vines™ series of meetings with the 7th Barossa Meeting on the theme of Cell Signalling in Cancer Biology and Therapy. We were delighted with the calibre of the international speakers and the vibrant atmosphere where students and all CCB staff mixed seamlessly with our guests to enjoy a feast of science (see following specific report by Professor Pitson).

Finally we would like to thank SA Pathology/SA Health and the University of South Australia for helping us strengthen and grow the CCB. Our vision and delivery of better health outcomes would not be possible without the strong support from their executives. Special thanks also goes to Professor Heddy Zola for his advice, Royal Adelaide Hospital patients, our supporters, and to all the staff for their continuous hard work and their team spirit.

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

Professor Sharad Kumar, Dr Leanna Read, joint Clifford Prize recipients Professor Inder Verma and Professor Jane Visvader, and Professor Angel Lopez

7th Barossa Meeting

On 18–21 November 2015 we hosted our 7th Barossa Meeting on the theme of Cell Signalling in Cancer Biology and Therapy. These biennial Barossa *Science Amongst the Vines*™ meetings are now established as one of the premier cell signalling meetings on the international scientific calendar, with a strong focus on discussing cutting edge discoveries in cell signalling and how this knowledge can be exploited to improve human health.

As with previous meetings in this series, this instalment hosted numerous high profile international speakers, including Rafi Ahmed (Emory University, USA), Ivan Dikic (Goethe University, Germany), Vishva Dixit (Genentech, USA), Zvi Fridlender (Hadassah-Hebrew University, Israel), Wanjin Hong (IMCB, Singapore), Richard Marais (Cancer Research UK Manchester Institute, UK), KJ Patel (Cambridge University, UK), Fred de Sauvage (Genentech, USA), John D Scott (University of Washington, USA), Inder Verma (Salk Institute, USA), Xiaomeng Wang (IMCB, Singapore) and Junying Yuan (Harvard University, USA). A further 13 invited interstate and 16 invited local speakers completed an impressive program that attracted the maximum capacity of 130 delegates to the meeting.

The meeting, for which a report has been published (Grimbaldeston M *et al*, *Cell Death and Disease* 7:e2129, 2016), was comprised of nine scientific sessions, including those entitled Cancer Cell Signalling Networks, Translational Medicine, Cancer Genomics, Molecular Oncology, Tumour Microenvironment, Cancer Signalling Architecture, Cancer Cell Biology, and Immunotherapies, as well as a poster session where 39 posters were presented. While covering several aspects of cancer, all sessions converged on the main theme of the meeting of understanding how cell signalling pathways direct the biology of cancer, and how to exploit this for the development of new therapies.

Our Barossa Meetings also provide a vehicle for the presentation of the Clifford Prize for Cancer Research for outstanding international achievement in cancer research. In 2015 we had joint recipients in Professor Inder Verma of the Salk Institute in La Jolla, California and Professor Jane Visvader of the Walter and Eliza Hall Institute in Melbourne. The Clifford Prize Selection Committee took into account the special mentor-mentee relationship of Professors Verma and Visvader, and sought to highlight the importance for Australian scientists to spend time in the best overseas laboratories. The Prize, presented by Dr Leanna Read, Chief Scientist for South Australia, comprised perpetual and keepsake trophies crafted by Nick Mount, and magnums of Penfolds Grange Hermitage. With this award Professors Verma and Visvader join an illustrious list of past winners which includes Axel Ullrich (Munich), Tony Hunter (San Diego), John Dick (Toronto), Vishva Dixit (San Francisco) and Arul Chinnaiyan (Ann Arbor).

As always the Barossa Meeting provided a rewarding four days of high-quality science, complemented by equally satisfying South Australian food and wine. The social highlight of the meeting was the food of Elli Beer at the Clifford Prize Dinner held at The Farm, Barossa Function Centre, where delegates were also treated to an array of carefully selected quality wines, introduced by wine expert John Leydon.

The Barossa Meetings continue to showcase the quality of South Australian science and provide outstanding opportunities for local researchers to mix with other world class scientists from interstate and abroad in a convivial, but scientifically rigorous atmosphere conducive to the development of collaborations.

Professor Stuart Pitson
Co-Convenor, 7th Barossa Meeting

Centre for Cancer Biology
2015 Laboratory Reports

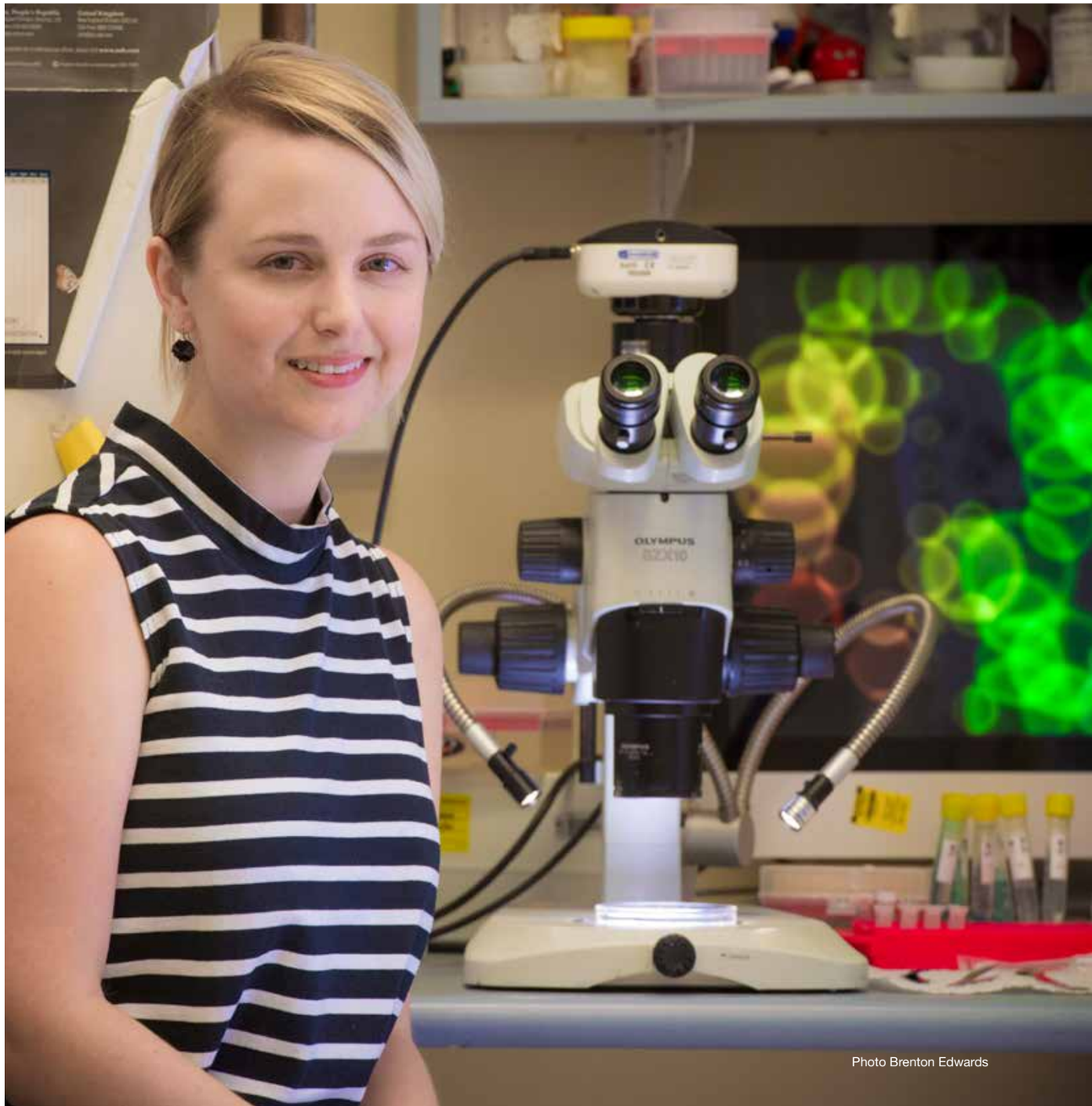
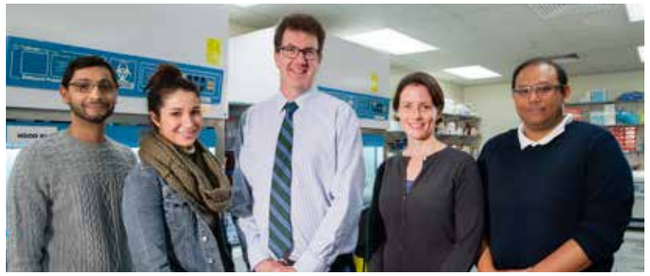


Photo Brenton Edwards

Saumya Samaraweera, Sarah Bray, Richard D'Andrea,
Nick (Ka Leung) Li, Tran Nguyen



Mahmoud Bassal, Nissa-Taylor Doswell, Ian Lewis,
Debora Casolari, Kyaw ZeYa Maung

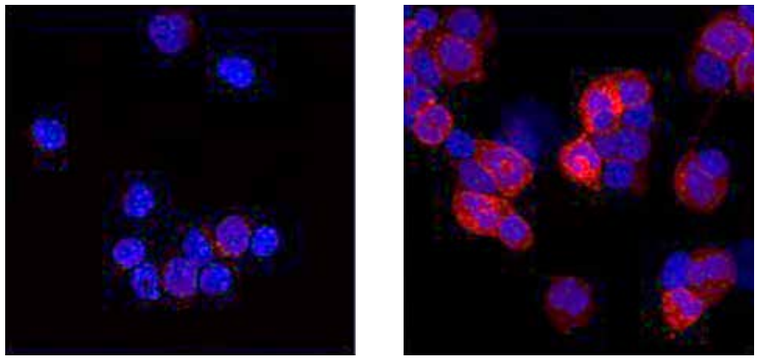
Acute Leukaemia Laboratory

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 lab 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) and related receptors in the Philadelphia Chromosome-negative Myeloproliferative Neoplasms (MPN), a group of chronic diseases associated with a predisposition for AML.



Immuno-fluorescent imaging showing that β-integrin expression (red) is reduced on blood progenitor cells when the *KLF5* gene is genetically ablated in mice (left panel), compared to control cells from wild-type mice (right panel)

Key discoveries 2015

The role of *KLF5* in myeloid differentiation

Krüppel-like factor 5 (Klf5) encodes a zinc-finger transcription factor and has been reported to be a direct target of C/EBPα, a master transcription factor critical for formation of granulocyte-macrophage progenitors (GMP) and leukaemic GMP (L-GMP). Using an *in vivo* blood-specific gene-ablation ($Klf5^{\Delta/\Delta}$) mouse model we have demonstrated that loss of *Klf5* function leads to a progressive increase in peripheral white blood cells, associated with increasing splenomegaly. Haematopoietic stem and progenitor cells were significantly reduced in the bone marrow of $Klf5^{\Delta/\Delta}$ mice and increased in the spleen. Using immuno-fluorescent techniques we have also shown expression of key adhesion molecules on hematopoietic progenitors is reduced, which suggests that the increased stem and progenitor cells in the spleen results from reduced retention in the bone marrow. $Klf5^{\Delta/\Delta}$ mice also show a significant reduction in the fraction of neutrophils in peripheral blood and bone marrow, and increased frequency of eosinophils in the peripheral blood, bone marrow and lung. These studies demonstrate that *Klf5* possesses dual functions in regulating hematopoietic stem and progenitor proliferation and localisation in the bone marrow, as well as influencing haematopoietic lineage choice of more committed progenitors, promoting increased neutrophil output at the expense of eosinophil production.

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 145 AML samples obtained (with ethics approval) from the SA Cancer Research Biobank (SACRB) 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 enrichment in the AML cohort of germline deleterious mutations in genes associated with the recessive disease Fanconi Anaemia (FA, FANC genes). While FA is caused when both copies of a single FANC gene are affected by deleterious mutations, and is associated with an extremely high risk of AML, our sequencing data suggests that rare heterozygous deleterious mutations affecting *FANC* genes may confer a more subtle phenotype associated with accumulation of mutations in blood stem cells over time, and increased risk of AML in adulthood. We are now investigating whether AML patients with heterozygous FANC mutations are relatively more sensitive than non-leukaemic cells to current clinical agents that target alternative DNA repair pathways that are essential when FANC-mediated DNA repair is impaired.

Clinical trials in AML

Our fundamental research is complemented by a number of clinical studies testing new therapies in AML and carried out in the Acute Leukaemia Laboratory, the Department of Haematology at SA Pathology and the Royal Adelaide Hospital. These studies give patients access to novel therapies, and parallel laboratory studies investigating the effects of these novel treatments on leukaemic cells from patients leads to improved understanding of the mechanism and factors that affect response.

Ongoing studies include:

- A clinical trial investigating agents that target the most common molecular mutation in the FLT3 gene, which is associated with an adverse outcome in AML. We are currently involved in clinical trials evaluating the role of two different inhibitors of FLT3, sorafenib and quizartinib. If these studies prove successful, it will open up new treatments for this high-risk group of patients.
- Testing whether a DNA methylation mark associated with the DNA methylation of the Growth Arrest and DNA Damage 45A gene (GADD45A) provides a marker for response to specific inhibitors targeting the products of mutant IDH genes. The IDH2 mutation is found in 10–15% of AML patients and a clinical trial evaluating a specific inhibitor of mutant IDH2 is ongoing in patients with relapsed AML.
- Coordination by our laboratory of a sponsored, multi-centre research study to determine the feasibility of using Next Generation Sequencing (NGS) approaches for assessing the efficacy of novel agents in targeting minimal residual disease in AML.

Outcomes for the Community

Our research includes molecular and genetic studies to increase fundamental knowledge about AML disease initiation, progression and response to therapy, linked to a number of studies to translate laboratory research findings through pre-clinical models to clinical trials. For example, the laboratory findings discussed above raise the possibility that AML cases with mutations affecting FANC genes may represent a new group that can be targeted with tailored therapies, already in clinical trial for other cancers. The ongoing clinical trials are of direct benefit to AML patients, allowing novel therapies to be tested with the hope of improving outcomes for high-risk AML patients currently facing poor prognoses with standard therapy options.

Xiaochun Li, Yeesim Khew-Goodall, Freya Gehling, Leila Belle, Ana Lonic

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 and metastatic state. In solid cancers, which constitute 80% of all 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.

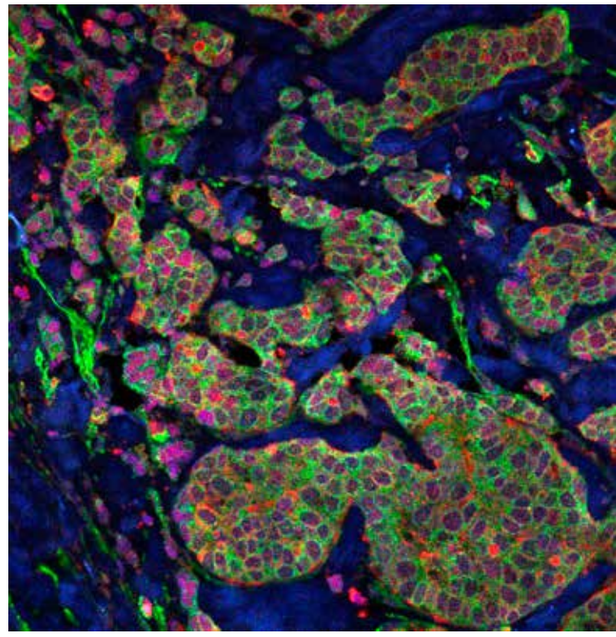
Molecular regulation of cell invasion

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.

Key discoveries 2015

This year we identified a novel regulator of protein trafficking, the protein tyrosine phosphatase PTPN14, which coordinately regulates secretion of pro-metastatic factors and receptor expression on breast cancer and other cells, and which acts as a suppressor of breast cancer metastasis.

This work is published in *Science Signalling* (Belle *et al* 2015) and now forms the backbone for studies to identify all the components of the signalling pathway and its mechanism of action. Our studies will be directed towards understanding how protein trafficking outcomes are regulated in normal cells and how this important signalling pathway is dysregulated in breast cancer.

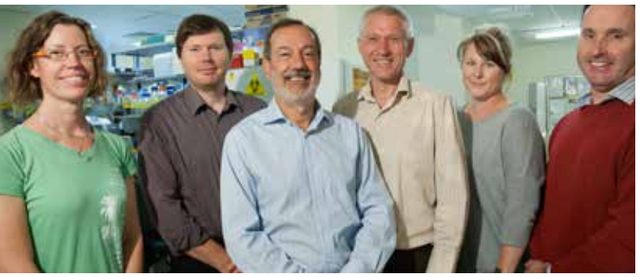


Novel phosphorylation site on PKCdelta detected in human breast cancer

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. Our studies which identified a novel pathway regulating protein trafficking have revealed some potential new biomarkers for identifying triple negative breast cancers that have increased likelihood to metastasise. Further work will be aimed at identifying therapeutic targets for this group of cancers.

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 five, 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.



Ceilidh Marchant, Denis Tvorogov, Angel Lopez, Frank Stomski, Melanie Pudney, Tim Hercus

Winnie Kan, Hayley Ramshaw, Mara Dottore, Anna Sapa
Helena van Schalkwyk, Rebecca Wright

Cytokine Receptor Laboratory

Professor Angel Lopez MBBS PhD FRCPA FAHMS FAA

Cytokines are regulatory molecules that control immune functions, inflammatory responses and haematopoiesis. Cytokines act via specific receptors on the cell surface and maintain homeostasis until cellular responses are required. Our laboratory is interested in the role of the family of cytokines known as the beta common (βc) family. This includes GM-CSF, IL-3 and IL-5.

Our work is particularly relevant in diseases such as leukaemia that exhibit abnormalities in expression and signalling by βc cytokine receptors, and in allergic disorders, like asthma, where excessive activation of βc cytokine receptors in myeloid cells in the lung contributes to restricting breathing and causing damage to the lungs.

Our major focus is to understand the how and why of GM-CSF, IL-3 or IL-5 activities in disease and to use this knowledge to develop therapies specifically targeting these cytokines or their cell surface receptors. Our program seeks to determine the detailed structure of these cytokines bound to their receptor to identify the mechanisms underlying receptor signalling and to develop new tools and candidate drugs for use in leukaemia and allergic diseases.

In collaboration with Professor Michael Parker we have solved the structure of IL-3 bound to its receptor in either a binary complex with the IL-3 receptor alpha subunit (IL3Rα) alone or as a ternary complex with IL3Rα and the βc subunit. This valuable structural information has revealed five key sites that contribute to the assembly of the cytokine receptor complex. This is already enabling a detailed understanding of how IL-3 functions and by comparison with other structures such as those already solved for GM-CSF receptor complexes, will allow us to understand why IL-3 and GM-CSF have both unique and shared biological functions.

Our translational studies with antibodies to the βc family receptors are continuing apace. The monoclonal antibody CSL362, developed with CSL Limited from our 7G3 antibody that targets the IL-3 receptor, has now been taken into Phase II/III clinical trials by Janssen Biotech Inc in patients with acute myeloid leukaemia. The monoclonal antibody CSL311 that targets the cytokine binding site of βc is being advanced together with CSL Limited and Associate Professor Michele Grimbaldeston's laboratory for the treatment of allergic inflammatory disease. In collaboration with Professor Pitson's and Dr Samuel's laboratories we are developing compounds that can regulate the function of the 14-3-3 family of proteins to cause the death of cancer cells and also regulate the healing process. Improving and accelerating wound healing in patients is high in our list of priorities as a means to prevent skin infections in diabetic patients.

As the IL-3 receptor is overexpressed in acute myeloid leukaemia as well as in chronic myeloid leukaemia in collaboration with Professor Timothy Hughes (SAHMRI and CCB) we are elucidating how this receptor signals within the cell. We are using an unbiased proteomics approach with tagged IL-3 to identify the signalling machinery coupled to the IL-3 receptor. In collaboration with Drs Jarrod Sandow and Andrew Webb (Walter and Eliza Hall Institute), we have identified a distinct set of proteins that associate with the IL-3 receptor. Of these, JAK-1 and Cullin 5 are particularly interesting as they may form part of the mechanism though which initiation and termination of IL-3 signalling is controlled.

Key discoveries 2015

Antibody CSL311 binds βc and potently blocks the activity of GM-CSF, IL-3 and IL-5

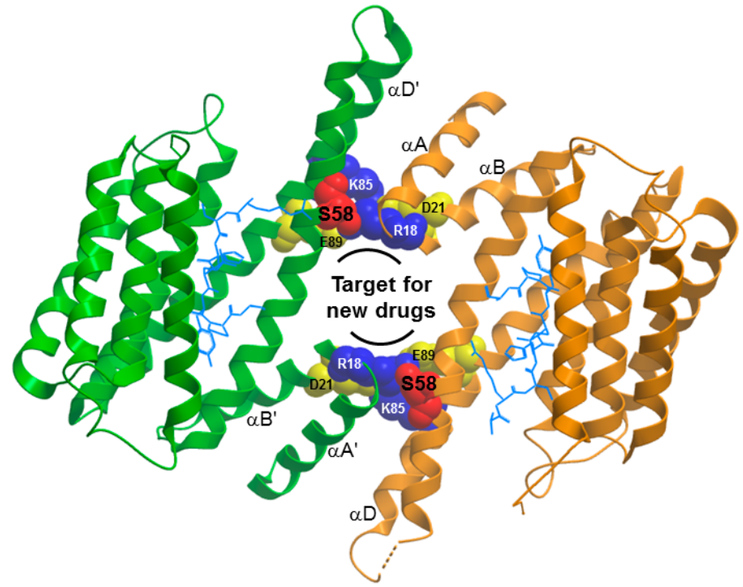
In collaboration with Professor Michael Parker and Dr Urmi Dhagat (St Vincent's Institute of Medical Research), Associate Professor Michele Grimbaldeston (CCB) and Dr Cathy Owczarek (CSL Limited), we identified, characterised and solved the structure of a human antibody that binds βc and potently blocks the activity of GM-CSF, IL-3 and IL-5 (Panousis *et al*, *MAbs* 2015). The antibody, CSL311, is being developed for treatment of chronic inflammatory diseases where the βc family of cytokines are pathologically important.

New inhibitors to 14-3-3 proteins rapidly induce the death of cancer cells

In collaboration with Professor Stuart Pitson (CCB) and Professor Robert Bittman (City University of New York) we have rationally designed new inhibitors to 14-3-3 proteins that rapidly induce the death of cancer cells (Woodcock *et al*, *Oncotarget* 2015). These compounds provide proof-of-principle for our 14-3-3 protein targeting anti-cancer approach and are the first-in-class inhibitors of 14-3-3 protein function.

14-3-3 protein regulates epidermal stromal signalling interactions

In collaboration with Dr Michael Samuel (CCB) we determined how the 14-3-3 protein regulates epidermal stromal signalling interactions and shown that our new 14-3-3 inhibitors accelerate wound healing (Kular *et al*, *Developmental Cell*, 2015).

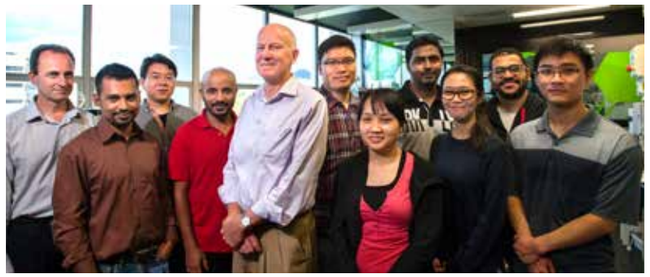


New 14-3-3 inhibitors to induce cancer cell death
The 14-3-3 family of proteins are dimeric multi-functional adaptor proteins within the cell that bind and regulate many important signalling proteins. The subunits within the 14-3-3 dimers (shown as green and orange ribbons) are held together by salt bridges (represented by blue and yellow spheres) that are conserved across the 14-3-3 family. We are identifying compounds that disrupt the salt bridges and thereby inhibit 14-3-3 proteins. A serine residue (S58, shown in red) can be phosphorylated when the 14-3-3 dimer is disrupted and provides us with a screening tool for identifying new 14-3-3 targeting drug candidates.

Outcomes for the Community

We are analysing the growth, survival and activation of blood cells using cell line models and material from patients suffering from leukaemia or allergic conditions in order to develop new therapies for people with these diseases.

Laychiluh Bantie, Sunita KC Basnet, Longjin Zhong, Shudong Wang, Saiful Md Islam, Muhammed Rahaman, Malika Kumarasiri, Cheuk Ying Tai, Yi Long



Hugo Albrecht, Vaskor Bala, Peng Li, Solomon Tadesse-Zeleke, Robert Milne, Mingfeng Yu, Sapphire Le, Stephen Philip, Theodosia Teo, Ahmed Abdelaziz, Chen Sheng Su

Drug Discovery and Development Laboratory

Professor Shudong Wang PhD FRSC

The Drug Discovery and Development Laboratory strives to develop new drug candidates targeting various cancers in the hope of bringing them to the clinic. We currently have several major programs at different stages of drug development.

Once we identify a protein target, molecules that can inhibit its oncogenic activity are designed and synthesised using our cutting-edge *in silico* and medicinal chemistry methods. Inhibitory activities of these molecules are then carefully studied *in vitro* and *in vivo* by employing a wide range of biological and pharmacological approaches. Promising drug candidates are further profiled for their efficacy, DMPK and toxicology, preparing them for clinical trials.

One of our main focuses is drug discovery targeting cyclin-dependent kinases (CDKs) are key players in cell cycle progression and transcription. Unfortunately, their aberrant behaviour is implicated in cancer progression. For example, in > 80% of cancers, CDK4/6 dysregulation can be observed. CDK7/8/9 promote transcription of the genes encoding key apoptotic regulators such as Bcl-2 family and onco-proteins such as c-Myc and HDM. Consequently, CDKs are prime targets in targeted cancer therapy. We mainly focus on CDK4/6, CDK8 and CDK9, and have identified several highly potent and selective CDK inhibitors with impressive safety profiles. We are developing them towards clinical trials for acute myeloid leukaemia, chronic lymphocytic leukaemia, and advanced prostate, breast and ovarian cancers.

We have also investigated the inhibition of MAPK-interacting kinases (Mnks), extensively. Mnks activate the eukaryotic initiation factor 4E (eIF4E), whose function is a key determinant of the Pl3K/Akt/mTOR and Ras/Raf/MEK/ERK mediated oncogenic activities. Inhibition of Mnks effectively blocks the oncogenic activity of eIF4E, while having only a minimal effect on normal development. Hence, Mnk inhibitors offer a minimally toxic route to effectively treat cancers. We have identified several classes of inhibitors which have potential to be developed as anti-leukemic agents. We are also investigating Mnk related cell and structure biology.

Key discoveries 2015

Discovering highly selective CDK9 inhibitors

CDK9 is a key transcriptional regulator and a lucrative target for the treatment of various cancer. As such, several CDK9 inhibitors have found their way to clinical trials. Unfortunately, all of them lack selectivity towards CDK9, resulting in significant off-target effects. Thus, there is a pressing need for highly selective CDK9 inhibitors. We have recently identified a highly potent class of CDK9 inhibitors (Shao *et al*, *J Med Chem* 2013) and are tailoring this scaffold to increase the selectivity significantly while maintaining potency. We expect to advance these inhibitors into clinical development and trials.

Novel CDK4/6 inhibitors as anti-cancer agents

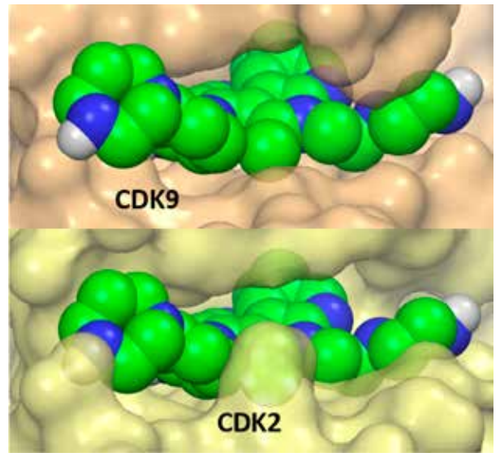
Cyclin D dependent kinases CDK4 and CDK6 play a vital role in cell cycle progression, but also maintain important functions in carcinogenesis due to their deregulation. As > 80% of tumours show aberrance in CDK4/6 cyclin D-INK4-pRb-E2F pathways, the discovery and development of highly selective inhibitors would be highly valuable in treating cancers (Tadesse *et al*, *Cell Cycle* 2015). Therefore, we set out to develop CDK4/6 inhibitors as cancer therapeutics. We have successfully identified two novel chemical classes and filed two patent applications. Several lead drug candidates have demonstrated high potency and very high specificity for CDK4/6, against a larger panel of kinases. Moreover, these compounds possessed favourable drug properties with high oral bioavailability.

Highly selective inhibitors of MAPK-interacting kinases

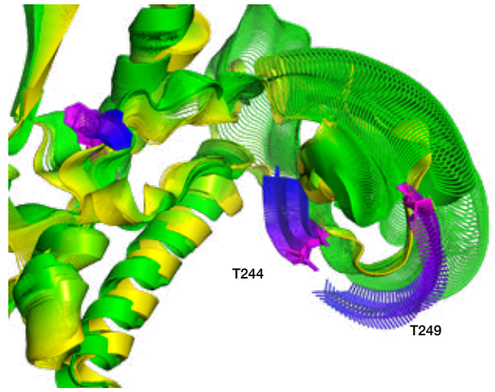
We have identified several classes of highly potent and selective Mnk inhibitors (Teo *et al*, *Mol Pharm* 2015; Yu *et al*, *Eur J Med Chem* 2015). The lead compounds suppressed proliferation and blocked cell cycle progression in cancer cells. To explore the binding modes of our inhibitors, we computationally modelled them in to the active state of Mnk2. In the process we elucidated the molecular basis of Mnk2's activation process, in unprecedented atomistic detail. These models provide us a front row view of inhibitor binding dynamics of Mnk2 (Kumarasiri *et al*, *Fut Med Chem* 2015). Interestingly, extensive *in vitro* investigations into the actions of our Mnk inhibitors demonstrate that slight changes in inhibitor structures may lead to dramatic shifts in binding modes, including binding to an unknown allosteric binding site (Basnet *et al*, *Mol Pharm* 2015).

Preclinical drug development

Our preclinical drug candidate I-073 is one of the most potent CDK9 inhibitors identified to date. It suppresses cancer survival genes and induces cancer cell apoptosis. I-073 is an orally deliverable drug with favourable pharmacological and toxicological profiles. We have shown that I-073 was highly efficacious against multiple *ex vivo* and *in vivo* cancer models, including the models of chronic lymphocytic leukaemia, acute myeloid leukaemia, prostate and ovarian cancers. We are currently working to understand its CDK9-targeted anti-cancer mechanism and to identify potential biomarkers of therapeutic outcome. This offers a very exciting therapeutic prospect with excellent potential for its progress towards the clinic.



Designing highly selective CDK9 inhibitors



Dramatic conformational changes during Mnk2 activation

Outcomes for the Community

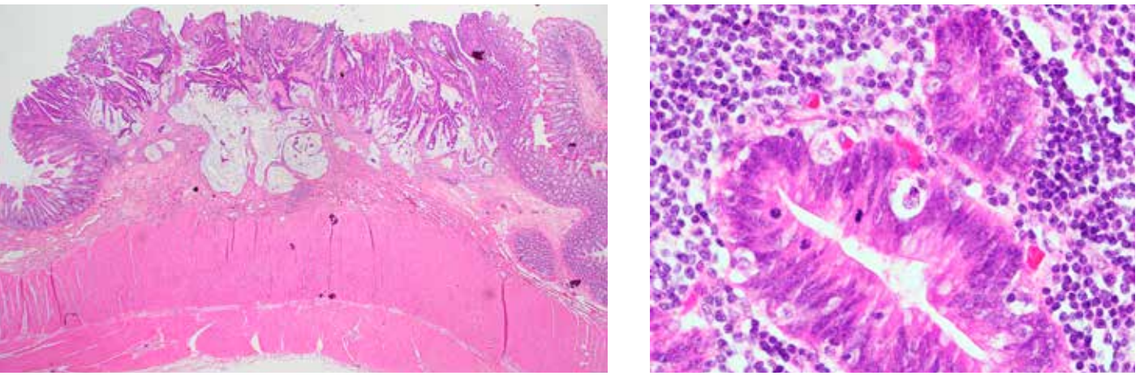
Cancer remains the most common cause of disease-borne human death. Our research aims at the development of novel, highly effective and minimally toxic anti-cancer therapies. While we strive to improve the prognosis of cancer patients, we also leave trails of invaluable scientific data and novel techniques that may assist the scientific community in tackling other complex diseases or biological puzzles.

Teresa Tin, Vinh-An Phan, Andrew Ruszkiewicz, Melissa Thompson, Stephanie Wong

Gastroenterology Research Laboratory

Associate Professor Andrew Ruszkiewicz MD FRCPA

The Gastroenterology Research Laboratory is involved in research spanning a broad spectrum of benign and malignant processes affecting the gastrointestinal tract. Our work focuses on a range of gastroenterology pathologies including malignancies of the colorectum, oesophagus, pancreas and their precursors. In colorectal cancer, we are particularly interested in screening methods and in improving the early detection of this disease.



Impact of colorectal cancer stage on survival
Detecting colorectal cancer in early clinical stage when a tumour is limited to the bowel wall without lymph node involvement or distant spread offers the best chance of cure by surgical resection alone (five year survival more than 90%). Adenocarcinoma Stage I (left image, detected by screening in asymptomatic patient) invades into the submucosa without distant spread. Involvement of regional lymph nodes carries a worse prognosis and spread of the cancer to distant organs (stage IV) is associated with the lowest five year survival (5–10%). The image on the right shows metastatic cancer in regional lymph node found in surgically resected colon from symptomatic patient.

Key discoveries 2015

Colorectal cancer
Colorectal cancer imparts a significant burden of disease to affected individuals and to the Australian healthcare system. It affects 1 in 20 individuals and is estimated to account for 13.4% of all new cancers diagnosed in 2016, second only to prostate cancer. Colorectal cancer is currently the second most common cause of cancer related death in Australia and is expected to remain so in 2016.

Precursor lesions and early, organ confined colorectal cancers are eminently treatable with surgical resection. However, advanced cases where the cancer has spread beyond the bowel wall to involve a distant organ confers a dismal prognosis with a five year survival of between 5 and 10 percent. Early detection of colorectal cancer and it's precursors has the capacity to vastly reduce the morbidity and mortality associated with colorectal carcinoma.

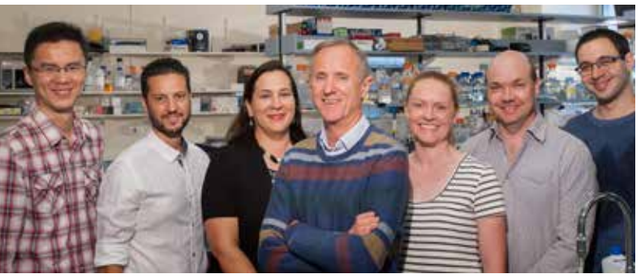
Currently, the most widely used screening test for colorectal carcinoma is faecal occult blood testing. However, participation rates in stool-based screening methods are suboptimal with only 30–40 percent of at risk individuals participating. There is strong evidence that a robust, blood based diagnostic assay would increase screening compliance resulting in increased detection of precursor lesions and early stage colorectal cancer. Our laboratory together with clinicians from major Adelaide hospitals is involved in the CSIRO-led project aiming to develop a non-invasive blood-based screening test for colorectal cancer. We successfully identified a panel of three biomarkers (IGFBP2, DKK3 and PKM2) that discriminated between controls and CRC with 73% sensitivity at 95% specificity. This project has been funded by BUPA Health Foundation and NHMRC Development grant and was named by NHMRC as one of the 'Ten of the Best Research Projects 2015'. Modification of this test is currently being evaluated as a prognostic and surveillance tool.

Eosinophilic oesophagitis
Eosinophilic oesophagitis is an increasingly recognised inflammatory disorder of the oesophagus that is responsible for significant upper gastrointestinal morbidity. The prevalence of eosinophilic oesophagitis in Australia is estimated to be 1 in 100 adults and 1 in 10,000 children and appears to be increasing. It primarily affects adults under the age of 40 and children. Children frequently present with failure to thrive and vomiting, while adults typically experience dysphagia. Of patients presenting to an emergency department with oesophageal food bolus impaction, between 46 and 63 % will have eosinophilic oesophagitis. It's aetiology, pathogenesis and natural history are not well understood. Our laboratory is undertaking research to help delineate the pathophysiology of this disease.

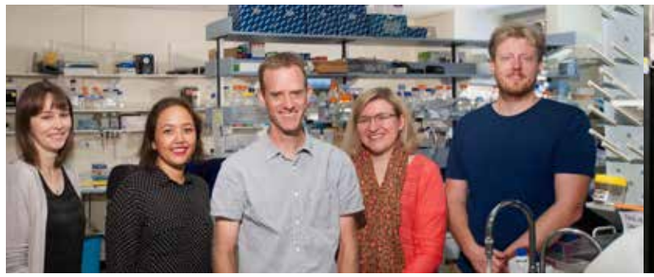
Histopathology support
Our laboratory provides histopathology support for all Centre for Cancer Biology laboratories and other researches on our campus. The facility offers tissue processing, sectioning including frozen tissue cutting, automated immunohistochemistry and tissue microarray construction. In addition, our existing collection of gastrointestinal tissue samples is a valuable source of research material for the CCB laboratories.

Outcomes for the Community

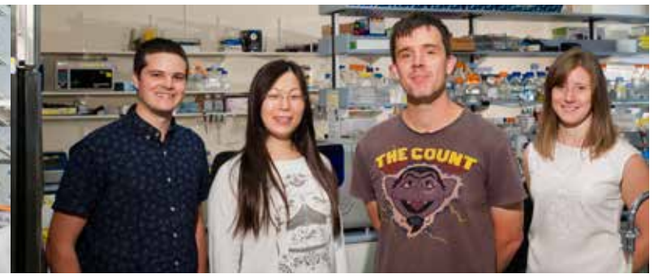
Our work towards a blood-based test for colorectal cancer will result in effective early detection and surveillance of this malignancy and will ultimately reduce the morbidity and mortality associated with this disease.



Liu Dawei, John Toubia, Rosemary Sladic, Greg Goodall, Katherine Pillman, Andrew Bert, Francisco Sadras



Caroline Phillips, Suraya Roslan, Phil Gregory, Victoria Arnet, Daniel Neumann



Klay Saunders, Feng Yu, Cameron Bracken, Kaitlin Scheer

Gene Regulation Laboratory

Professor Greg Goodall PhD, FAHMS
Dr Philip Gregory PhD Dr Cameron Bracken PhD

Our research investigates molecular mechanisms controlling cancer cell plasticity, cancer invasion and metastasis. The majority of solid cancers arise from epithelial cells. Most deaths from these cancers are due to the transition of the cancer to an invasive form, a step that involves at least a partial recapitulation of the developmental process known as epithelial to mesenchymal transition (EMT).

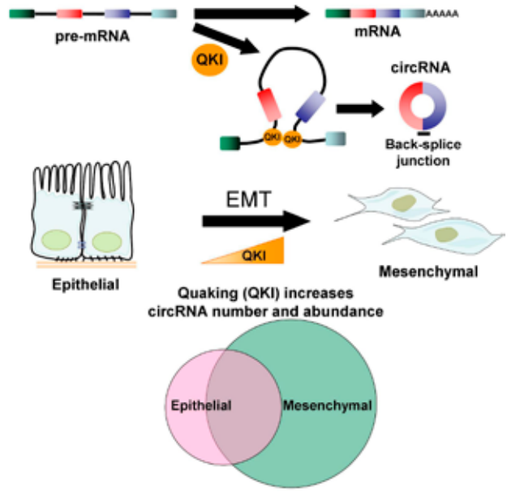
The term Epithelial-Mesenchymal Plasticity (EMP) is sometimes used in recognition of the ability of epithelial-derived cancer cells to transition partially between cell states that are intermediate between fully epithelial and fully mesenchymal.

Where cells lie within the continuum between the highly adherent, immotile, epithelial cell state and the less adherent, highly motile, mesenchymal cell state determines their invasiveness. This, along with the recent discoveries that cancer stem cells have mesenchymal-like features and that EMT typically confers resistance to chemotherapy, places studies on the mechanisms that control epithelial plasticity at the nexus of investigations of the cause of cancer progression and resistance. Our vision is to apply multidisciplinary cutting edge approaches to make significant discoveries of genes, RNAs and regulatory networks that determine the malignancy of cancers through their influence on EMP.

EMT is driven by coordinated changes in the expression of hundreds of structural and regulatory proteins. These changes are determined by integrated gene expression networks that themselves involve numerous components. We are contributing to the understanding of this process by determining how microRNAs play a central role in controlling and coordinating the regulatory networks that underlie EMT in cancer cells. In the past few years the almost ubiquitous involvement of microRNAs in shaping cellular properties has become evident, along with the recognition that longer non-coding RNAs also have a range of regulatory functions, but much remains to be discovered in this burgeoning area. We recently opened a new avenue in this area with our discovery of regulated production of circular RNAs in EMT (Conn SJ *et al*, *Cell* 2015). Our current work focusses on developing our understanding of how microRNAs, circular RNAs and their targets control EMP, and examining their consequences for cancer progression.

Outcomes
for the **Community**

Our discoveries indicate new potential avenues that could eventually lead to development of drugs that block cancer metastasis. Our previous discoveries have influenced many laboratories around the world to take up the investigation of the role of the microRNA, miR-200, in cancer metastasis. Our discovery of the production of circular RNAs during EMT is similarly likely to spark much additional investigation of their roles in cancer.
In 2015 our publications received 1,337 citations.



CircRNAs are purposefully synthesised and regulated by cell-type specific mechanisms

Key discoveries 2015

The formation of circular RNAs occurs in cells that have undergone EMT and is regulated by the RNA-binding protein Quaking

Circular RNAs are single-stranded, covalently circularised RNA molecules whose functions remain largely unknown. It has only recently become evident that this unusual class of RNA molecules is widespread in human cells; they have been overlooked until now because they are difficult to detect by traditional methods. CircRNAs have been shown to be abundant (in some cases more abundant than the linear form of the RNA), but their functions are mostly yet to be discovered.

We have made the important finding (Conn SJ *et al*, *Cell* 2015) that some circRNAs are specifically regulated in their abundance in response to TGF-β-initiated epithelial to mesenchymal transition (EMT). This indicates they have functions associated with EMT and the cellular response to TGF-β, and may be involved in promoting cell migration and invasion, hallmarks of cancer progression to metastasis. We found that the formation of these regulated circRNAs is controlled by the RNA-binding protein Quaking (QKI), which itself is regulated during EMT. Furthermore, by modulating QKI levels we show the effect on circRNA abundance is dependent on intronic QKI binding motifs. Critically, the addition of QKI motifs is sufficient to induce *de novo* circRNA formation from transcripts that are normally linearly spliced. These findings demonstrate circRNAs are both purposefully synthesised and regulated by cell-type specific mechanisms, suggesting they play specific biological roles in EMT.

Discovery of a cancer-associated small RNAs

There are several thousand annotated microRNAs in the human genome, though recent high-throughout sequencing technologies have revealed a plethora of additional microRNA-sized RNAs derived from the processing of other larger non-coding RNAs. Understanding if these also act as microRNAs is important as it could significantly expand the repertoire of microRNAs and imply even more complex layers of gene regulation. We identified a number of such candidate small RNAs and investigated their microRNA-like roles, observing both novel small RNAs capable of acting as if they are microRNAs, and other small RNAs that clearly do not function in this capacity despite their high levels of expression (Thompson DW *et al*, *Nucleic Acids Res* 2015).

We focused our attention on one of these small RNAs and identified a novel microRNA (called sno-miR-28) derived from a larger type of RNA called a small nucleolar RNA (snoRNA). We found that the key tumour suppressor p53 transcriptionally suppresses this microRNA, while sno-miR-28 in turn regulates the expression of the p53 stabilising gene TAF9B. Collectively therefore, p53, TAF9B and sno-miR-28 form a regulatory loop. Importantly, sno-miR-28 is upregulated in breast tumours and promotes cell proliferation, suggesting cancer-associated roles (Yu F *et al*, *PLoS One* 2015).

Monique Smith, Michael Beard, David Newman, Nicholas Eyre, Byron Shue

Hepatitis C Virus Research Laboratory

Associate Professor Michael R Beard PhD

RNA viruses infect hundreds of millions of people each year, causing significant morbidity and mortality. Chief among these pathogens are the flaviviruses, which include Dengue virus, West Nile virus and the *hepacivirus*, hepatitis C virus (HCV). Despite their medical importance, there are very few prophylactic or therapeutic treatments for these viruses with the exception of HCV for which there are now effective antiviral therapeutics.

Our laboratory is interested in the host cellular response to viral infection and identification of genes and signaling pathways that are induced in an attempt to control viral replication in particular 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. In 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.

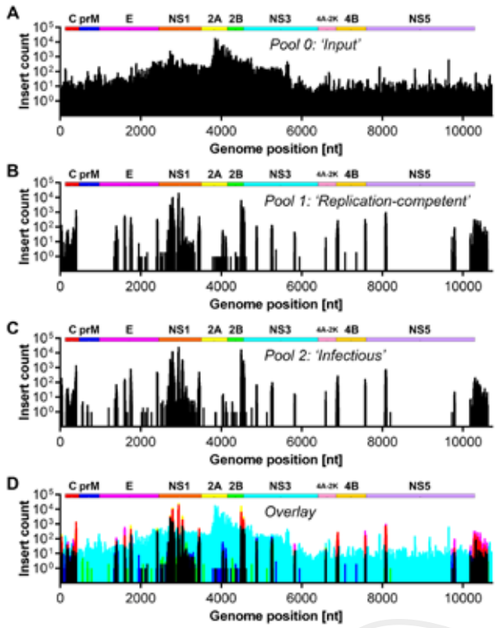
Outcomes
for the **Community**

For many viral infections including the flaviviruses there are no viable therapeutics or effective vaccines. Thus 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. Our work aims to identify essential host factors responsible for viral replication and modulators of cellular innate immunity that in the long term may be targets for antiviral therapy.

Key discoveries 2015

Mapping the Dengue virus genome

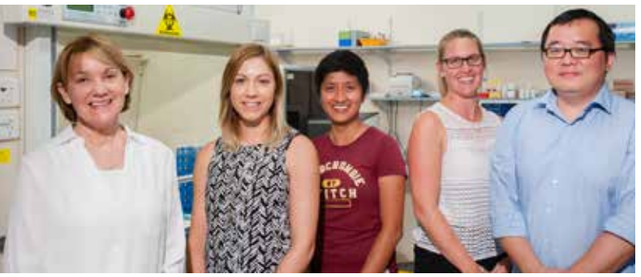
Dengue virus (DENV) is the major mosquito-borne virus that affects humans. Globally it is estimated to infect approximately 400 million people and cause 25,000 deaths each year. An improved understanding of the molecular details of the DENV life cycle will enable the development of desperately required and effective antivirals to combat DENV. In recent studies we have used high-throughput random insertion mutagenesis coupled with next-generation sequencing to identify regions of the DENV genome and encoded proteins that are essential to viral replication and infectious virus production in cell culture (functional genome mapping). We are now applying this technique to investigate and compare the impact of these mutations in other relevant cell types including macrophages and mosquito cells. Furthermore, we have used the functional genome map to identify sites that tolerate insertion of reporter proteins for advanced imaging and proteomics analysis. These studies will reveal new details about the DENV life cycle that may be targeted in antiviral drug development strategies.



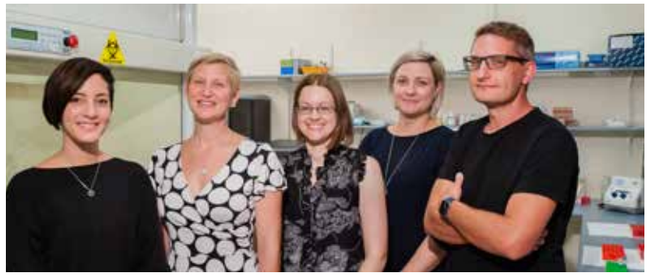
DENV *in vitro* transcribed RNA harbouring 15 nucleotide random insertions was introduced into cells and released virus was passaged to naive cells At each stage of infection DENV RNA was isolated and NGS used to determine the sites of the random 15-nucleotide insertions in replication competent virus

Host innate response to viral infection

The early cellular innate response to a viral infection involves various signaling cascades that culminate in the production 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. We have identified two ISGs, viperin and the IFITM family as having significant antiviral properties. The IFITM family consists of IFITM1, M2 and M3 and while they are similar they have differences in their cellular localisation and mode of antiviral action. IFITM1 localises to the cell surface and interacts with the HCV receptor CD81 to block HCV entry. However, M2 an M3 localise to early and late endosomes and inhibit the release of HCV from these compartments and target HCV for degradation (Narayana S *et al*, *J Biol Chem* 2015). We also have a long history in defining the antiviral nature of the ISG viperin, and recently shown that viperin interacts with peroxisomes and redirects their location to the lipid droplet and mitochondria. This is significant in that peroxisomes are now involved in innate immune signalling to viral infection and consistent with this we have shown that viperin can modulate innate immune signalling by interaction with peroxisomes. Thus viperin may play a master regulatory role in the early innate response to viral pathogens.



Sue Branford, Alex Yeoman, Nathalie Nataren, Justine Marum, Paul Wang



Zoe Donaldson, Doris Stangl, Linda Welden, Jasmina Georgievski, Adrian Purins

Leukaemia Unit, Genetics and Molecular Pathology

Associate Professor Susan Branford PhD, FFSc (RCPA)

Chronic myeloid leukaemia (CML) represents the prototype of genetically based diagnosis and management, and tyrosine kinase inhibitors (TKIs) exemplify the success of molecularly targeted therapy. Although long term survival is now possible for most patients, responses are heterogeneous.

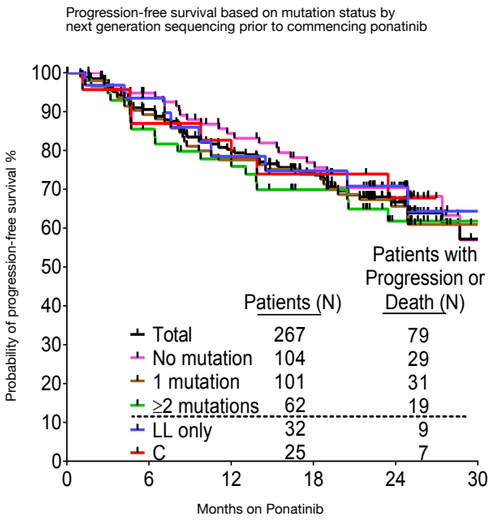
Therapy failure occurs in up to 30%, which has directed the development of more potent second generation TKIs that rescue response in some patients. Treatment intervention strategies have been introduced for patients failing therapy. However, no studies have shown improved outcome with early switch to a second generation TKI, which likely reflects our lack of understanding of inherent resistance mechanisms and a need for supplementary therapies. Furthermore, all TKIs are ineffective when the disease progresses to a fatal acute leukaemia, termed blast crisis, and the second generation TKIs have not demonstrated a survival benefit. The use of these more potent inhibitors must be carefully considered due to cardiovascular toxicity.

Our laboratory has a long standing research interest aimed at understanding the molecular basis for the heterogeneity of response to TKIs. The genetic processes that drive diverse treatment response and progression are largely unknown. This has limited the the development of diagnostic tools to more accurately predict outcome and progression, and therapeutic options to prevent or treat blast crisis. A major aim is to identify biomarkers at diagnosis of CML that will predict response and to guide the most appropriate type of drug the patient should receive. We investigate drug response kinetics by measuring molecular markers to predict outcome and to evaluate non-adherence to drug therapy, which surprisingly is a common problem in this otherwise fatal disease. The varying clinical pathogenicity of drug resistant mutations is assessed and we determine the relevance of subclonal mutations for response prediction and to guide therapy choices. We are also investigating biological factors, such as inherited genetic makeup, to determine drug response for individual patients. Crucial targets in addition to the primary genetic lesion, the BCR-ABL1 fusion, may need to be inhibited to prevent and treat disease progression, and to eliminate or suppress leukaemic stem cells to improve treatment-free remission rates.

Outcomes for the Community

Our research continues to offer guidance to haematologists for appropriate monitoring of treatment response and the early prediction of drug resistance. The research findings and those of others have significantly influenced the way patients are monitored and have been translated into international treatment intervention guidelines to optimise patient outcomes and to limit the risk of progression and death.

Key discoveries 2015



Compound mutations in BCRABL1 are not major drivers of primary or secondary resistance to ponatinib in CML patients
Patients with more than one resistant *BCR-ABL1* mutation in the same molecule were predicted to be resistant to ponatinib, a third generation inhibitor drug. However, sensitive mutation detection using next generation sequencing demonstrated that this is not the case. The graph shows the progression-free survival for patients who were resistant to prior therapy, divided by their mutation status at the time of starting ponatinib. There was no difference in outcome.
LL = low level mutation; C = compound mutation.

An individualised approach and optimised treatment intervention for patients with CML

Although the use of second generation TKIs for newly diagnosed patients may lead to an increased number of optimal responders, their use must be carefully considered due to cardiovascular toxicity, which is associated with major morbidity. We evaluated a strategy that incorporated initial treatment with the well tolerated drug imatinib, and when needed due to signs of pending treatment failure, a switch to a more potent second generation inhibitor nilotinib (Yeung *et al*, *Blood* 2015). The study was called the Therapeutic Intensification in De Novo Leukaemia (TIDEL)-II study and 210 patients were enrolled. The study design was based on the hypothesis that some patients will need a more potent inhibitor to achieve an optimal outcome, while this is achievable in other patients with the less toxic drug imatinib. A strategy of treatment optimisation as needed may be preferable to universal use of second generation inhibitors. Treatment was modulated based on serum imatinib trough levels, achievement of molecular targets, and tolerability. Overall, the effect of the individualised approach led to high rates of optimal responses and encouraging rates of other treatment targets. The benefits were mostly seen in the patients who switched to nilotinib who were intolerant rather than resistant to imatinib. This is likely related to some patients having a degree of intrinsic resistance to TKIs due to poorly understood mechanisms. Understanding intrinsic resistance mechanisms in CML is an active area of research.

Compound mutations in BCR-ABL1 are not major drivers of primary or secondary resistance to ponatinib in CP-CML patients

The main mechanism of drug resistance for patients with CML is the acquisition of a mutation within the *BCR-ABL1* gene. More than 100 different mutations can interfere with drug binding and most patients only require a single mutation for resistance to develop. A change of therapy restores drug sensitivity for most of the mutations, although specific mutations confer resistance to certain second generation TKIs. One mutation termed T315I confers resistance to all first and second generation TKIs. Furthermore, a proportion of patients have more than one mutation, which can alter sensitivity to rescue therapy. Ponatinib is a third generation drug, which overcomes resistance to all types of single mutants, including T315I.

Pre-clinical studies demonstrated that when two mutations occur on the same *BCR-ABL1* molecule, termed a compound mutation, high-level resistance to ponatinib can occur. Early clinical data seemed to confirm this possibility. However, in an expanded study of >250 patients who had failed their first and second line therapy and were treated with ponatinib, we demonstrated that compound mutations are not a major cause of resistance to ponatinib (Deininger *et al*, prepublished online, November 24, 2015).

Two different methods were used to assess the presence of *BCR-ABL1* mutations: standard DNA sequencing termed Sanger sequencing, and a next generation sequencing technique that detects subclonal mutations. An algorithm was used to determine compound mutation status and exclude false positive compound mutations that occur due to methodological factors. We found that 88% of possible compound mutations were likely false positives. In contrast to our previous studies, which demonstrated that the presence of multiple low level mutations at the time of switching therapy after treatment failure signals poor outcome to rescue therapy, this was not the case for ponatinib.

Paul Reynolds, Greg Hodge, Dr Hai Tran, Hubertus Jersmann, Sandra Hodge, Miranda Ween, Rebecca Harper, Rhys Hamon, Jonathan Whittall, Eugene Roscioli

Lung Research Program

Professor Paul Reynolds MBBS, PhD, FRACP

Lung cancer is the most common cause of cancer death in both men and women, with just 15% of patients surviving five years after diagnosis. The Lung Research Program conducts studies using samples obtained directly from patients to make new discoveries in the understanding of the biological basis of cancer and to develop novel therapies. This link between the clinic and the laboratory provides an ideal environment for the translation of laboratory discoveries into early phase human trials.

Tobacco smoking is the greatest risk factor for developing lung cancer and smoking-induced Chronic Obstructive Pulmonary Disease (COPD) is an independent risk factor for cancer development, even when corrected for the amount smoked. We discovered some years ago that smoking impairs macrophage function, leading to a build-up of apoptotic and necrotic material in the airways and perpetuating the inflammatory response. Importantly, this problem persists in COPD even after stopping smoking and may have relevance to cancer development.

Macrophage dysfunction provides a new therapeutic target that may have a substantial impact in pulmonary disease. We are investigating macrophage modulating therapies including new generation macrolide molecules and mannose binding lectin, with the aim of progressing this work to new clinical therapies. We are also studying the pro-inflammatory effects of electronic cigarettes (vaping) which have grown rapidly in popularity, but are not 'safe' as is being promoted.

Pulmonary disease also has a major impact on the pulmonary vasculature and in this regard we are studying Pulmonary Arterial Hypertension (PAH), a condition caused by abnormal vascular cell proliferation, which has features in common with malignancy, including monoclonal expansions of endothelial cells. We have been investigating a gene and cell therapy approach targeting the bone morphogenetic protein receptor 2 (BMPR2) pathway which we have shown counteracts TGF-b mediated endothelial to mesenchymal transition (EndMT). We have shown that upregulating this pathway *in vivo* is an effective treatment for the vascular remodelling seen in PAH, using a viral-vector based gene therapy approach. To advance this strategy to clinical translation we are now working on using endothelial progenitor cells (EPCs) engineered to overexpressed BMPR2, and evaluating both the cells themselves and exosomes derived thereof as therapies. This approach has proven successful in our models and holds great promise fro clinical translation.

In addition to these major themes, the Lung Research Program also conducts a range of projects looking at markers of lung transplant graft rejection, new therapies in asthma, and interstitial lung disease.

Key discoveries 2015

Macrolides in smoking-related lung disease

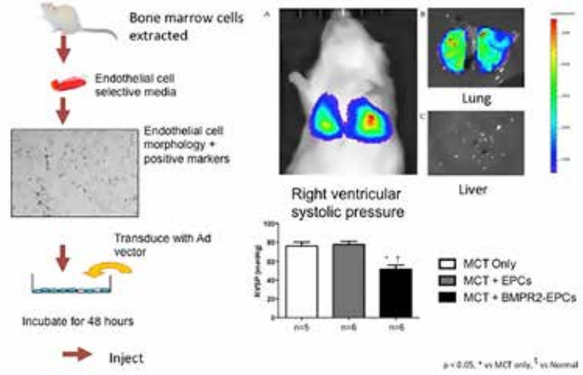
Following our *in vitro* and *in vivo* animal model work indicating macrolides improved inflammation and macrophage dysfunction we have conducted short term human trials on the effects of macrolides on bronchoalveolar lavage-derived macrophages and other inflammatory cell populations. We showed that macrophage function was improved in patients and also that a number of pro-inflammatory mediators were reduced eg increased CD8 T-cell granzyme B in COPD is suppressed by treatment with low-dose azithromycin (Hodge S *et al*, *Respirology*, 2015).

Inflammatory mediators and mechanisms in COPD

We have identified that CD28null T cells are important mediators in COPD and likely play a key role in the relative resistance to steroids due to downreguation of the steroid receptor (Lymphocyte senescence in COPD is associated with loss of glucocorticoid receptor expression by pro-inflammatory/cytotoxic lymphocytes. Hodge G *et al, Respir Res*, 2015). What this means is that alternative anti-inflammatory strategies are needed: we have exciting new data that a combination of steroids with low-dose cyclosporine A can overcome steroid resistance in patient-derived cells *ex-vivo*, and have now commenced a clinical trial using this approach.

Engineered cell therapy for pulmonary hypertension

We have developed an engineered EPC strategy to up-regulate BMPR2 expression in the lungs, which is an innovative evolution of our viral vector work, and BMPR2 gene delivery reduces mutation-related PAH and counteracts TGF-β-mediated pulmonary cell signalling. We have used the new EPC approach to achieve a therapeutic outcome in a rat PAH model which was presented at the Thoracic Society of Australia and New Zealand Annual Scientific Meeting, 2015 Young Investigator Award session. Rebecca Harper was the national winner (manuscript in preparation). The novelty of the approach lies in the capacity of these delivered cells to achieve a widespread effect throughout the pulmonary vasculature which we believe is due to the release of exosomes and soluable factors, which we are now studying. This approach thus offers potential in a range of diseases, and the cell therapy strategy already has been established as safe for clinical use, so there is a high possibility of advancing this strategy to clinical trial.

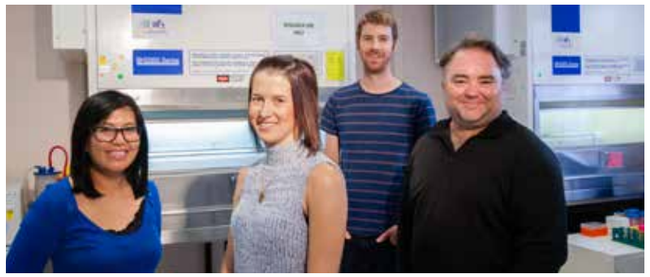


Transduced EPCs traffic to the lung and increase pulmonary BMPR2 to treadt MCT-induced PAH

Outcomes for the Community

Diseases affecting the lungs are the most common cause of general practitioner consultation and are responsible for huge economic and healthcare costs, morbidity and mortality. Our program is providing new insights into these diseases and new approaches to therapy that will lead to improved health outcomes through addressing currently unmet clinical needs.

Jan Kazenwadel, Natasha Harvey, Genevieve Secker



Melinda Tea, Kelly Betterman, Drew Sutton, Ian Nicholson

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. Abnormalities in the growth and development of lymphatic vessels underlie human disorders including lymphoedema, vascular malformations, autoimmune diseases and cancer.

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 important for lymphatic vessel growth, patterning and maturation. Once we understand how lymphatic vessel growth and development is normally controlled, we will gain insight into how this process becomes flawed 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.

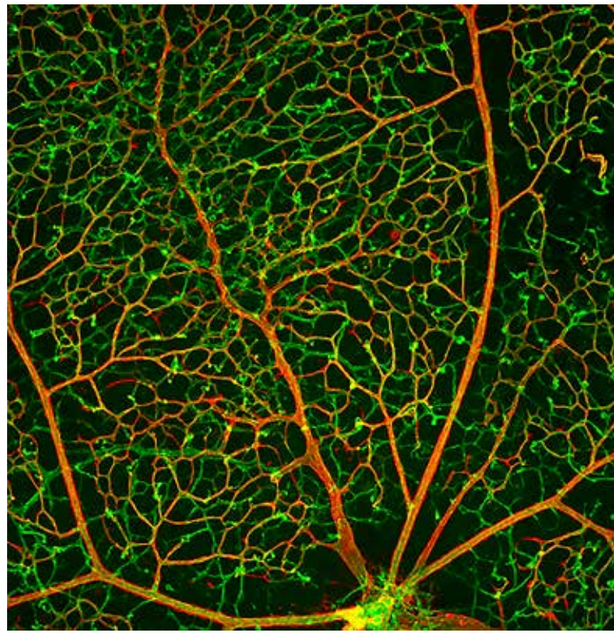
Outcomes for the **Community**

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 2015

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

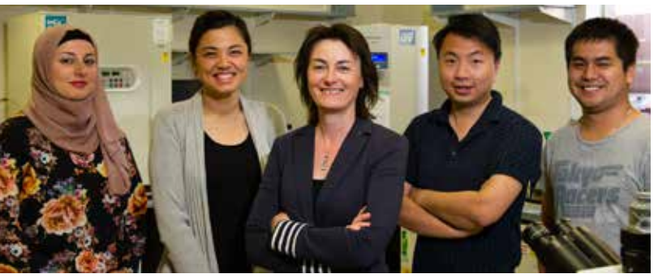
In collaboration with Professor Hamish Scott’s team at the Centre for Cancer Biology, we recently discovered that heritable mutations in the transcription factor GATA2 predispose carriers to lymphoedema and myelodysplasia syndrome (MDS)-acute myeloid leukaemia (AML) (Kazenwadel *et al*, *Blood*, 2012). 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 most recent work has established that GATA2 is required both to initiate the process of lymphatic vessel valve development and maintain their architecture once they have formed (Kazenwadel *et al*, *J Clin Invest*, 2015). Our current work aims 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 treatments of lymphoedema could be designed.



Sprouting blood vessels in the retina

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.



Noor Al-Dasooqi, Natasha Kolesnikoff, Michele Grimbaldeston, Dave Yip, Houng Taing

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 aid the process of restoring tissue homeostasis.

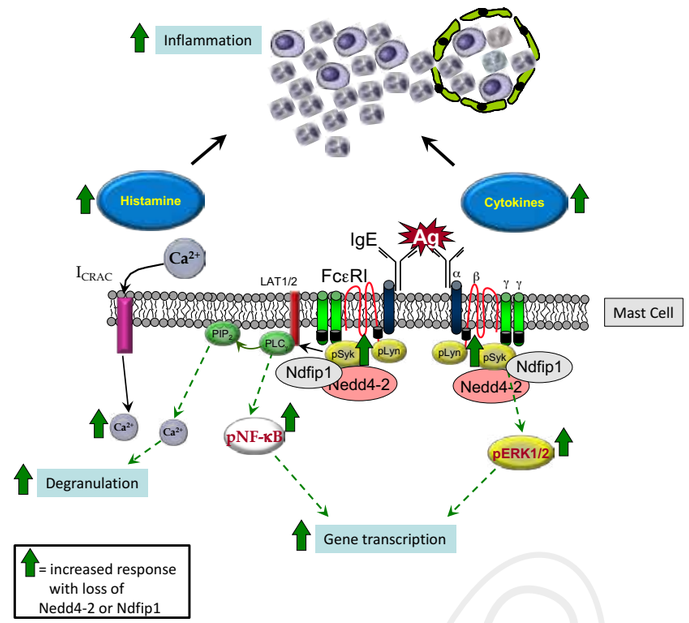
Research being undertaken by the Mast Cell Laboratory focuses on the novel regulatory abilities of mast cells, with an emphasis on how this dynamic cell contributes to the regulation of inflammation associated with skin cancer development, stroke and allergy. In collaboration with Dr Michael Samuel (Centre for Cancer Biology), Dr Thomas Gebhardt (University of Melbourne), 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), we discovered that human papillomavirus (HPV) 16 E7 protein expression in squamous epithelium induces thymic stromal lymphopoietin secretion, infiltration of type 2 innate lymphoid cells and atopic dermatitis-like lesions (Bergot S, *Immunol Cell Biol*, 2015).

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 2015

The Nedd4-2-Ndfip1 axis is a negative regulator of IgE-mediated mast cell activation

In collaboration with Professor Sharad Kumar (CCB), we have made the important discovery that the ligase Nedd4-2 and the adaptor Ndfip1 limit the intensity and duration of IgE-FcεRI-induced positive signal transduction by a mechanism dependent on phosphorylated Syk, a tyrosine kinase that is indispensable for downstream FcεRI signalosome activity. With the use of genetic and cell transfer approaches in mice, we identified that loss of Nedd4-2 in mast cells results in exacerbated and prolonged IgE-mediated cutaneous anaphylaxis *in vivo*. How mast cells intrinsically negatively regulate their activity is poorly understood. Our findings reveal a novel mechanism whereby Nedd4-2 and Ndfip1 are essential to restrain mast cell function; importantly, a recent whole genome sequencing study identified that an intron deletion in Nedd4L (human Nedd4-2 gene) is associated with increased risk of asthma in asthma-enriched families.

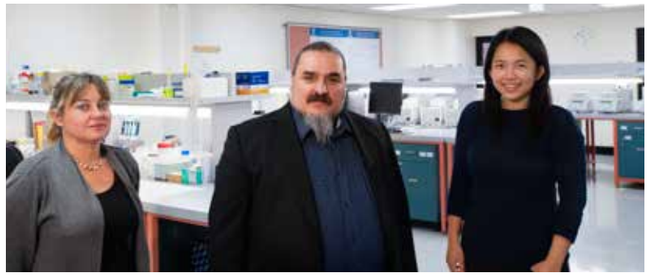


Loss of mast cell-Nedd4-2 or-Ndfip1 exacerbates IgE-mediated FcεRI signalosome activity, causing sustained mediator release and elevated levels of inflammation *in vivo*

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.

Marta Bayly, Xenia Iona, Leanne Dibbens, Sarah Heron



Natasha Radcliffe, Michael Ricos, Chiao Xin Lim

Molecular Neurogenomics Research Laboratory

Associate Professor Leanne Dibbens PhD

Our group studies a variety of neurological disorders including epilepsy, intellectual disability and autism spectrum disorders. These disorders each have a strong genetic basis and some are associated with abnormal growths in the brain such as tubers and cortical malformations, which have features similar to tumours.

We employ a number of different methods to identify the genetic cause of these disorders. Some patients are from families with a history of the disorder while others are isolated cases with no family history of the disorder. The strategies we use include genetic linkage, genome and exome sequencing and targeted re-sequencing of specific genes along with bioinformatics analysis. We have discovered a number of genes involved in neurological disorders including *PCDH19* in epilepsy and intellectual disability in females, *KCNT1* in focal epilepsy with psychiatric features and more recently, genes from the mammalian target of rapamycin receptor pathway (*DEPDC5*, *NPRL2* and *NPRL3*) in focal epilepsies with or without brain malformations. We also use animal models including Drosophila and Mouse to understand the biological processes by which mutations in these genes lead to neurological disorders. Such knowledge will assist in developing improved treatments for patients.

Outcomes for the Community

Identifying the genes that cause epilepsy and associated disorders informs the development of new diagnostics and treatments for patients. Identifying a gene mutation in a patient with epilepsy eliminates the need for further investigative testing to identify a cause, saving the associated distress, costs and hospital visits. Providing a genetic diagnoses allows genetic counselling to be provided to patients and facilitate their optimised clinical care including the selection of drugs for treatment. Together these outcomes have a large impact on improving the clinical care and the quality of life of patients with epilepsy. In addition, new gene discoveries show which biological processes in the brain are disrupted in epilepsy and pave the way for future development of new epilepsy drugs and treatments.

Key discoveries 2015

Mutations in KCNT1 cause a spectrum of focal epilepsies
Previously we discovered that autosomal dominant mutations in the sodium-gated potassium channel subunit gene *KCNT1* cause nocturnal frontal lobe epilepsy (NFLE). Another group showed that mutations in this gene also cause malignant migrating focal seizures of infancy (MMFSI). To further explore the phenotypic spectrum associated with *KCNT1*, we examined individuals affected with focal epilepsy or an epileptic encephalopathy for mutations in the gene.

We identified *KCNT1* mutations in 12 previously unreported patients with focal epilepsy, multifocal epilepsy, cardiac arrhythmia, and in a family with sudden unexpected death in epilepsy (SUDEP), in addition to patients with NFLE and MMFSI. In contrast to the 100% penetrance so far reported for *KCNT1* mutations, we observed incomplete penetrance.

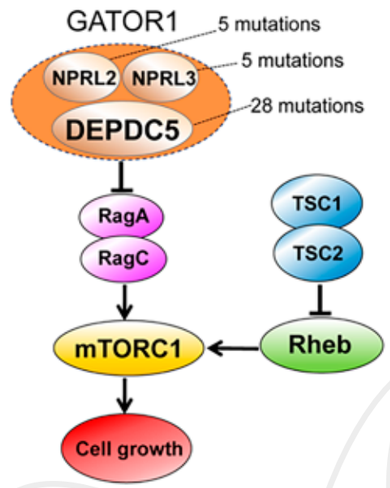
It is notable that we found that the same *KCNT1* mutation, p.Arg398Gln, can lead to either of the two distinct phenotypes, ADNFLE or MMFSI, even within the same family. This indicates that genotype-phenotype relationships for *KCNT1* mutations are not straightforward. We showed that *KCNT1* mutations are highly pleiotropic and are associated with phenotypes other than ADNFLE and MMFSI. *KCNT1* mutations are now associated with Ohtahara syndrome, MMFSI, and nocturnal focal epilepsy. They may also be associated with multifocal epilepsy and cardiac disturbances.

Mutations in the mTOR pathway regulators NPRL2 and NPRL3 cause focal epilepsy
Focal epilepsies are the most common form observed and have not generally been considered to be genetic in origin. Recently, we identified mutations in *DEPDC5* as a cause of familial focal epilepsy. Using targeted capture and next-generation sequencing technologies we have now identified *NPRL2* and *NPRL3* as two new focal epilepsy genes that also play a role in the mammalian target of rapamycin (mTOR) signaling pathway. In our cohort of 404 unrelated patients with focal epilepsy, we identified five mutations in *NPRL2* and five in *NPRL3*. Some patients had focal epilepsy associated with brain malformations. We also identified 18 new mutations in *DEPDC5*.

Our findings show that mutations in GATOR1 complex genes are the most significant cause of familial focal epilepsy identified to date, including cases with brain malformations. This study shows that deregulation of cellular growth control may play a more important role in epilepsy than is currently recognized.

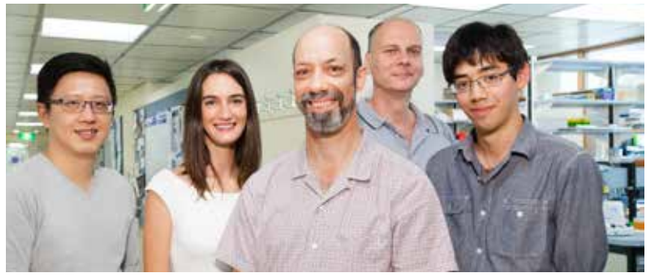
***NPRL2* / *NPRL3* / *DEPDC5* phenotypes**

Focal epilepsy
Onset usually childhood–adolescence
Epilepsy usually mild
Intellectual disability rare
Autistic spectrum disorders rare
Familial or de novo mutations
Variable penetrance
Dysplastic lesions in some



***NPRL2*, *NPRL3* and *DEPDC5* are all part of the GATOR1 complex that negatively regulates mTORC1 signaling** Mutations in *NPRL2*, *NPRL3* and *DEPDC5* show overlapping phenotypes in epilepsy and associated comorbidities

Milena Babic, Parvathy Venugopal, Hamish Scott, Anna Brown



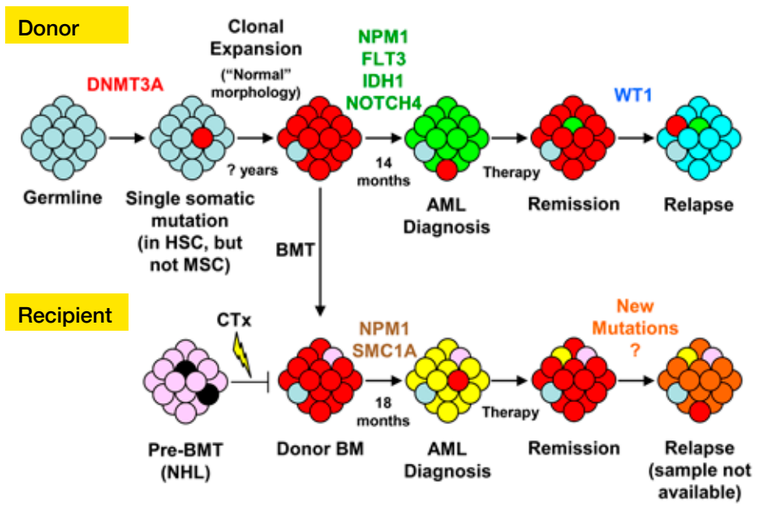
Chan Eng Chong, Alicia Byrne, Chris Hahn, Peter Brautigan, Jesse Cheah

Molecular Pathology Research Laboratory

Professor Hamish S Scott PhD FFSc (RCPA) FAHMS

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 for 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 co-occur. We also study rare or orphan diseases with unmet clinical need such as genetic diagnoses for family planning.



Mutational evolution of independent AMLs in two brothers
Mutation acquisition and clonal expansion in donor and recipient bone marrow during independent evolution of their AMLs

Key discoveries 2015

Novel germ line DDX41 mutations define families with a lower age of MDS/AML onset and lymphoid malignancies
Recently our group and others have identified DDX41 mutations both as germ line and acquired somatic mutations in families with multiple cases of late onset myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML), suggesting that DDX41 acts as a tumor suppressor. To determine whether novel DDX41 mutations could be identified in families with additional types of hematologic malignancies, our group screened two cohorts of families with a diverse range of hematologic malignancy subtypes. Among 289 families, we identified nine (3%) with DDX41 mutations. As previously observed, MDS and AML were the most common malignancies, often of the erythroblastic subtype, and one family displayed early-onset follicular lymphoma. Five novel mutations were identified, including missense mutations within important functional domains, and start-loss and splicing mutations predicted to result in truncated proteins. We also show that most asymptomatic mutation carriers have normal blood counts until malignancy develops. This study expands both the mutation and phenotypic spectra observed in families with germ line DDX41 mutations. With an increasing number of both inherited and acquired mutations in this gene being identified, further study of how DDX41 disruption leads to hematologic malignancies is critical.

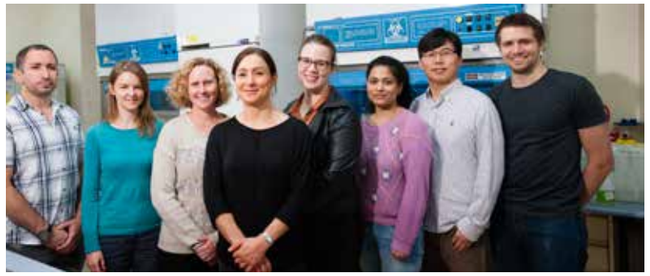
A tale of two siblings: two cases of AML arising from a single pre-leukemic DNMT3A mutant clone
We used Next Generation Sequencing (NGS) to follow acquisition of driver mutations in 12 AML progression samples in two brothers following haematopoietic stem cell transplantation of a pre-leukaemic mutant clone. This provided for the first time direct evidence that pre-leukaemic mutations can rapidly cause genetically divergent AMLs.

Delayed diagnosis leading to accelerated phase chronic eosinophilic leukemia due to a cytogenetically cryptic imatinib-responsive *TNIP1-PDFGRB* fusion gene
Rearrangements of the platelet-derived growth factor receptor genes (PDGFRA/B) are associated with imatinib-responsive myeloproliferative neoplasms (MPN). We have identified a novel imatinib-responsive *TNIP1–PDGFRB* fusion gene in MPN resulting from an interstitial deletion of chromosome 5, analogous to the chromosome 4 deletion that causes FIP1L1–PDGFRA. This case was atypical at presentation in two respects: the degree of eosinophilia was minor until disease progression several years later; and a normal karyotype is unusual in CEL/MPN with rearrangement of the PDGFRB locus.
As imatinib treatment can alter the natural history of MPN with rearrangements of PDGFRA/B it is important to identify all cases, whether by an empirical trial of imatinib treatment or by genetic testing. FISH and PCR are arguably more cost-effective than an empirical trial of imatinib, and in our health-care system imatinib is not available for the treatment of CEL/MPN unless there is laboratory evidence of a PDGFRA/B rearrangement. In cases of CEL or MPN with a high suspicion of PDGFRB rearrangement (for example, eosinophilia with elevated tryptase) FISH or an assay to detect the over-expression of PDGFRB should be considered even if the karyotype is normal.

Outcomes for the Community

We have identified four Australian and five American families with a predisposing mutation in the DDX41 gene. The Australian families have been offered counselling and genetic screening to identify their their family's specific mutation assays (developed by Genetics and Molecular Pathology, SA Pathology). One family is the first case of predisposition to lymphoma and thus DDX41 screening should be considered in familial cases of lymphoma. We have also identified a case of Chronic Eosinophilic Leukaemia (CEL) with a novel gene fusion involving PDGFRB that may indicate response to a drug (imatinib) that is commonly used for CML. The patient was treated and responded to the drug. We suggest that cases of CEL are tested for PDGFRA/B re-arrangements or expression to facilitate appropriate therapy.

Ian Nicholson, Andrej Nikolic, Sharad Kumar, Jantina Manning, Donna Denton, Cindy Xu, Shannon Nicolson



Omri Alfassy, Tanya Henshall, Natalie Foot, Claire Wilson, Kelly Gembus, Swati Dawar, Yoon Lim, Dylan De Bellis

Molecular Regulation Laboratory

Professor Sharad Kumar MSc PhD FAHMS FAA

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 enzymes and establish their roles in human diseases.

Outcomes for the Community

The goal of our recent projects is to provide a greater understanding of the biology of cell death mechanisms and diseases associated with disruption of normal cell death and oxidative stress. Our work in 2015 has discovered that 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 better be targeted for potential discovery and development of new disease markers and therapeutic candidates.

Key discoveries 2015

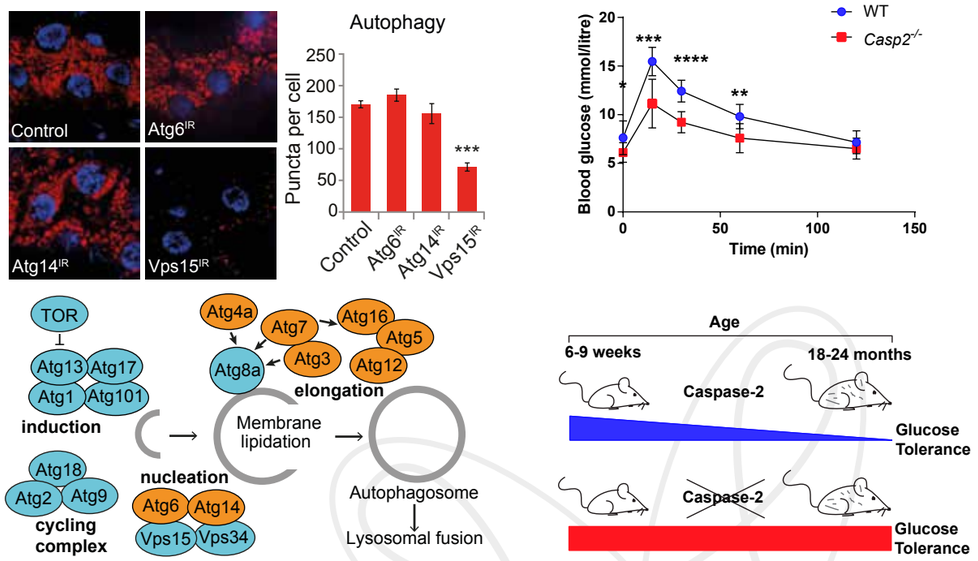
Autophagy-dependent cell death utilizes only specific autophagy-related (*ATg*) genes of canonical autophagy pathway

We have previously identified an alternate form of cell death that is dependent on autophagy, the catabolic process of cellular self-digestion through the action of lysosomal enzymes. In a recent publication using *Drosophila* midgut as a model system (Xu *at al*, *Cell Death Differ* 2015) we reported that genes required for autophagy-dependent cell death are distinct to those that are involved in starvation-induced autophagy. We discovered that while autophagy machinery components involved in the induction and recycling complexes are essential for autophagy-dependent cell death, several components of the nucleation and elongation steps of autophagy are not required (see figure). This suggests that autophagy-dependent cell death may involve distinct regulatory proteins and mechanisms. We also found that despite these differences, the induction of autophagy during midgut removal requires down-regulation of TOR activity, similar to that required during starvation-induced autophagy. Our observations indicate that autophagy-dependent cell death is only partly dependent on canonical machinery that mediates autophagy in response to nutrient limitation. This work has important implications in the understanding of autophagy in different contexts.

Tumour suppression and regulation of metabolism by caspase-2

Our previous work has shown that caspase-2 is a tumour suppressor in a number of mouse models of cancer. This observation was extended in a recent collaborative study (Peintner *et al*, *Cell Death Differ* 2015), which also confirmed that caspase-2 deficiency results in increased aneuploidy in tumour cells. In further studies (Shalini *et al*, *Oncogene* 34: 4995-5002) we demonstrated that caspase-2 deficiency exacerbates cellular stress in mice following low dose challenge with the potent reactive oxygen species generator, paraquat. This was due to an increased inflammatory response (IL-1b and IL-6) and impaired response to oxidative stress, including failure to upregulate the antioxidant defence mechanism in animals lacking caspase-2.

Expanding on these findings we carried out a screen to assess global changes in proteins and metabolites of liver and serum during ageing of mice lacking caspase-2. This work showed that caspase-2 affects remodelling of a substantial (>60 %) cohort of proteins during ageing and revealed important roles for this enzyme in lipid metabolism and glucose homeostasis (Wilson *et al*, *Cell Death Dis* 2015). Importantly, we found that aged caspase-2 deficient mice are resistant to age-induced glucose intolerance and we are now investigating this further in our ongoing studies. Our current work focuses on mechanisms that govern the tumour suppressor and metabolic functions of caspase-2.



Specific *Atg* genes are required for autophagy-dependent midgut removal Autophagy of the midgut (detected as red puncta using mCherry-*Atg8a)* is inhibited by knockdown of *Vps15*, but not *Atg6* or *Atg14* (upper panels).Using this approach, we could identify those genes required for autophagy-dependent midgut removal (blue) and those not essential for this process (orange)

Caspase-2 deficient mice are resistant to age-related glucose intolerance Compared to fasted 18-24 month old wild-type mice (blue), fasted caspase-2 deficient mice of the same age` have lower blood glucose levels, and a reduced response following glucose injection. This difference is not observed at 6–9 weeks of age, but is observed at 16 weeks.

Jason Powell, Paul Moretti, Heidi Neubauer, Melissa Pitman, Stuart Pitson, Briony Gliddon, Alex Lewis

Carl Coolen, Maurizio Costabile, Houng Taing, Layla Zhu, Jo Woodcock, Melissa Bennett, Lorena Davies, Craig Wallington-Beddoe

Molecular Signalling Laboratory

Professor Stuart Pitson PhD

The Molecular Signalling Laboratory examines the regulation of cell signalling pathways by sphingolipids; to both determine how defects in this contribute to cancer, wound healing, inflammation and other conditions, and to develop agents to target these pathways to improve human health.

Sphingolipids, including ceramide, sphingosine and sphingosine 1-phosphate regulate a diverse range of cellular processes by acting as intracellular signalling molecules, while sphingosine 1-phosphate also acts as a ligand for a family of cell surface receptors. Sphingolipid metabolism is controlled by a complex network of enzymes that are regulated by subcellular localisation and post-translational modifications. Sphingosine kinase is one of the key enzymes controlling sphingolipid metabolism, and through this action can regulate central processes such as cell survival and proliferation. We and others have shown that high levels of sphingosine kinase contributes to many of the hallmarks of cancer, including enhanced cell survival and proliferation, promotion of new blood vessel formation, increased cell invasive properties and deregulating cellular energetics. 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 appears a central player in inflammation and many diabetic complications, where it and its downstream sphingosine 1-phosphate receptors are potential targets for therapeutic intervention.

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 and agents for potential use in future cancer treatment.

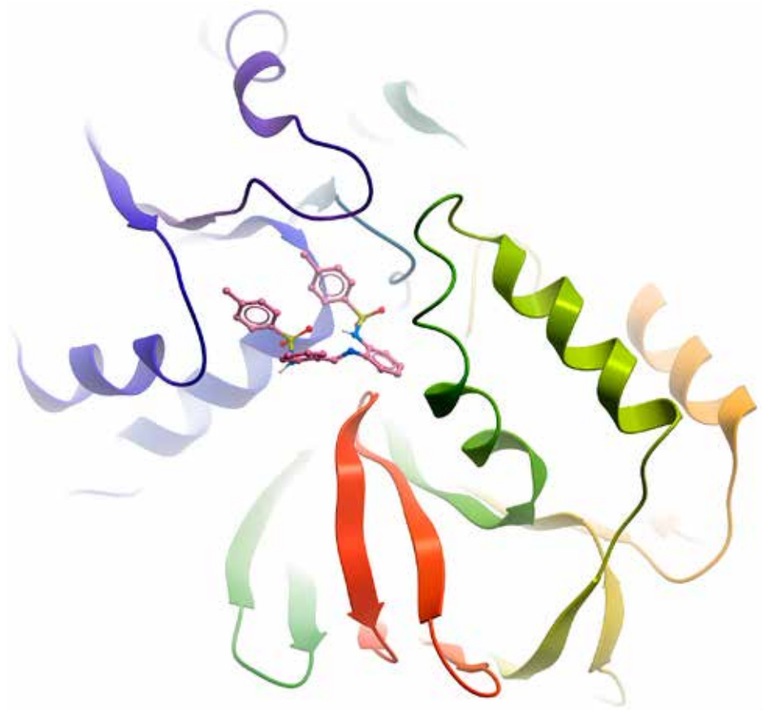
Key discoveries 2015

Development of sphingosine kinase inhibitors as anti-cancer agents

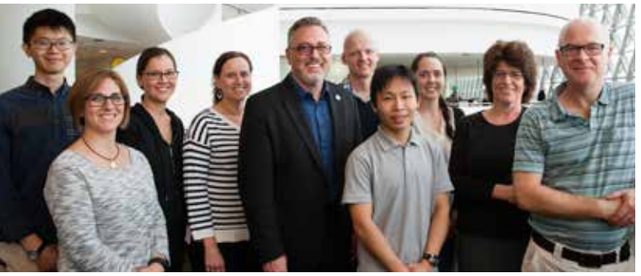
The importance of the sphingolipid pathway in the development of many cancers has provided impetus for the development of small molecule modulators of this pathway as potential anti-cancer agents. To this end we have employed a structure-based approach to develop first-in-class sphingosine kinase inhibitors 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 (Pitman *et al*, *Oncotarget* 2015).

Exploiting the sphingolipid pathway to development inhibitors of the 14-3-3 proteins

In collaboration with Professors Angel Lopez (CCB) and Robert Bittman (City University of New York) we have developed new small molecule inhibitors to the pro-survival 14-3-3 proteins based on our eariler findings that these proteins are regulated by sphingosine. Furthermore, we showed that these inhibitors have anti-cancer properties (Woodcock *et al*, *Oncotarget*, 2015), and in collaboration with Dr Michael Samuel (CCB) demonstrated that they can also improve healing of skin wounds (Kular *et al*, *Developmental Cell* 2015).



Docking of one of our novel sphingosine kinase inhibitors into the crystal structure of sphingosine kinase 1



Jiabin Zhang, Rosa Harmer, Sally Martin, Sharon Paton, Andrew Zannettino, Krzysztof Mrozik, Soo Siang Ooi, Elyse Bell, Vicki Wilczek, Duncan Hewett

Khatora Said, Ankit Dutta, Jacqueline Noll, Natasha Friend, Stephen Fitter, Kimberley Evans, Chee Man Cheong

Myeloma Research Laboratory

Professor Andrew Zannettino PhD

Myeloma is 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 10-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 contributes to patient outcomes by contributing to clinical practice guidelines for treatment of patients with multiple myeloma who are not eligible for stem cell transplantation. In addition, new guidelines for the treatment of patients with multiple myeloma who are eligible for stem cell transplantation were also published.

Key discoveries 2015

Osteoclasts control reactivation of dormant myeloma cells by remodelling the endosteal niche

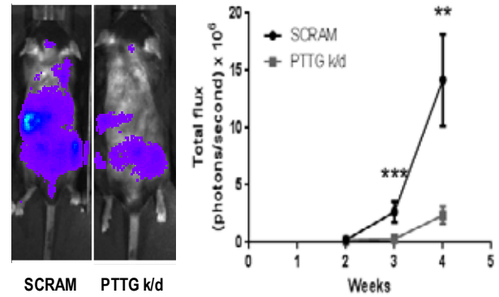
Multiple myeloma is largely incurable, despite development of therapies that target myeloma cell-intrinsic pathways. Disease relapse is thought to originate from dormant myeloma cells, localized in specialized niches, which resist therapy and repopulate the tumour. However, little is known about the niche and how it exerts cell-extrinsic control over myeloma cell dormancy and reactivation. In this study, we tracked individual myeloma cells by intravital imaging as they colonize the endosteal niche, enter a dormant state and subsequently become activated to form colonies. We also demonstrated that dormancy is a reversible state that can be switched 'on' by engagement with bone-lining cells or osteoblasts, and switched 'off' by osteoclasts remodelling the endosteal niche. Furthermore, we showed that dormant myeloma cells are resistant to chemotherapy that targets dividing cells and the endosteal niche is pivotal in controlling myeloma cell dormancy. These findings highlight the potential for targeting cell-extrinsic mechanisms to overcome cell-intrinsic drug resistance and prevent disease relapse.

PTTG1 expression is associated with hyperproliferative disease and poor prognosis in multiple myeloma

We have previously identified pituitary tumour transforming gene 1 (Pttg1) as a gene that is significantly upregulated in the haematopoietic compartment of the myeloma-susceptible C57BL/KaLwRij mouse strain, when compared with the myeloma-resistant C57BL/6 mouse. Over-expression of PTTG1 has previously been associated with malignant progression and an enhanced proliferative capacity in solid tumours. In this study, we investigated PTTG1 gene and protein expression in MM plasma cells from newly diagnosed MM patients. Gene expression profiling was used to identify gene signatures associated with high PTTG1 expression in MM patients. Additionally, we investigated the effect of short hairpin ribonucleic acid (shRNA)-mediated PTTG1 knockdown on the proliferation of the murine myeloma plasma cell line 5TGM1 *in vitro* and *in vivo*. We found that PTTG was over-expressed in 36-70 % of MM patients, relative to normal controls, with high PTTG1 expression being associated with poor patient outcomes. In addition, patients with high PTTG1 expression exhibited increased expression of cell proliferation-associated genes including CCNB1, CCNB2, CDK1, AURKA, BIRC5 and DEPDC1. Knockdown of Pttg1 in 5TGM1 cells was found to decrease cellular proliferation, without affecting cell cycle distribution or viability, and decreased expression of Ccnb1, Birc5 and Depdc1 *in vitro*. Notably, Pttg1 knockdown significantly reduced MM tumour development *in vivo*, with an 83.2 % reduction in tumour burden at 4 weeks. Collectively, these studies support a role for increased PTTG1 expression in augmenting tumour development in a subset of MM patients.

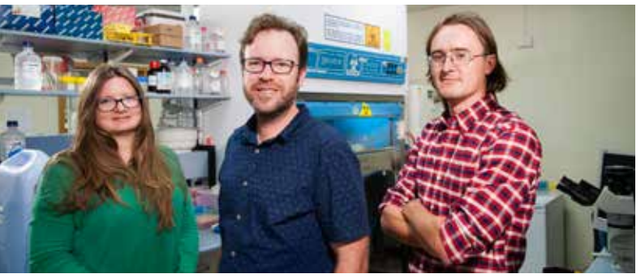
Tetraspanin 7 (TSPAN7) expression is upregulated in multiple myeloma patients and inhibits myeloma tumour development *in vivo*

Increased expression of the tetraspanin TSPAN7 has been observed in a number of cancers; however, it is unclear how TSPAN7 plays a role in cancer progression. We investigated the expression of TSPAN7 in MM and assessed the consequences of TSPAN7 expression in the adhesion, migration and growth of MM plasma cells (PC) *in vitro* and in bone marrow (BM) homing and tumour growth *in vivo*. Finally, we characterised the association of TSPAN7 with cell surface partner molecules *in vitro* and found that TSPAN7 was highly expressed at the RNA and protein level in CD138+ MM PC from approximately 50% of MM patients. TSPAN7 overexpression in the murine myeloma cell line 5TGM1 significantly reduced tumour burden in 5TGM1/KaLwRij mice 4 weeks after intravenous administration of 5TGM1 cells. While TSPAN7 overexpression did not affect cell proliferation *in vitro*, TSPAN7 increased 5TGM1 cell adhesion to BM stromal cells and transendothelial migration. In addition, TSPAN7 was found to associate with the molecular chaperone calnexin on the cell surface. Collectively, these results suggest that elevated TSPAN7 may be associated with better outcomes for up to 50% of MM patients.



Pttg1 knockdown reduces tumour growth *in vivo*

Representative bioluminescent images of mice injected with 5TGM1-SCRAM controls (left) and 5TGM1-Pttg-kd (right) cells at four weeks post tumour cell inoculation are shown. A significant reduction in total tumour burden was observed in the Pttg kd group (n=15) compared to SCRAM controls (n=10) at both three and four weeks; **p<0.01, ***p<0.001, Mann Whitney U test.



Rachael Lumb, Quenten Schwarz, Peter McCarthy

Xiangjun Xu, Reem Hasaneen, Zarina Greenberg, Sophie Wiszniak

Neurovascular Research Laboratory

Dr Quenten Schwarz PhD

Over 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.

The driving force behind the research conducted in 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 debilitating disorders.

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, our laboratory is interested in understanding how neural crest cells coordinate the development of other seemingly unrelated organ systems such as the vasculature, the heart, the craniofacial skeleton and adrenal gland. Our findings point to previously unrecognised co-dependencies between these cell and organ systems and demonstrate 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 connections that are essential for cognition and other behaviours, 2) blood vessels sense their environment to form functional networks, 3) neural crest cells sense there environment to position themselves in appropriate locations to form a functional nervous system, 4) neural crest cells differentiate into bone and cartilage to control craniofacial morphogenesis, 5) blood vessels signal to other cell types to modulate their development, and 6) neural crest cells communicate with blood vessels and cardiac precursors to control formation of the heart.

Outcomes for the **Community**

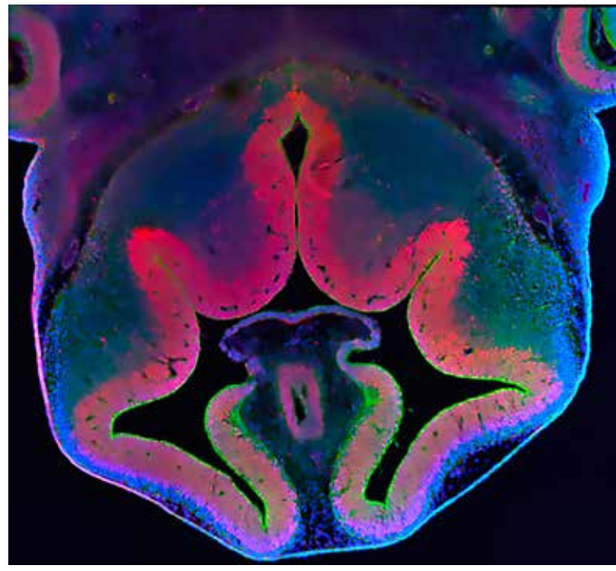
Our work is providing novel insight to the origins of a large number of common congenital birth defects, including autism, schizophrenia, craniofacial disorders and cardiac outflow tract defects. Aberrant developmental processes sit at the heart of these disorders and our findings offer hope of innovating new diagnostic and prognostic tests, and for the generation of innovative new cell replacement therapies. Our advances in understanding how angiocrine factors promote chondrocyte proliferation also provides real life hope of better treatment approaches for a wide range of birth defects and common sporting injuries. Finally, taking advantage of our finding that deficiency of 14-3-3ζ leads to neurodevelopmental disorders we are now working toward the testing the efficacy of using 14-3-3ζ expression as a diagnostic test for schizophrenia and autism.

Key discoveries 2015

In 2015 the Neurovascular Research Laboratory had several key discoveries that provide novel insight to embryonic development and the origins of congenital birth disorders.

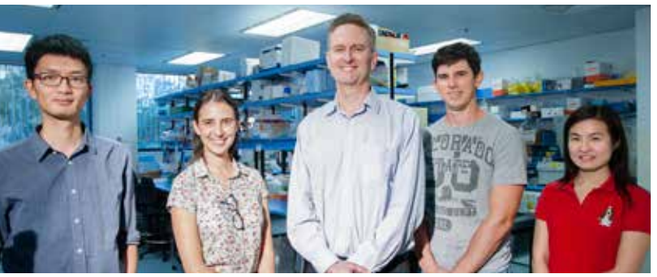
The origins of craniofacial disorders have traditionally been thought to arise from developmental defects in neural crest cell development. Our recent work identifies a novel basis of disease progression by demonstrating that blood vessels play an important role in promoting chondrocyte proliferation and formation of the cartilage that forms the lower jaw. We found that proteins secreted from arterial endothelial cells act as angiocrine factors to control growth of the jaw (Wiszniak S *et al* PNAS 2015). Our current work is aimed at identifying the factors secreted by blood vessels to control this process. Such factors represent ideal candidates for future therapies to treat cranio-facial disorders, but more broadly for the treatment of any defect affecting cartilage such as achondrodysplasia and common sporting injuries.

Our previous work in mouse models identified an essential role for the protein 14-3-3ζ in neuronal development and 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 publications (Xu X *et al*, *Sci Rep* 2015) demonstrate 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. In collaboration with colleagues in Japan we are now sequencing 14-3-3ζ in cohorts of schizophrenia and autistic patients to determine if deficiencies of this protein arise form genomic alterations.



Coronal section through an E12.5 mouse brain stained for β-catenin (green) and the neural stem cell marker Sox2

Over the past five 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 series 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 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.



Stanley Yu, Tessa Gargett, Michael Brown, Alex Staudacher, Yann 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.

We continue to recruit patients with metastatic melanoma into the NHMRC-funded CARPETS phase 1 clinical trial of autologous, GD2-specific, chimeric antigen receptor (CAR) T-cell therapy. Four patients have been recruited at the first two dose levels in this study with three dose levels, have not recorded any adverse events related to the gene-modified T cells. RAH Human Research Ethics Committee approval has now been given to continue recruitment at the final dose level of 2×10^8 cells/m^2. In three of the four patients enrolled in the CARPETS study, the GD2-CAR T-cell infusion has been given with concurrent oral BRAF and MEK inhibitor therapy. We have performed *in vitro* studies of patient GD2-CAR T cells in combination with therapeutically relevant combinations of BRAF and/or MEK inhibitors. The results showed variable perturbation of GD2-CAR T-cell function after at least several days of culture with BRAF and/or MEK inhibitors, and suggest that concurrent BRAF and MEK inhibitor therapy may not have a deleterious effect on GD2-CAR T-cell function *in vivo*.

In addition, we have commenced *in vitro* studies on CAR T cells specific for two different tumour antigens: (i) CD123, an antigen important of the leukaemic stem cells in acute myeloid leukaemia, and (ii) Ephrin A3 (EphA3), an antigen with a significant role in the tumour initiating cells of glioblastoma multiforme, which is a common lethal primary tumour of adults.

Our novel, cancer cell death-specific antibody, APOMAB®, has been coupled to the long-lived positron emitter, Zirconium-89. This work has enabled us to perform the first small-animal immuno-positron emission tomography (immunoPET) in South Australia. We successfully imaged the tumour response of tumour-bearing mice given chemotherapy using the small-animal PET scanner based at SAHMRI. We are continuing mechanism-based studies of the bystander anti-tumour activity of APOMAB antibody-drug conjugates (ADCs) in pre-clinical lung cancer models. In addition, we are performing staining of rectal cancer tissues before and after pre-operative short-course radiotherapy to show patterns of response of the La/SSB antigen, which is the target of APOMAB®.

Key discoveries 2015

We found that the retroviral transduction efficiency and the yield of T cells after *in vitro* expansion were optimal using the cytokines, IL-7 and IL-15, in the T-cell cultures. These conditions were subsequently adopted in the phase 1 CARPETS protocol of GD2-CAR T-cell therapy (Gargett T *et al*, *Cytotherapy* 2015).

Using a novel autoradiography technique (Timepix), we discovered significantly higher alpha-particle discharge from tumours of mice treated with the combination of chemotherapy and targeted alpha-therapy using Thorium-227 (^{227}Th) coupled to APOMAB than with ^{227}Th-APOMAB alone (Fig A). In these experiments, mice bearing subcutaneous implants of lung cancer were given ^{227}Th-APOMAB to target dead cancer cells or were first given chemotherapy to create more dead cancer cells before tumour targeting with ^{227}Th-APOMAB (Fig B). The Timepix semiconductor detector was used to record the tracks of beta-particles (electrons) and the charge clusters of alpha-particles, both emanating from necrotic areas of the tumour section (Darwish AL *et al*, *Comput Math Meth Med* 2015).

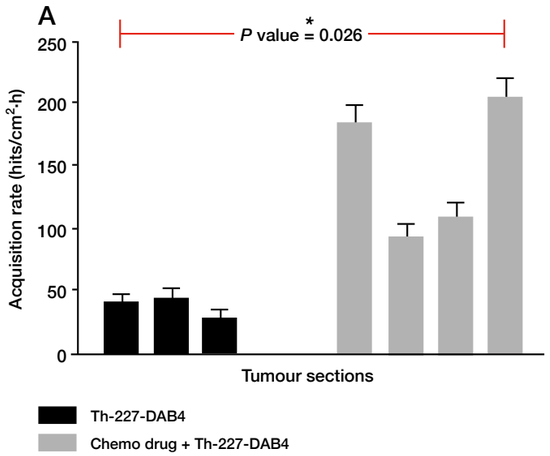


Figure A Measured alpha particle hits per unit tumour area per one hour for two groups of Lewis lung tumour sections: three sections from mice given 227Th-APOMAB alone and four sections from mice given chemotherapy before administration of 227Th-APOMAB

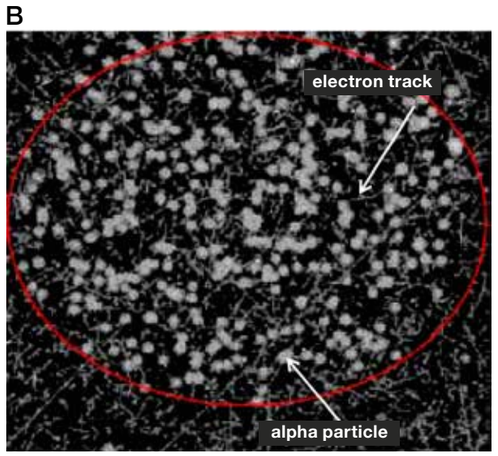


Figure B Image of a Lewis lung tumour section from a mouse given chemotherapy before administration of 227Th-APOMAB
Red circle indicates approximate tumour section boundary
Figure modified from AL Darwish *et al*, *Comput Math Meth Med* 2015

Outcomes for the Community

Melanoma, lung cancer, myeloid leukaemia, and glioblastoma are common cancers with currently poor survival prospects. We are developing new therapeutic approaches for these cancers based on recruiting components of the immune system such as T-cells and antibodies so that, in future, patient outcomes might be improved.

Michael Samuel, Noor Al-Dasooqi, Sarah Boyle, Noé Guilloy
Absent: Natasha Pyne, Jasreen Kular, Brock Le Cerf

Tumour Microenvironment Laboratory

Dr Michael Samuel PhD

The importance of mechanical force in regulating tissue homeostasis is becoming increasingly well-established. Nevertheless, the molecular mechanisms underlying the interplay between force and cell signalling are not well understood.

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.

The ROCK signalling pathway lies at the interface between mechanical and biochemical signalling. We have previously shown that ROCK signalling promotes epidermal proliferation by increasing extracellular matrix (ECM) production, elevating dermal stiffness and enhancing integrin-mediated mechanotransduction signalling. In turn, elevated dermal stiffness further stimulates ROCK activation, initiating a mechano-reciprocal positive feedback loop that promotes cutaneous tumours.

We are working to determine the mechanisms by which ROCK activation in the parenchyma causes ECM stiffening in cancer. Following on from our discovery that the molecular adaptor protein 14-3-3ζ negatively regulates signal flux through ROCK, we are also working to determine whether 14-3-3ζ inhibition may be useful to accelerate healing of diabetic wounds.

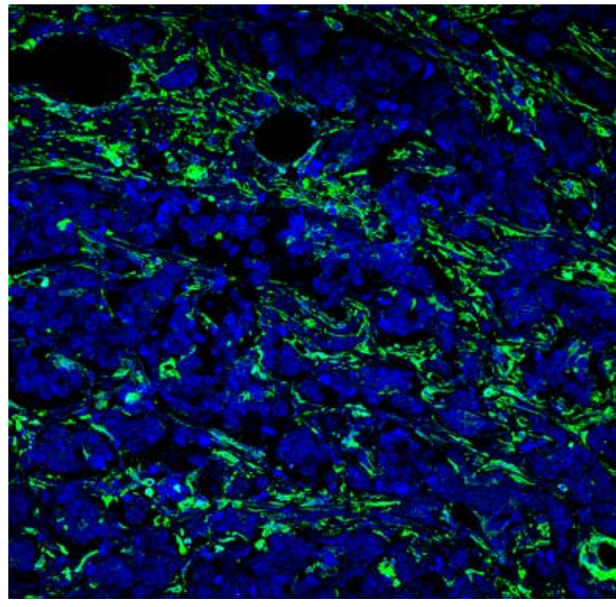
Key discoveries 2015

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

The Rho signalling pathway is known to be activated at wound margins to permit the establishment of an actomyosin ring that facilitates wound closure. However, 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 thereby reestablish normal mechano-reciprocity (Kular, Scheer *et al*, *Developmental Cell* 2015).

Signalling through ROCK is selectively tuned down by the molecular adaptor protein 14-3-3ζ, which promotes the function of an antagonist of ROCK signalling, Mypt1, by hindering its inactivation by ROCK. In 14-3-3ζ-deficient mice, hyper-activated ROCK signalling at wound margins led to elevated ECM production via paracrine communication between keratinocytes and dermal fibroblasts, consequently increasing dermal stiffness. Moreover, in collaboration with Dr Paul Timpson (Garvan Institute of Medical Research), we have demonstrated that 14-3-3ζ-deficient dermal fibroblasts failed to remodel the ECM, further increasing dermal stiffness and enhancing mechanotransduction signalling, which increased epidermal proliferation and accelerated the healing of 14-3-3ζ-deficient skin wounds. Accordingly, 14-3-3ζ-deficient mice developed larger, squamous cell carcinomas (SCCs) with stiffer ECM than wild-type mice when placed on the multi-stage chemical carcinogenesis protocol.

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. We are now working to determine whether 14-3-3ζ inhibition may be useful to accelerate healing in diabetic wounds.



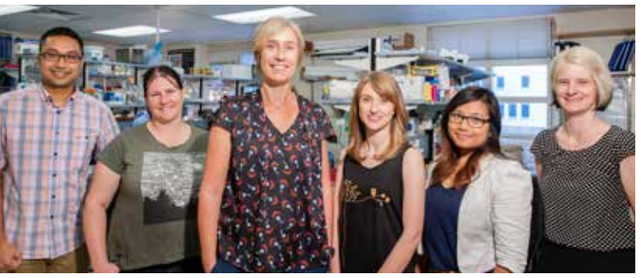
A histological section through an invasive human breast cancer shows extensive infiltration of cancer-associated fibroblasts (green) throughout. Nuclei are blue.

ROCK activation accelerates tumour progression in mechano-responsive tissues

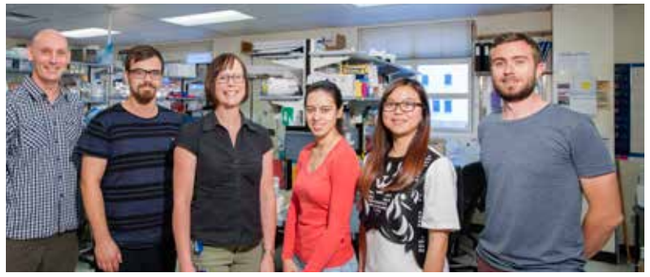
The Rho signalling pathway is well known to promote tumour cell invasion by regulating the synthesis and contractility of the actomyosin cytoskeleton. However, we have previously demonstrated that activation of ROCK within the skin also causes increased production of collagen, a major ECM protein of 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 SCC (Samuel S *et al*, *Cancer Cell* 2015). Crucially, we have now shown that these mechanisms are active in the progression of human SCCs and identified a novel therapeutic approach to target this disease (Ibbetson J *et al Am J Pathol* 2013). 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) and intestinal epithelia enhances tumour progression.

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.



Zahied Johan, Michaelia Cockshell, Claudine Bonder, Emma Thompson, Kay Khine Myo Min, Natasha Pyne



Brenton Ebert, Jake Treloar, Lisa Ebert, Carmela Martino, Lih Tan, Eli Moore

Vascular Biology and Cell Trafficking Laboratory

Associate Professor Claudine Bonder PhD

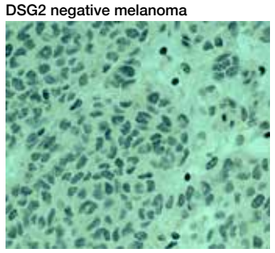
Blood vessels make up the vascular system that transports cells, oxygen and nutrients throughout all tissues and organs. Blood vessels are critical in the fight against disease and improved understanding of endothelial cells (ECs, specialised cells which form the inner lining of blood vessels), will provide new treatment options for cancer and cardiovascular disease.

Our laboratory has three main areas of interest. Firstly, vasculogenic mimicry (VM), a process wherein cancer cells themselves form vascular-like structures to increase access to the blood supply to assist in tumour growth. In both breast cancer and melanoma, increased VM is associated with poor clinical outcome. We have begun to identify novel elements in VM and are now targeting these in an attempt to provide better outcomes for patients with of breast cancer and melanoma.

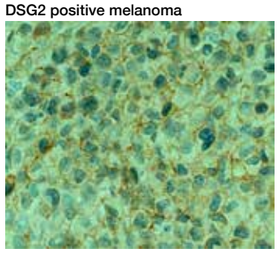
Secondly, endothelial progenitor cells (EPCs) directly contribute to blood vessel formation (vasculogenesis) and can be administered to support successful organ transplantation. We are developing smart surface biomaterials to co-transplant EPCs with insulin-producing beta islet cells for increased cure rate of patients with type 1 diabetes.

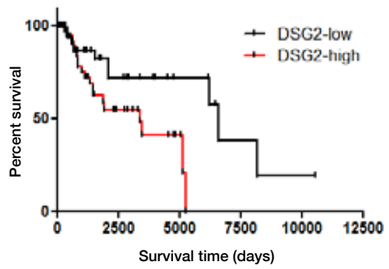
Finally, the blood vasculature is intimately involved in the development of allergic inflammation with ECs rapidly recruiting circulating leukocytes such as neutrophils. As neutrophils contribute to the most severe and difficult to treat allergies, understanding how they are recruited by the vasculature is key to preventing this prevalent and debilitating disease.

DSG2 negative melanoma



DSG2 positive melanoma





Desmoglein-2 (DSG2) is expressed in a subset of human primary and metastatic melanoma tissue and correlates with poor clinical outcome
DSG2 expression was examined in a metastatic melanoma TMA by immunohistochemistry (brown) with hematoxylin nuclear staining (blue)
The TCGA database was used to stratify melanoma patients with high and low DSG2 expression and a Kaplan-Meier analysis of overall survival time from initial diagnosis was performed

Key discoveries 2015

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 Professor Toby Coates we have demonstrated *in vivo* 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*, 2015). As part of the Cell Therapy Manufacturing Co-operative Research Centre (CTM-CRC) we are utilising our list of novel EPC biomarkers (Appleby SL *et al*, *PLoS ONE* 2012), and working with Professor Nico Voelcker (Future Industries Institute, University of South Australia) to functionalise biomaterials for the capture and transport of human islets and EPCs to cure patients with diabetes.

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 varies; thus, a better understanding of acute allergic reactions is required. In collaboration with Professor Stuart Pitson (CCB) we have examined the role of sphingosine kinase (SK) mediated P-selectin expression on ECs for the rapid recruitment of neutrophils. We recently identified that (i) histamine-induced P-selectin expression on human umbilical vein ECs is SK-1 dependent and (ii) histamine-induced neutrophil rolling along the vasculature *in vitro* and *in vivo* is SK-1 dependent. Of great interest is that administration of Fingolimod (approved pro-drug for treatment of multiple sclerosis) attenuates histamine-induced neutrophil recruitment *in vivo* (Sun WY *et al Am J Pathol* 2012). In collaboration with Professor Robert Heddle (Chief Pathologist at SA Pathology and Head of the Clinical Immunology Unit RAH) and Associate Professor Michele Grimbaldeston (CCB) we have extended our preliminary data to show that topical application of Fingolimod prevents allergic responses in human skin.

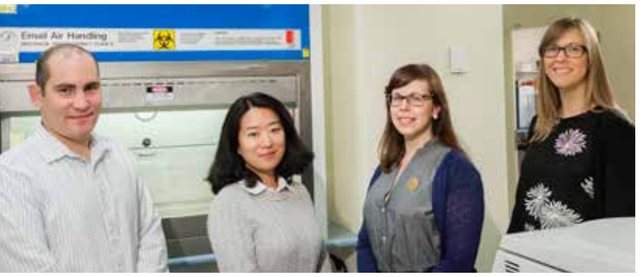
Vasculogenic mimicry:
a key contriibutor to cancer progression
The growth and spread of solid tumours such as melanoma and breast cancer is dependent on an ability to access the blood supply. To meet this requirement, cancer cells not only promote blood vessel sprouting (angiogenesis) but can also form vessel-like structures themselves, a process known as vasculogenic mimicry (VM). The presence of VM networks in primary cancers is tightly linked to increased metastasis and poor survival, suggesting that targeting VM in the clinic holds enormous therapeutic potential.

Using our recently identified novel biomarkers on human endothelial progenitor cells (EPCs) (Appleby SL *et al*, *PLoS ONE* 2012) we have begun to reveal the molecular mechanisms controlling VM in melanoma. More specifically, we have discovered that desmoglein-2 (DSG2), an adhesion molecule belonging to the desmosomal cadherin family, is ectopically expressed in human melanoma and plays a critical role in regulating melanoma VM. Tube formation assays revealed that the $DSG2^{+}$ melanoma cell lines can self-organise into tube-like structures and that this is significantly inhibited with siRNA-mediated knockdown of DSG2. Together, these studies reveal DSG2 as a key regulator of melanoma VM activity, and suggest that this molecule could be targeted to reduce tumour perfusion and metastatic spread.

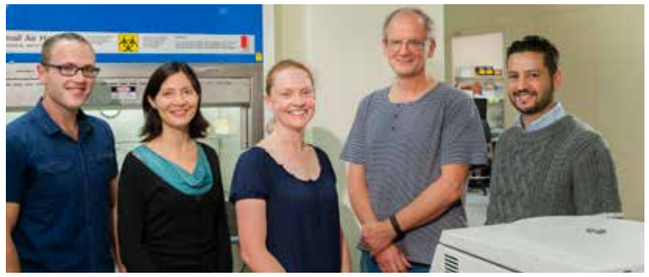
In breast cancer, we have growing evidence that the growth factor interleukin-3 (IL-3) is upregulated in a subset of patients with the most aggressive and invasive ductal carcinoma (IDC). In collaboration with Professor Angel Lopez (CCB) and Professor Geoff Lindeman (WEHI) we have shown that a monoclonal antibody targeting the IL-3 receptor (IL-3R) blocks VM formation and tumour growth by breast cancer cells *in vitro* and *in vivo*. With these IL-3R antibodies already in phase II clinical trials for leukaemia, we propose that these antibodies may be repurposed for breast cancer and thus may be able to fast-track a new treatment option for patients with this life threatening disease.

Outcomes for the Community

With particular focus on cancer, diabetes and allergic inflammation, we study the intricate network of blood vessels that carry white blood cells throughout our body and contribute to disease. If successful, our work will provide new opportunities to, on the one hand, ablate blood vessel development in cancer patients and on the other hand, augment blood vessel development in patients requiring organ transplant.



Joel Geoghegan, Ming Lin, Rosalie Kenyon, Wendy Parker



David Lawrence, Marie Gauthier, Katherine Pillman, Andreas Schreiber, John Toubia

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

Since opening in 2012, the ACRF Cancer Genomics Facility has become an integral part of the cutting edge research occurring within the Centre for Cancer Biology.

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 in a diagnostic setting.

Over the course of 2015, working in close collaboration the Genetics and Molecular Pathology directorate of SA Pathology, the ACRF Cancer Genomics Facility has processed over 2400 patients' samples for constitutional and cancer cytogenetic screens using SNP microarrays. In previous years, these samples were sent interstate for processing leading to slower turnaround times and costly shipping expenses. In addition, hundreds more samples have been sequenced using the latest next-generation sequencing technologies to screen for mutations in familial cancer genes, cardiomyopathies and other inherited disorders. Development and testing continues on new assays to detect gene fusion events that drive haematological malignancies, somatic mutation detection in solid tumours and compound mutations that confer resistance to molecular therapies.

In addition to working with diagnostics, the Genomics Facility has processed over 2000 research samples throughout the year across a range of applications including targeted and whole genome DNAseq, RNAseq and ChIPseq 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.

Outcomes for the Community

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.

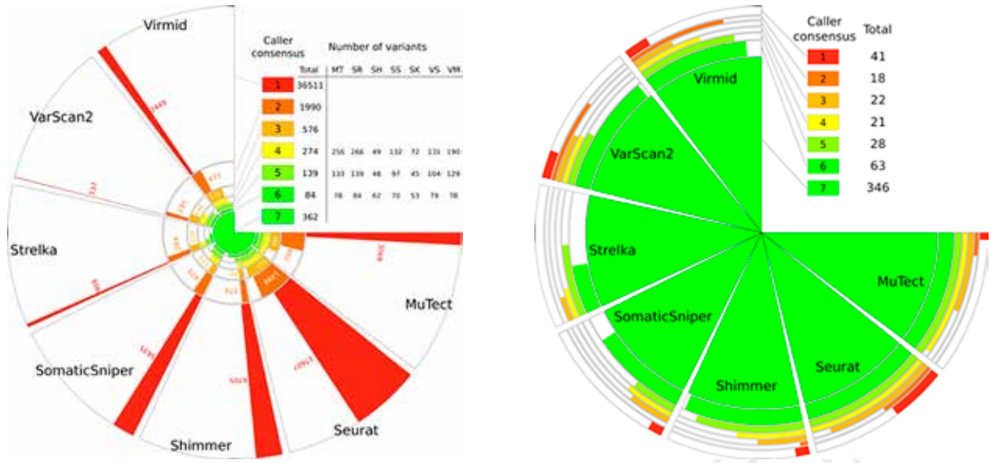
Key discoveries 2015

Bioinformatics

Two aspects of the genomics revolution brought about by exponentially decreasing sequencing costs largely shape the landscape that the field of bioinformatics inhabits: a continuous demand for increasingly efficient algorithms, pipelines and workflows to cope with data volumes growing much more rapidly than availability of computing hardware and an ongoing need for algorithmic and statistical developments to keep up with and exploit new opportunities afforded by continuously changing wet-lab techniques. The bioinformatics group is active in both these areas, while at the same time maintaining its role in data analysis associated with research projects of various research groups in the CCB and beyond.

Mutation detection is a primary use of next generation sequencing technology and, accordingly, we have devoted considerable resources to this topic. We have been rebuilding our germline variant-calling pipeline from the ground up, using efficient parallelization enabled by the Snakemake bioinformatics workflow engine. We recently used this to analyse 11 whole genomes (approx 1.0TB), sequenced at the Garvan Institute with the Illumina X Ten, in a few days. This is a great improvement when compared to the four weeks taken to analyse our first large scale exome sequencing project (0.5TB) in 2013. The pipeline's annotation tool is also constantly being updated and and improved, with around 100 different annotation entries per variant currently available. We also have current projects seeking to improve the reliability and sensitivity of somatic variant calling, using either traditional or tagged reads, and are continuing the development of VariantGrid, an exceedingly versatile variant database tool enabling analyses and meta-analyses of large collections of exome-level variant data.

The second major focus of the group is characterization of gene expression and regulation, particularly through whole transcriptome- and, more recently, capture- RNASeq. Apart from ongoing analysis projects regarding the regulation of circRNA and alternate splicing, the group is also developing appropriate pipelines for Genome Facility projects designed to improve identification of PCR duplicates via barcoding as well as improved gene fusion detection using these types of data.



Performance of somatic variants callers for detecting mutations in chronic myeloid leukaemia patients
The coloured slices correspond to numbers of variants called by seven popular variant callers, with overlapping variants in the centre (green) and caller-specific variants nearer the periphery (red). The left-hand plot depicts the well-known lack of concordance between callers using default settings, while the right-hand plot shows the improvements in the consensus that were obtained after our optimization of various filters.

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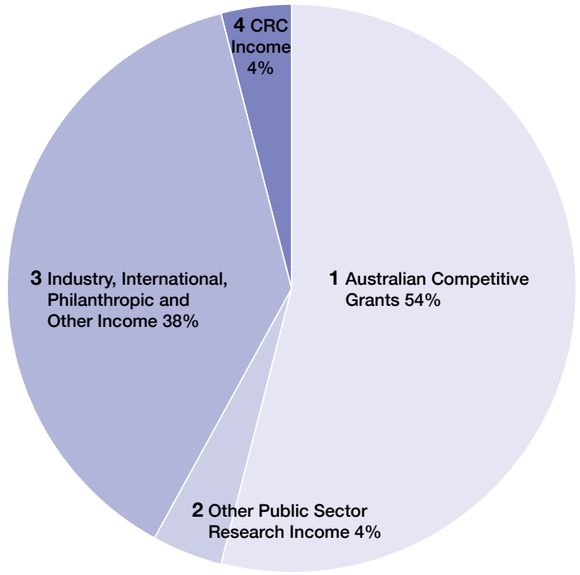
Financial Highlights

Research Income 2015

1	Australian Competitive Grants	5,697,964
2	Other Public Sector Research Income	468,473
3	Industry, International, Philanthropic and Other Income	3,990,447
4	Cooperative Research Centre (CRC) Income	392,450
	Total	AUD 10,549,334

Note: The figures above do not include funding for the following laboratories which are administered separately: Drug Discovery and Development Laboratory; Hepatitis C Virus Research Laboratory; Lung Research Program; Molecular Neurogenomics Research Laboratory and Myeloma Research Laboratory



New Grants and Fellowships

Investigator	Title	Granting Body
Abramson M, Walters E, Corte T, Benke G (Reynolds PN AI)	Occupational and environmental exposures associated with idiopathic pulmonary fibrosis in australia	NHMRC
Bennett M	$2000 Research scholarship	Hallett Cove Lions Club
Bennett M	RAH Research Honours scholarship	Royal Adelaide Hospital Research Fund
Bonder CS, Coates PTH, Voelcker NH, Jessup CJ	Desmoglein-2: a novel lifeline to treat diabetes	NHMRC
Bonder CS, Lopez AF, Lindeman GJ	Targeting the IL-3/IL-3 receptor axis to prevent breast cancer progression	Cancer Australia and National Breast Cancer Foundation
Brown MP	Data Manager Funding	Beat Cancer Project
Chambers D, Hopkins P, Glanville A, Westall G, Holmes M (Hodge S (AI))	Conquering the final frontier in lung transplantation: Mesenchymal stromal cell therapy for chronic lung allograft dysfunction	NHMRC
Conn S	CNRS Permanent Researcher Fellowship	CNRS
Cowin AJ, Garg S, Samuel MS	Developing new topical and systemic treatments for skin cancers	UniSA Research Themes Investment Scheme
D'Andrea RJ, Dickins R, Gonda T, Nilsson S, Perugini M, Lewis I	The role of the GADD45A gene in AML pathogenesis and response to therapy	Cancer Council SA
D'Andrea RJ, Dickins R, Gonda T, Nilsson S, Perugini M, Lewis I	The role of the GADD45A gene in AML pathogenesis and response to therapy	Royal Adelaide Hospital Research Fund
Dibbens LM	Exploring the role of DEPDC5 mutations in childhood brain abnormalities	Channel 7 Children's Research Foundation
Dibbens LM	NHMRC Senior Research Fellowship: Identifying the genetic causes of epilepsy	NHMRC
Dibbens LM	Understanding the genetics of childhood diseases with next generation sequencing	Channel 7 Children's Research Foundation
Ebert LM, Brown MP, Bonder CS	Checkpoint blockade immunotherapy in melanoma: getting tumour-killing T cells to their site of action	Royal Adelaide Hospital Research Fund
Ebert LM, Zannettino A, Wallington-Beddoe C, Bonder CS, Vandyke, K	Validation of a novel therapeutic target in multiple myeloma	Royal Adelaide Hospital Research Fund
Ekert TG, Ramshaw HS	Interleukin-3 receptor signalling is a driver of myeloid leukaemia and a significant therapeutic target	NHMRC
Francois M, Harvey, N	Deciphering the transcriptional program that instructs lymphatic endothelial cell fate	NHMRC
Gibson, Marks, McDonald, Wark, Upham, Thien, James, Reddell, King, Smith, (Hodge S and Reynolds PN AIs)	Phenotyping severe asthma for improved outcomes: a translational CRE	NHMRC
Goodall G, Conn S, D'Andrea RJ	Formation and function of circular RNAs in human cells	NHMRC
Goodall GJ	Do circular RNAs affect breast cancer progression?	National Breast Cancer Foundation
Goodall GJ, Khew-Goodall Y	Control of the actin cytoskeleton by miR-200 family microRNAs in neuroblastoma	The Kids' Cancer Project
Grimbaldeston M	Novel approaches to control mast cell function	Channel 7 Children's Research Foundation
Grimbaldeston M, Lopez A	*In vivo* characterisation of CSL311 mAb in human mast cell-driven diseases	CSL Limited
Heron SE	Career Development Fellowship	NHMRC
Heron SE	Understanding the contribution of parental mosaicism to the causes of childhood genetic epilepsies	Channel 7 Children's Research Foundation

New Grants and Fellowships continued

Investigator	Title	Granting Body
Hiwase DK, Scott H, Hahn CN, Moore S, Schreiber A	Comprehensive mutational screening to differentiate between hypoplastic MDS and aplastic anaemia	Royal Adelaide Hospital Research Fund
Hodge S, Chang A, Upham J	Studies into the mechanisms that progress protracted bacterial bronchitis to bronchiectasis in children, and therapeutic targeting of these processes	Channel 7 Children's Research Foundation
Hodge S, Reynolds PN	Targeting the defective airway macrophage function in chronic obstructive pulmonary disease (COPD): a new therapeutic approach	NHMRC
Hodge S, Zalewski P, Roscioli E (Reynolds PN AI)	Exploiting increased autophagy in bronchial epithelial cells: a new therapeutic approach for chronic obstructive pulmonary disease (COPD)	NHMRC
Hughes TP, Brown MP, Yong A, Lopez AF	Advancing T-cell therapy for leukaemia and glioblastoma	Beat Cancer Project
Keefe DMK, Brown MP	Research Infrastructure Block Grant for Equipment	Royal Adelaide Hospital Research Fund
Khew-Goodall Y	New signalling pathways regulating receptor tyrosine kinase trafficking	Royal Adelaide Hospital Research Fund
Khew-Goodall Y	Regulating EGFR in breast cancer	Cancer Council
Kumar S	Senior Principal Research Fellowship Regulation of cell death, cell survival and ubiquitination in normal physiology and disease	NHMRC
Kumar S, Smyth I, Saunders D	Nedd4-2: a new player in polycystic disease	NHMRC
Lewis ID, D'Andrea RJ, Perugini M	The significance of Gadd45A promoter hypermethylation and IDH1/2 and TET2 mutations in AML.	Royal Adelaide Hospital Research Fund
Lopez A, Geoghegan J, Scott H	Translating Health Discovery	Therapeutic Innovation Australia
Marum J, Yeung D, Schreiber A, Branford S	Assessment of the prognostic significance of somatic mutations in addition to BCR-ABL1 at diagnosis of chronic myeloid leukaemia	Royal Adelaide Hospital Research Fund
McColl SR, Comerford I, Brown MP	Regulation of the anti-tumour immune response by the chemokine decoy receptor CCX-CKR	Cancer Council SA
Mitchell C, Schwarz Q	Investigation of the role of PI3-kinase in the regulation of angiogenesis	NHMRC
Nguyen P, Reynolds PN	The biological impact of bronchial thermoplasty for astma	NHMRC
Parker W, Branford S	Sensitive BCR-ABL1 mutation analysis using molecular barcodes in patients treated with PF-114	Fusion Pharma
Parker W, Yeung D, Branford S, Scott H	Investigating the clinical significance of BCR-ABL1 compound mutants in tyrosine kinase inhibitor resistant patients with chronic myeloid leukaemia	Royal Adelaide Hospital Research Fund
Pitson SM	Targeting sphingosine kinase 1c degradation to enhance chemosensitivity	Royal Adelaide Hospital Research Fund
Powell J, Lewis I, Pitson SM	Targeting sphingosine kinase sensitizes acute myeloid leukaemia to BH3 mimetic therapy	Royal Adelaide Hospital Research Fund
Ramshaw HS	An unexpected function for CD123 in AML	Royal Adelaide Hospital Research Fund
Ramshaw HS	Peter Nelson Leukaemia Research Fellowship	Cancer Council SA
Reynolds PN, Bonder CS	Engineered Cell Therapy for pulmonary vascular disease	Royal Adelaide Hospital Research Fund
Reynolds PN, Harper RL	The role of extracellular vesicles in pulmonary arterial hypertension: pathogenesis and therapeutic platform	Royal Adelaide Hospital Research Fund
Roscioli E, Hodge S, Jersmann H	The role of autophagy in airway epithelial cells exposed to bush fire smoke	Royal Adelaide Hospital Research Fund
Samuel MS, Beattie DA, Cowin AJ, Hill JM	Harnessing the mechanical properties of tissues to reveal information about disease progression in cancer and wound healing	UniSA Research Themes Investment Scheme
Samuel MS, Grimbaldeston MG, Ibbetson J	Determining the function of mast cell protease 4 in squamous cell carcinoma progression using patient samples	Royal Adelaide Hospital Research Fund
Samuel MS, Grimbaldeston MG, Ruszkiewicz A	Defining the function of ROCK in establishing a tumour-promoting microenvironment	NHMRC
Samuel MS, Grimbaldeston MG	Determining the function of mast cell chymase in squamous cell carcinoma progression using patient samples	Royal Adelaide Hospital Research Fund
Samuel MS, Pitson SM, Cowin AJ	Defining the mechanisms regulating tissue mechano-reciprocity in wound healing	NHMRC
Schwarz Q	Future Leader Fellowship: Defining the role of neural crest cells in cardiac outflow tract development	National Heart Foundation
Scott H	Genetic autopsy of perinatal death: diagnosis and discovery by Whole Genome Sequencing	Royal Adelaide Hospital Research Fund
Scott H, D'Andrea RJ, Hahn C, Brown A, Lewis ID	Co-operation between GATA2 mutations or expression and RAS signalling in AML	NHMRC
Selth LA, Tilley WD, Goodall GJ, Gregory PA, Hollier BG	Targeting microRNA-driven mesenchymal to epithelial transition to suppress prostate cancer metastasis.	NHMRC
Staudacher A, 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 Research Fund
Wang S	Development of a new and effective therapeutic agent to treat childhood leukaemia	Tour de Cure Established Research Grant
Wang S	New Treatment for childhood leukaemia	Channel 7 Children's Research Foundation
Wang S	Development of anti-cancer agents	Yabao Development Grant
Wang S and D'Andrea R	Targeting CDK9 for treatment of AML	Bio Innovation South Australia
Wang S, Marshall G, Ziegler D	Targeting CDK6 for treatment of childhood medulloblastoma	The Foundation for Children
Ween M, Hodge S	Are e-cigarettes as harmless as sellers would have you believe? Investigating the effect of Vaping on macrophage function	Royal Adelaide Hospital Research Fund
Wiszniak S	Investigating causes of congenital heart disease	Channel 7 Children's Research Foundation
Wiszniak S	Mary Overton Award: Investigating causes of congenital heart disease	Royal Adelaide Hospital Research Fund
Zannettino A, Andrikopoulos, Baldock P	Skeletal endocrine signalling in the regulation of glucose metabolism	ARC
Zannettino A, Baldock P, Proud C	Targeting skeletal mTORC1 as a novel approach for the treatment of diet-induced insulin resistance	NHMRC
Zannettino A, Worthley D, Croucher P, Mukherjee S, Leedham S, Fink L	Why is the bone marrow a 'hot-spot' for myeloma plasma cell metastasis: are there Gremlins in the system	NHMRC
Zannettino A, Worthley D, Croucher P	The role of Gremlin1 in the metastasis of cancer to bone	Worldwide Cancer Research Fund

Seminar Program

Dr John Lock
Assistant Professor, Systems Microscopy Team Leader, Clinical Molecular Biology Lab, NOVUM, Karolinska Institute, Sweden
Plasticity in the functional networks that comprise and control cell migration 12/01/2015

Dr Daniel Thomas
Institute of Stem Cell & Regenerative Med, Hematology Dept, School of Medicine, Stanford University, San Francisco
Deciphering methylation patterns in acute myeloid leukemia for drug target discovery 15/01/2015

Professor Kathryn North AM
Director, Murdoch Children's Research Institute;
Director, Victorian Clinical Genetics Service
Integrating genomics into clinical practice: a local and international perspective 27/01/2015

Professor Stephen Dalton
GRA Chair in Molecular Cell Biology, Dept of Biochemistry and Molecular Biology, University of Georgia, USA
How stem cells make decisions 16/02/2015

Dr Michael Hansen
Senior Scientist and Technical Specialist, Exiqon A/S, Denmark
Towards detection of diagnostic microRNA biomarkers in biofluids and the functional analysis of microRNAs and long non-coding RNA Targets 20/03/2015

Dr Steve Turner
Founder and CTO, Pacific BioSciences, California
News from the Front: PacBio's Latest Achievements 26/03/2015

Associate Professor Dagmar Wilhelm
ARC Future Fellow, Department of Anatomy and Developmental Biology, Monash University, Melbourne
The battle of the sexes: new regulators of mammalian testis and ovary development 02/04/2015

Professor Wallace Langdon
School of Pathology and Laboratory Medicine, University of Western Australia, Perth
Inhibiting Chemotherapy-induced Myelosuppression 09/04/2015

Dr Connie Wong
Centre for Inflammatory Diseases, Department of Medicine, Monash University, Melbourne
Imaging the Innate Immunity 23/04/2015

Dr Erica Sloan
National Breast Cancer Foundation ECR Fellow, Group Leader, Neural Regulation of Cancer, Monash University, Melbourne
Beta-blockade of breast cancer: Repurposing old drugs to block metastasis 30/04/2015

Dr Mark Shackleton
Cancer Development and Treatment Laboratory, Peter MacCallum Cancer Centre, Melbourne
Studies in Melanoma Evolution 07/05/2015

Professor Ricky Johnstone
Assistant Director of Research, Co-Head, Cancer Therapeutics Program, Gene Regulation Laboratory, Peter MacCallum Cancer Centre, Melbourne
Harnessing the immune system to enhance epigenetic-based anti-cancer therapies 14/05/2015

Professor David Thomas
Director, Kinghorn Cancer Centre, and Division Head, Genomic Cancer Medicine, Garvan Institute of Medical Research, Sydney
Genomics, genetics and cancer 21/05/2015

Professor Christopher Proud
Nutrition and Metabolism Theme Leader, SAHMRI
(Dys)regulation of protein synthesis in cancer cells 28/05/2015

Professor Paul Reynolds
Director, Lung Research Program, Hanson Institute;
Clinical Director, Medical Specialties, CALHN Respiratory and Sleep Physician
Development of Gene and Cell Therapy for Pulmonary Vascular Disease 04/06/2015

Dr Luke Selth
Senior Research Fellow and Prostate Cancer Foundation Young Investigator, Dame Roma Mitchell Cancer Research Labs and Freemasons Foundation Center for Men's Health, School of Medicine, University of Adelaide
New insights into targeting and monitoring lethal prostate cancer 11/06/2015

Dr Alicia Oshlack
Head of Bioinformatics, Murdoch Children's Research Institute, Melbourne
Special Bioinformatics Seminar 17/06/2015

Professor Jonathan Cebon
Medical Director and Head of Cancer Immunobiology Laboratory, Olivia Newton-John Cancer Research Institute, Melbourne
The transformative impact of immunotherapy in cancer medicine 02/07/2015

Professor Andrew Scott
Head, Tumour Targeting Laboratory, Olivia Newton-John Cancer Research Institute, Melbourne
Insights into EGFR structure/function for cancer therapy 09/07/2015

CCB Annual General Meeting
Invited Speaker: Professor Brendan Crabb AC
Director and CEO, Burnet Institute, Melbourne
16/07/2015

Professor David Vaux
Deputy Director and Joint Division Head,
Walter & Eliza Hall Institute, Melbourne
Promise and pitfalls of cell death research 23/07/2015

Professor Robin Anderson
Head, Metastasis Research Laboratory, Peter MacCallum Cancer Centre, Melbourne
BMP4 inhibits metastasis through multiple mechanisms 30/07/2015

Professor Tom Gordon
Flinders Medical Science and Technology, Head of Immunology, Allergy and Arthritis, Flinders University, Adelaide
Molecular characterisation of systemic autoantibodies in lupus and Sjogren's syndrome at the level of the secreted proteome: public clonotypes rule 13/08/2015

Professor Marcela Bilek
Applied and Plasma Physics Research Group, School of Physics, University of Sydney
Plasma activation with energetic ions: enabling a new generation of biologically functionalized materials and structures 20/08/2015

Professor David James
Leonard P Ullmann Chair in Metabolic Systems Biology, The Charles Perkins Centre, University of Sydney
Proteomic strategies to investigate signal transduction pathways 26/08/2015

Professor Justine Smith
Strategic Professor of Eye and Vision Health, Flinders Faculty of Medicine, Nursing and Health Sciences, Flinders University, Adelaide
Mechanisms of human ocular toxoplasmosis 03/09/2015

Professor John Hamilton
Department of Medicine, Royal Melbourne Hospital, University of Melbourne
Regulation of the mononuclear phagocyte system by CSF-1 and GM-CSF 10/09/2015

Professor Maria Kavallaris
Head, Tumour Biology and Targeting Program, Children's Cancer Institute Australia, Lowy Cancer Research Centre, Sydney
Microtubules, Cancer and Nano-based Therapeutics 17/09/2015

Dr Christina Bursill
Immunology Group Leader, Heart Research Institute, Sydney
Novel roles of high-density lipoproteins in angiogenesis and stent biocompatibility 24/09/2015

Professor Andrew Zannettino
Deputy Head of School of Medical Sciences, Faculty of Health Sciences, University of Adelaide; Senior Principal Research Fellow, Cancer Theme, SAHMRI and Group Leader, CCB, Adelaide
Molecular and cellular mechanisms of myeloma pathogenesis 08/10/2015

Dr Dan Peet
Head, Hypoxic Signaling Laboratory, Dept of Molecular and Cellular Biology, University of Adelaide
Oxygen-sensing hydroxylases: a quick TRP from ion channels to photoreceptors 15/10/2015

Professor Shaun McColl
Director of Adelaide Centre for Molecular Pathology, University of Adelaide
Novel insights into chemokine receptor patho/biology 22/10/2015

Professor Thomas Preiss
Professor of RNA Biology, Genome Biology Department, The John Curtin School of Medical Research, The Australian National University
A compendium of cardiomyocyte RNA-binding proteins: l inks to mitochondria, metabolism and disease 29/10/2015

Dr Daniel Worthley
Principal Research Fellow, University of Adelaide
From connective tissue stem cells to colorectal cancer 05/11/2015

Associate Professor Kiarash Khosrotehrani
Experimental Dermatology Group Leader, University of Queensland Centre for Clinical Research (UQCCR) and UQ Diamantina Institute, Brisbane
Progenitors and hierarchy within the adult vascular endothelium 12/11/2015

7th Barossa Meeting
Cell Signalling in Cancer Biology and Therapy
18–21/11/2015

Professor Scott Summers
Head, Translational Metabolic Health Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne
Tissue-specific roles of ceramides in metabolic diseases 26/11/2015

Professor Guillermo Oliver
Feinberg Cardiovascular Research Institute, Northwestern University, Feinberg School of Medicine, Chicago USA
Cellular and molecular mechanisms controlling eye and lymphatic vasculature development 02/12/2015

Dr Justin Jong-Leong Wong
Head, Gene Regulation in Cancer Laboratory, Gene and Stem Cell Therapy Program, Centenary Institute, Sydney
Intron retention: no longer nonsense 03/12/2015

Professor Mark Hogarth
Burnet Principal for Research Strategy; Head, Inflammation, Cancer and Infection, Burnet Institute, Melbourne
Fc receptor and antibody interactions: new insights and implications for engineering therapeutic antibodies 10/12/2015

Invited Presentations

Acute Leukaemia Laboratory

Professor Richard D'Andrea

Chair

HAA HSANZ Symposium: Advances in Myelodysplastic Syndromes. Adelaide, Australia. October

Invited Speaker

Brisbane Diamantina Health Partners Blood Cancers Program. Diamantina Institute, Brisbane, Australia. June

7th Barossa Meeting: Cell Signalling in Cancer Biology and Therapy. Barossa Valley, South Australia. November

Associate Professor Ian Lewis

Convener

HAA 2015 Annual Meeting. Adelaide, Australia, October

Chair

HAA BMTSANZ / HSANZ / BMTSAA Combined Symposium: Alternative Donor Transplantation. Adelaide, Australia. October

Co-Chair

CIBMTR Autoimmune Diseases and Cellular Therapies Committee, Tandem BMT Meeting. San Diego, United States of America. February

Cell Signalling Laboratory

Assoc Professor Yeesim Khew-Goodall

Co-Chair

The international Epithelial-Mesenchymal Transition meeting. Melbourne, Australia, October

Invited Speaker

FASEB Summer Research Conferences: The TGFβ Superfamily: Signaling in Development and Disease. Snowmass, Colorado, United States of America. July

Europhosphatase 2015. Turku, Finland. June

Dr Ana Lonic

Invited Speaker

EMBO Conference: The multidisciplinary era of endocytic mechanics and functions. Mandelieu-la-Napoule, France. September

4th ANZSCDB Meeting. Adelaide, Australia. November

Cytokine Receptor Laboratory

Professor Angel Lopez

Invited Speaker

John Curtin School of Medical Research. ANU, Canberra, Australia. September

European Academy of Allergy and Clinical Immunology Congress 2015. Barcelona, Spain. June

Cell Signaling and its Therapeutic Implications (CSTI). Mornington Peninsula, Victoria, Australia. May

Translational Research Institute (TRI). Queensland, Australia. March

Drug Discovery and Development Laboratory

Professor Shudong Wang

Invited Speaker

10th AFMC International Medicinal Chemistry Symposium. Jeju, Korea. October

The Gordon Research Conferences. Newry, Maine, United States of America. August

5th Annual World Congress of Molecular and Cell Biology. Nanjing, China. April

China-Australia New Drug Discovery symposium. Suzhou, China. April

Gastroenterology Research Laboratory

Assoc Professor Andrew Ruszkiewicz

Invited Speaker

55th International Academy of Pathology, Thailand Annual Meeting. Aetas Lumpini Hotel, Bangkok. July

Gene Regulation Section

Professor Greg Goodall

Invited Speaker

36th Lorne Genome Conference. Victoria, Australia. February

School of Biotechnology & Biomolecular Sciences Seminar Program. University of New South Wales, Sydney, Australia. April

Mario Negri Institute for Pharmacological Research Seminar Program. Milan, Italy. June

Memorial Sloan Kettering Cancer Centre Seminar Program. New York, United States of America. July

Gordon Research Conference, Hormone-dependent Cancers. Sunday River, ME, United States of America. August

Children's Medical Research Institute Seminar Program. Sydney, Australia. August

The 74th Annual Meeting of the Japanese Cancer Association. Nagoya, Japan. October

TEMTIA-VII, The EMT International Association. Melbourne, Australia. October

Menzies Health Institute at Griffith University Seminar Program. Gold Coast, Queensland, Australia. October

Selected Speaker

Keystone MicroRNAs and Noncoding RNAs in Cancer, Keystone. Colorado, United States of America. June

FASEB Research Conference, The TGF-β Superfamily: Signalling in Development and Disease. Snowmass, Colorado, United States of America. July

Dr Phil Gregory

Chair

Coordinator of Early Career Research Forum, The International EMT Association (TEMTIA). Melbourne, Australia. October

Invited Speaker

Centenary Institute Seminar Program. Sydney, Australia. December

Flinders Centre for Innovations in Cancer Seminar Program. Adelaide, Australia. December

Dr Simon Conn

Chair

15th Genetics Society of Australasia Meeting. Adelaide, Australia. July

Invited Speaker

15th Genetics Society of Australasia Meeting. Adelaide, Australia. July

4th ANZSCDB Meeting. Adelaide, Australia. November

Hepatitis C Virus Research Laboratory

Assoc Professor Michael Beard

Chair

Lorne Infection and Immunity Conference. Victoria, Australia. February

Invited Speaker

Doherty Institute, University of Melbourne, Australia. August

Lorne Infection and Immunity Conference. Victoria, Australia. February

Dr Karla Helbig

Invited Speaker

The Westmead Institute. Sydney, Australia. October

Leukaemia Unit, Molecular and Genetic Pathology

Assoc Professor Susan Branford

Chair

Satellite meeting at the Haematology of Australia and New Zealand conference: Future directions in BCR-ABL1 monitoring with evolving CML treatment targets. Adelaide, Australia. October

Plenary Speaker

Annual Meeting of the Indian Haematology Society: Haematacon 2015. Bangalore, India. November

Invited Speaker

17th Annual John Goldman meeting on chronic myeloid leukaemia. Estoril, Portugal. September

Human Genetics Society of Australasia (HGSA) 12th One-Day Symposium. Adelaide, Australia. September

CML Speaking Tour. Kuala Lumpur, Malaysia. September

CML Speaking Tour. Bangkok, Thailand. August

Journal Club Meeting: Canberra Region Cancer Centre. Canberra, Australia. July

European Haematology Society Meeting Satellite Education Symposium. Vienna, Austria. June

European Haematology Society Updates in Hematology Symposium. Vienna, Austria. June

CML Global Opinion Leaders Summit. Berlin, Germany. March

Journal Club Meeting: Monash Medical Centre. Melbourne, Australia. March

GET Haematology Weekend meeting on Haematologic malignancies. Sydney, Australia. March

Lung Research Program

Professor Paul Reynolds

Chair

Interstitial Lung Disease Symposium, Thoracic Society of Australia and New Zealand, Annual Scientific Meeting. Gold Coast, Australia. March–April

Dr Rebecca Harper

Invited Speaker

The role of BMPR2 in Pulmonary Arterial Hypertension, Japanese Respiratory Society Annual Scientific Meeting. Tokyo, Japan. April

Lymphatic Development Laboratory

Assoc Professor Natasha Harvey

Chair

COMBIO2015. Melbourne, Australia. September

Invited Speaker

First Asia-Australia Vascular Biology Meeting. Busan, South Korea. October

Invited Seminar

Centenary Institute. Sydney, Australia. September

Flinders Centre for Innovation in Cancer. Adelaide, Australia. September

WEHI Postgraduate Lecture Series. Melbourne, Australia. April

Mast Cell Laboratory

Assoc Professor Michele Grimbaldeston

Co-Chair

7th Barossa Meeting: Cell Signalling in Cancer Biology and Therapy. Barossa Valley, Australia. November

Australasian Society for Immunology, SA/NT 11th Adelaide Immunology Retreat. Adelaide, Australia. August

Invited Speaker

John Curtin School of Medical Research, ANU. Canberra, Australia. November

7th Barossa Meeting: Cell Signalling in Cancer Biology and Therapy. Barossa Valley, Australia. November

Charité-Universitätsmedizin. Berlin, Germany. September

Imperial College. London, United Kingdom. September

European Society for Photobiology Congress. Aveiro, Portugal. September

University of South Australia School of Pharmacy Symposium. Adelaide, Australia. June

Australian Society for Dermatology Research. Adelaide, Australia. April

Science in the Pub, Adelaide. The power of the immune system in health and disease, Australasian Society for Immunology 'Day of Immunology'. Adelaide, Australia. May

Molecular Neurogenomics Research Laboratory

Assoc Professor Leanne Dibbens

Invited Plenary Speaker

The Genetics of Epilepsy: Judging Official for Oral Presentations, 11th Malaysia Genetics Congress. Selangor, Malaysia. August

Invited Speaker

Advances in identifying the genetic causes of epilepsy, Taylors University Research Symposia. Malaysia. December

Latest discoveries in the genetics of epilepsy, Neuroscience Symposium, Flinders University. Adelaide, Australia. September

Molecular Pathology Research Laboratory

Professor Hamish Scott

Keynote Address

Genetics Society of Malaysia: The Mendel Lecture, 11th Malaysia Genetics Congress. Kuala Lumpur. August

Invited Speaker

HGSA-SA Branch seminar. December

7th Barossa Meeting: Cell Signalling in Cancer Biology and Therapy, Genetics Society of Australasia. Barossa Valley, Australia. November

National Association of Research Fellows symposium, 54th ASMR National Scientific Conference. Adelaide, Australia. November

The 2015 Australian Diamond Blackfan Anaemia Program retreat. Canberra, Australia. November

Hospital Kuala Lumpur and the Medical Genetics Society of Malaysia. Kuala Lumpur. August

Princess Alexandra Hospital Health Symposium: Transforming discoveries to better health. Brisbane, Australia. August

Short Course in Medical Genetics and Genetic Pathology RCPA, Quarantine Station, Manly. Sydney, Australia. June

Dr Anna Brown

Invited Speaker

Leukemia Predisposing Genes Meeting, University of Perugia. Italy. October

Molecular Regulation Laboratory

Professor Sharad Kumar

Invited Speaker

Plenary Lecture, 2015 Hunter Meeting. New South Wales, Australia. March

Cell Death and Differentiation Retreat. Capri, Italy. May

Cell Death Workshop. Rome, Italy. May

University of Lausanne. Lausanne, Switzerland. May

International Cell Death Society Meeting: Implementation of knowledge of cell death. Prague, Czech Republic. May

AusFly2015, Australian Fly Meeting. Victoria, Australia. August

2015 NextGen Genomics, Biology, Bioinformatics and Technologies (NGBT) Conference. Hyderabad, India. October

Plenary Lecture, Japan Australia Meeting on Cell Death. Melbourne, Australia. November

Dr Donna Denton

Chair

Australia and New Zealand Society for Cell and Developmental Biology, 5th Annual Meeting, Adelaide, Australia, November

Invited Speaker

7th Barossa Meeting: Cell Signalling in Cancer Biology and Therapy. Barossa Valley, Australia. November

AusFly2015, Australian Fly Meeting. Victoria, Australia. August

Dr Loretta Dorstyn

Invited Speaker

Zing Genomic Integrity Conference. Queensland, Australia. August

Dr Natalie Foot

Chair

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

Molecular Signalling Laboratory

Professor Stuart Pitson

Co-Convenor

7th Barossa Meeting: Cell Signalling in Cancer Biology and Therapy. Barossa Valley, Australia. November

Co-Chair

Cancer Session: ASMR SA Conference. Adelaide, Australia. June

Invited Speaker

FASEB Science Research Conference on Lysophospholipids and Related Mediators: From Bench to Clinic. Banff, Canada. August

Dr Jason Powell

Co-Chair

Cancer Session: ASMR SA Conference. Adelaide, Australia. June

Invited Speaker

175th Anniversary of the RAH, Research Fund High Tea. Adelaide, Australia. July

Myeloma Research Laboratory

Professor Andrew Zannettino

Invited Speaker

PACIFICHEM 2015 Conference. Honolulu, Hawaii. December

Invited Presentations continued

Neurovascular Research Laboratory

Dr Quenten Schwarz

Chair

Molecular Biology session, ASMR State Scientific Meeting. Adelaide, Australia. July

Post-Doctoral Short Talks session, South Australian 4th ANZSCDB Meeting. UniSA, Adelaide, Australia. December

Cardiac Development and Regeneration session, ANCVDB Meeting. UniSA, Adelaide, Australia. December

Invited Speaker

Brisbane Developmental Biology Seminar Series. Brisbane, Australia, March

Dr Sophie Wiszniak

Chair

Invited speaker session at South Australian 4th ANZSCDB Meeting. UniSA, Adelaide, Australia, December

Invited Speaker

4th ANZSCDB Meeting. Adelaide, Australia. November

ANCVDB. Adelaide, Australia. December

Stowers Institute for Medical Research. United States of America. July

Ms Zarina Greenberg

Chair

Synaptic inhibition through development session. Gordon Research Seminar, Inhibitory neuron specialization and function. Maine, United States of America. August

Dr Peter McCarthy

Chair

Cancer session at the ASMR State Scientific Meeting. Adelaide, Australia. July

Ms Racahel Lumb

Invited Speaker

4th ANZSCDB Meeting, Adelaide, Australia. November

Translational Oncology Laboratory

Professor Michael Brown

Convenor

Melanoma Education Day, Royal Adelaide Hospital. Adelaide, Australia. February

Inaugural Medical Oncology Group of Australia Immuno-Oncology Forum. Melbourne, Australia. October

Chair

Novartis symposium: Melanoma Management Matters. Adelaide, Australia. October

Inaugural Medical Oncology Group of Australia Immuno-Oncology Forum. Melbourne, Australia. October

Melanoma Education Day, Royal Adelaide Hospital. Adelaide, Australia. February

7th Barossa Meeting: Cell Signalling in Cancer Biology and Therapy. Adelaide, Australia. November

Invited Speaker

Oncology Group of Adelaide, Australia. August

Novartis symposium: Melanoma Management Matters. Adelaide, Australia. October

Melanoma Education Day, Royal Adelaide Hospital. Adelaide, Australia. February

QIMR Berghofer Medical Research Institute. Brisbane, Australia. September

Queensland University of Technology School of Biomedical Sciences Seminar Series. Translational Research Institute, Brisbane, Australia. September

Immuno-Oncology Breakfast Symposium, Clinical Oncology Society of Australia Annual Scientific Meeting. Hobart, Tasmania. November

7th Barossa Meeting: Cell Signalling in Cancer Biology and Therapy. Adelaide, Australia. November

Dr Tessa Gargett

Co-Chair

Australian Society for Immunology Adelaide Immunology Retreat. Adelaide, Australia. August

Invited Speaker

International Society for Cell Therapy Regional Meeting. Adelaide, Australia. October

Tumour Microenvironment Laboratory

Dr Michael Samuel

Co-Convenor

5th Adelaide Cell and Developmental Biology Meeting. Adelaide, Australia. November

Co-Chair

Molecular Oncology Session, 7th Barossa Meeting. Adelaide, Australia. November

Invited Speaker

School of Medical Sciences Seminar Series, University of New South Wales. Sydney, Australia. March

Tumour Microenvironment Session, 7th Barossa Meeting: Cell Signalling in Cancer Biology and Therapy. Adelaide, Australia. November

Vascular Biology and Cell Trafficking Laboratory

Assoc Professor Claudine Bonder

Invited Speaker

Australian and New Zealand Microcirculation Society, Leura. New South Wales, Australia. April–May

7th Barossa Meeting: Cell Signalling in Cancer Biology and Therapy. Adelaide, Australia. November

Australian Network of Cardiac and Vascular Developmental Biologists. Adelaide, Australia. December

Session Chair

Australian Network of Cardiac and Vascular Developmental Biologists. Adelaide, Australia. December

Dr Lisa Ebert

Chair

Australasian Society for Medical Research (ASMR) SA Scientific Meeting. Adelaide, Australia. June

Invited Speaker

Australasian Society for Dermatology Research (ASDR) Annual Conference. Adelaide, Australia. May

ACRF Cancer Genomics Facility

Dr Andreas Schreiber

Invited Speaker

Human Genetics Society of Australasia. Adelaide, Australia. September

Centre for Cancer Biology 2015 Awards

Photo Liam West

Awards

Acute Leukaemia Laboratory

Mr Mahmoud Bassal
UniSA Winner and National Semi-Finalist, University of Queensland Trans Tasman 3 Minute Thesis (3MT) Competition, Brisbane, Queensland

Drug Discovery and Development Laboratory

Dr Malika Kumarasiri
CASS Foundation Travel Award

Gene Regulation Laboratory

Professor Greg Goodall
Fellow of the Australian Academy of Health and Medical Sciences

Dr Simon Conn
Simpson Cancer Research Prize, Royal Adelaide Hospital, Adelaide, Australia

South Australian Young Tall Poppy Science Award, Adelaide, Australia

French Embassy, Scientific Mobility Program Recipient

Leukaemia Unit, Molecular and Genetic Pathology

Dr Justine Marum
ASMR Early Career Researcher Best Poster Award, Adelaide, Australia

Advanced Molecular Diagnostics for Biomarker Discovery Meeting Young Scientist Poster Award 2nd Prize Munich, Germany

Lymphatic Development Laboratory

Dr Genevieve Secker
Winner, UniSA Images of Research; Engaged Research, Enterprising Researchers Photography Competition

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

Best Postdoctoral Poster Presentation, 4th Meeting of the Australian Network of Cardiac and Vascular Developmental Biologists, Adelaide, Australia

Dr Kelly Betterman and Ms Jan Kazenwadel
Best Postdoctoral Poster Presentation, 4th ANZSCDB Meeting, Adelaide, Australia

Mast Cell Laboratory

Assoc Professor Michele Grimbaldeston
CCB Best Primary Research Publication in 2014

Dr Anastasia Yu
CCB PhD Excellence Award

Molecular Pathology Research Laboratory

Professor Hamish Scott
Fellow of the Australian Academy of Health and Medical Sciences (FAHMS)

Lucia Gagliardi
Best of JCEM 2014: *ARMC5 mutations are common in familial bilateral macronodular adrenal hyperplasia.*
US Endocrine Society Meeting, San Diego, United States of America

SA Award for Excellence in Non-Clinical Research
Sharon Bain, Janice Fletcher, Hamish Scott, Karin Kassahn and Joel Geoghegan

Molecular Regulation Laboratory

Professor Sharad Kumar
Elected Fellow of the Australian Academy of Health and Medical Sciences

Dr Claire Wilson
Centre for Cancer Biology Early Career Investigator Award

Molecular Signalling Laboratory

Dr Melissa Pitman
Australian Society for Medical Research SA Early Career Researcher Presentation Award, Adelaide, Australia

Dr Maurizio Costabile
UniSA Digital Learning Citation for Outstanding Contributions to Student Learning 'For the creation of innovative, engaging and interactive digital simulations that facilitate student learning', Adelaide, Australia

Ms Heidi Neubauer
Best PhD Student Oral Presentation. Adelaide Protein Group Student Awards, Adelaide, Australia

Best Poster and Best Oral Presentation, FEBS Advanced lecture course *Molecular Mechanisms in Signal Transduction and Cancer*, Spetses, Greece

The David Walsh Prize for Best Student Oral Presentation, ComBio, Melbourne, Australia

Ms Wenying Zhu
Best Student Poster Prize, 7th Barossa Meeting, Adelaide, Australia

Neurovascular Research Laboratory

Dr Quenten Schwarz
ASMR South Australia Leading Light Award Adelaide, Australia

Dr Sophie Wiszniak
Best Post Doctorate talk at ANCVDB 2015, Adelaide, Australia

2nd Place Australian Science Media Centres SCIMEX Multimedia Hub Competition

CASS Foundation Travel Award

UniSA Early Career Networking Award, Adelaide, Australia

Translational Oncology Laboratory

Professor Michael Brown
2015 Publication of the Year, Immunology and Cell Biology:
Harata-Lee Y, Brazzatti JA, Gregor CE, Brown MP, Smyth MJ, Comerford I, McColl SR. A novel function for the chemokine receptor CCX-CKR in progression and metastasis of mammary carcinoma: regulation of EMT via induction of TGF-b.

Dr Tessa Gargett
Finalist, The Hospital Research Foundation 50th Anniversary Awards, Adelaide, Australia

Runner Up, Best Publication in Immunology and Cell Biology for 2014

Vascular Biology and Cell Trafficking Laboratory

Ms Lih Tan
Best Student Presentation: School of Pharmacy and Medical Sciences, Symposium I, UniSA, Adelaide, Australia

3 Minute Thesis Finalist: UniSA, Adelaide, Australia

Ms Kay Khine Myo Min
Best Honours Student Presentation Award, Australasian Society for Immunology Retreat, Lyndoch, South Australia

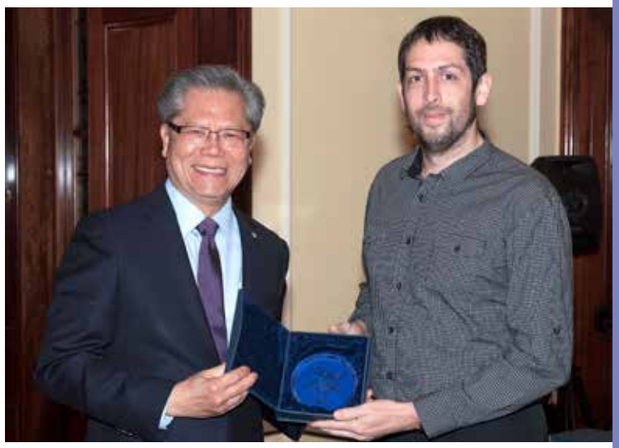
Ms Emma Thompson
Best Student Presentation: School of Pharmacy and Medical Sciences, Symposium II,UniSA, Adelaide, Australia

Best Student Poster Award, 7th Barossa Meeting: Cell Signalling in Cancer Biology and Therapy, Adelaide, Australia

ACRF Cancer Genomics and Genetics and Molecular Pathology Directorate

SA Health Awards for Excellence in Non-clinical Services for Implementation of Clinical Next Generation Sequencing. SCSS, SA Pathology, Adelaide, Australia

ASMR South Australia Leading Light Award
Dr Ian Johnson, SA Branch Co-Convernor presents Quenten Schwarz with the ASMR South Australia Leading Light Award
Photo Houng Taing



South Australian Young Tall Poppy Science Award
Governor of South Australia, The Honourable Hieu Van Le AC presents Simon Conn with the South Australian Young Tall Poppy Science Award
Photo Iain Bond

CCB PhD Excellence Award
Brendan Crabb, Michele Grimbaldeston for Anastasia Yu, Cara Fraser
Sponsored by Australian Society for Immunology

CCB Best Primary Research Publication in 2014
Ivor Butler (Stem Cell Technologies), Brendan Crabb, Michele Grimbaldeston, Dave Yip, Natasha Kolesnikoff
Sponsored by Stem Cell Technologies and Promega

CCB Best Student Research Publication in 2014
Brendan Crabb, Duyen Pham
Sponsored by BD Biosciences

CCB Early Career Investigator Award
Brendan Crabb, Claire Wilson, Briony Forbes, Jamie Triantis (Miltenyi Biotec)
Sponsored by Australian Society for Biochemistry and Molecular Biology and Miltenyi Biotec

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The Royal Adelaide Hospital Research Fund Team raises funds for the Centre for Cancer Biology
Morgan Pearse, Vicki Sage, Karen May, Matt Jackson, Alexia Rocha

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The biggest obstacles faced by clinical researchers are time and money. Making fundamental discoveries that lead to breakthroughs in the treatment of diseases such as cancer, heart disease, stroke, arthritis, diabetes and asthma can be a long and costly endeavour.
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www.centreforcancerbiology.org.au

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Thank you

Notes