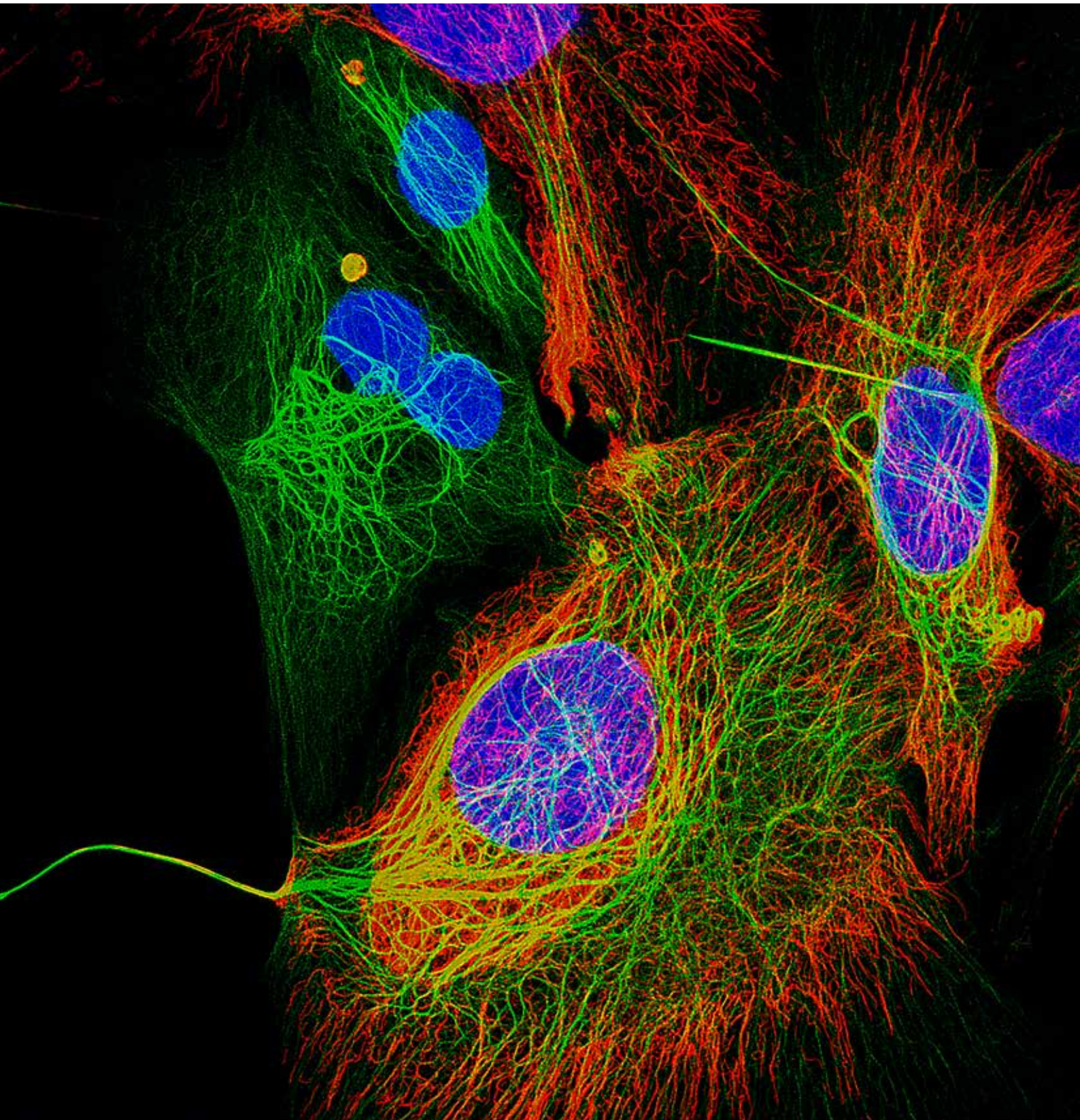
2016
Annual Report

Centre for Cancer Biology



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Annual Report

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
Mouse primary epididymal epithelial cells stained with antibodies to cytokeratin (green) and vimentin (red), and DAPI (blue). The image was captured using the Centre for Cancer Biology's Leica STED microscope that is part of the ACRF Cancer Discovery Accelerator Facility.
Photograph by Natalie Foot

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Organisation

The Honourable John Hill

Chairman's Report

The Honourable John Hill
Former Member for Kaurna and former Minister for Health

It is my pleasure to report on the progress of the Centre for Cancer Biology, its achievements and its plans for the future. The success of medical research institutes can be judged according to several criteria. The Directors have reported on the CCB's outstanding success in attracting highly competitive medical research funding, on publishing its research in the top medical research journals and on developing new candidate drugs. A success rate in NHMRC Project and Fellowship grants, about twice the national average, is truly exceptional.

These results cement our leading position in cancer research in South Australia and nationally. The CCB is particularly fortunate to be in collaboration with both SA Health and the University of South Australia and the benefits of this collaboration flow to all partners.

In particular, the alliance between SA Health and the University of South Australia uniquely positions the CCB to improve the health of the SA community. The CCB's research is strongly focused through the lens of practical benefit to patients. Several research leaders within the CCB are pathologists, senior scientists providing pathology services, or are actively practicing clinical specialists. CCB researchers have a strong track record in developing tests that identify cancer predisposing genes and that can differentiate between similar looking cancers responding differently to treatment. The early identification of cancer risks and differential diagnoses guides the choice of optimal therapeutic regimens.

I'm particularly pleased to see that our ACRF Cancer Genomics Facility, supported by major equipment grants from the Australian Cancer Research Foundation and the Government of South Australia, is a national leader in the development and application of these technologies to the benefit of South Australian patients.

In 2016 the CCB's Scientific Advisory Board, Chaired by Professor Ian Frazer AC, reported very positively on the CCB's science, and made important suggestions to help develop the CCB further and achieve wider recognition in the community. It is satisfying to see many of these recommendations crystallized in our five year Strategic Plan that sets the CCB's course for the future. It has also been satisfying to participate at the annual meeting of the Australian Association of Medical Research Institutes (AAMRI) in Canberra, in a year when the advent of the Medical Research Future Fund opens exciting new possibilities and the opportunity for us to be active participants in the new national funding landscape.

This has also been an exciting year as the new Health Innovation Building approaches completion. A busy year of providing input into the design and implementation of the new premises will surely be rewarded when we move into the excellent new facilities in early 2018.

The relocation of the CCB to the Adelaide BioMed City precinct will foster collaboration with SAHMRI and with University of Adelaide researchers. The proximity to the new Royal Adelaide Hospital will re-invigorate the strong tradition of collaboration with RAH clinicians. It is widely recognised that medical research is best done in a 'bench to bedside' effort that needs close interaction between researchers and clinicians. The CCB grew out of such a collaborative culture, has enhanced that culture, and seeks to continue to grow the culture. I'm also confident that the collaborative spirit of the CCB will contribute to bringing all of the partners in the new precinct closer together to make Adelaide BioMed City the vibrant medical research environment that is so strongly promoted by the Government of SA.

In closing I would like to congratulate the whole of the CCB for its achievements this year which will put us in good stead for further success in the future.

The Honourable John Hill

Professors Angel Lopez and Sharad Kumar

Keynote speaker Professor Suzanne Cory AC PhD FAA FRS

Foreground structures, looking south-west across the River Torrens: Adelaide Festival Centre, Adelaide Convention Centre and Riverbank Promenade, and cranes atop the Health Innovation Building that will house the Centre for Cancer Biology. Photograph courtesy BVN & Swanbury Penglase Architects

Directors' Report

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

As we write this report we can see with anticipation the changes to the skyline at the western end of North Terrace where the new Adelaide BioMed City Precinct is taking shape. Prominent already amongst the several impressive buildings is the Health Innovation Building of the University of South Australia (UniSA) which will accommodate the Centre for Cancer Biology (CCB) along with other University facilities in 2018.

A $40 million Federal Government grant, supplemented by University funds, to relocate the CCB from Frome Road to the new Precinct will enable us to enjoy modern facilities with the capacity to grow and facilitate collaborations with other stakeholders of the Precinct. We are indebted to the UniSA management team which has involved the CCB all the way in the design of laboratories and custom-made facilities for state-of-the-art equipment. What once seemed a date too far ahead to contemplate, March 2018 now looms high in the horizon and the whole of the CCB very much looks forward to the move to the new premises.

As we entered 2016 our Faculty was once again engaged in the yearly task of submitting funding applications to the National Health and Medical Research Council (NHMRC) and other federal funding bodies to sustain and expand their work. As it turned out, we had a very successful year in terms of competitive grants won and when the results were announced in November we were delighted to learn that the CCB had been successful in obtaining more than $9 million in Category 1 funding. This was about twice the Australia-wide average success rate, highlighting the quality of projects submitted and the calibre of CCB researchers. We were aware of the state's ambition to increase South Australia's share of NHMRC funding and we were very pleased to significantly contribute to this endeavour.

Congratulations to our successful leaders Professors Hamish Scott, Stuart Pitson, and Greg Goodall, Associate Professor Michele Grimbaldeston, and Drs Alex Staudacher and Phil Gregory for the support gained, and we were pleased that we were both also amongst the awardees. Special mention to Professor Greg Goodall and Associate Professor Sue Branford for being awarded highly competitive NHMRC Fellowships (two of three in South Australia) to enable them to continue their cutting-edge work on gene regulation and in chronic myeloid leukaemia respectively.

In 2016 we continued to advance our research with publications in some of the best medical and scientific journals such as *Nature Communications* and *Blood*. A major achievement has been our participation in the $25 million National Genomics Alliance, an NHMRC-funded national initiative to bring the benefits of the genomics revolution that is taking place worldwide, right to patients' bedsides. This promises to rapidly improve patient care whilst reducing costs to the health budget. Congratulations go to Professor Hamish Scott and his team who spearheaded CCB participation and have taken a national leadership role in this endeavour.

In June we bid farewell to Associate Professor Michele Grimbaldeston who left the CCB for a significant leadership position at Genentech and to be close to her family in San Francisco. We will miss Michele's intellect, energy and collaborative spirit, wish her the very best and will follow with enormous pride her new career in the Pharmaceutical Industry, hoping that our paths meet again in the future.

This year the CCB held its AGM in July. We were privileged to have Professor Suzanne Cory, AC, FAA, FRS as our keynote speaker. Her speech about her journey through her discoveries of the cell death machinery to their application to treat patients with cancer was an inspiration to the whole of the CCB. Suzanne was also gracious to join us, our Scientific Advisory Board members Professors Ian Frazer, Joe Trapani and Christina Mitchell, and our Alliance partners' representatives for helpful and constructive discussions about strengthening the CCB.

A significant event this year was the development and subsequent launch of our Strategic Plan. Facilitated by Professor Moira Clay, this was an excellent exercise that focused the mind and sharpened our vision of who we are and what we aim to achieve. Moira challenged our Faculty and brilliantly synthesized our thoughts to create a defined Strategic Plan that will guide the CCB over the next five years.

As a consequence of the Strategic Plan the CCB has formalised a mentorship group led by Professors Greg Goodall and Stuart Pitson who will help to develop our young talented researchers. Similarly, we have instituted a Consumer Advocacy Group, led by Associate Professor Claudine Bonder, which seeks to bring the CCB closer in touch with the needs and expectations of cancer patients.

As a member of the Association of Australian Medical Research Institutes (AAMRI), the CCB participated in its AGM in November in Canberra. Together with our Operations Manager, Mr Russell D'Costa, and our Chairman, the Honourable John Hill, we had the opportunity to participate in exciting discussions around the newly established Medical Research Future Fund and its potential to energize medical research in Australia. We are looking forward to collaborating closely with other like-minded institutes and forming meaningful alliances that improve healthcare.

Building works
Eastern elevation of the University of South Australia's Health Innovation Building, looking across Morphett Street Bridge
Photograph by Andrew Bert

In seeking synergies and collaborations we continue to work closely with the Institute of Molecular and Cellular Biology (IMCB) in Singapore through Professors Wanjin Hong and Vinay Tergaonkar and the Joint IMCB-CCB Laboratory, with SAHMRI, the Children's Cancer Institute, and the Peter MacCallum Cancer Centre. A visit by the CCB to the Peter MacCallum Cancer Centre in November identified clear areas of synergy which have already led to joint project grant applications and places for more formal interactions in several areas of cancer discovery and treatment.

As ever we would like to recognise the strong support we continue to receive from SA Pathology and the University of South Australia. In particular, we would like to recognize the support of Dr Glenn Edwards, Director of Pathology, SA Pathology. Being embedded in Health and being able to access patients' samples and collaborate with pathologists and clinical colleagues brings an extra dimension to our work. Similarly, Professors David Lloyd, Vice Chancellor; Tanya Monro, Deputy Vice Chancellor; and Robert Vink, Pro Vice Chancellor, have been unfailing in their efforts to support and strengthen the CCB.

We are indebted to South Australian patients for allowing us to use their specimens to advance cancer research, and for the faith and support of the South Australian public who continue to donate generously to accelerate the work of the CCB. We are grateful to the teams at the Royal Adelaide Hospital Research Fund, the Health Services Charitable Gifts Board (HSCGB) and the Hospital Research Foundation for promoting our work and so professionally channelling donors' support.

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

Professor Hamish Scott

Centre for Cancer Biology 2016 Laboratory Reports

PhD students Alexander Lewis and Melissa Bennett may be researching differing blood cancers, but their goal is the same: to enhance current treatments in the hope of improving survival outcomes for patients. Both researchers are investigating sphingosine kinase, a protein that plays an all important role in promoting the growth of cancer cells.

Bringing Cancer Genomics to South Australia

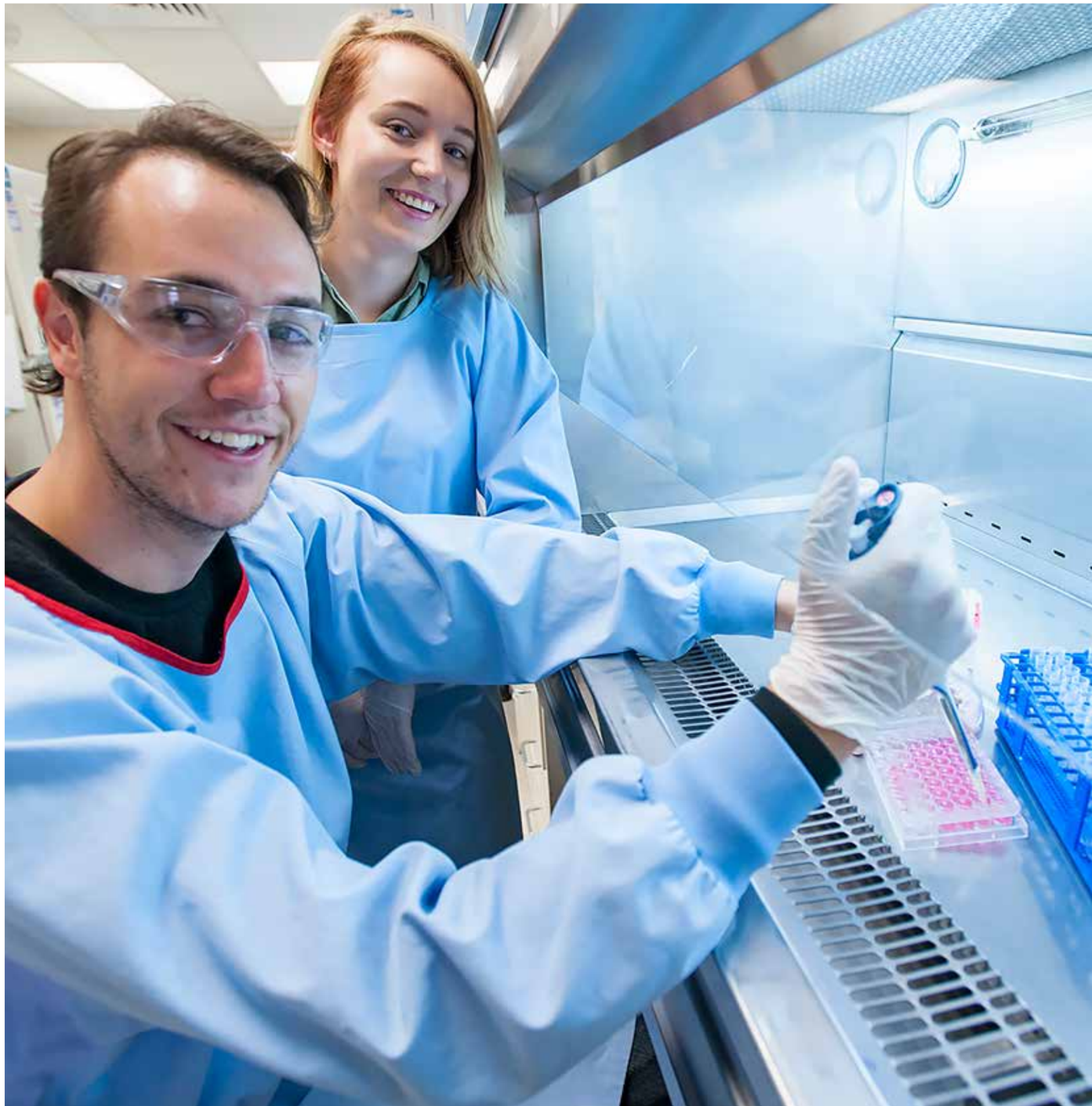
Australian Genomics is an alliance of over 78 partners linking together hospitals, research institutes, consumer groups and universities. This multi-disciplinary team is designed to capitalise on the strengths of each partner and allows the nation's best researchers, clinicians and educators to work together to integrate genomic medicine into everyday healthcare.

Across Australia patients with cancer and rare diseases are benefitting from a $25M National Health and Medical Research (NHMRC) Targeted Call for Research into Preparing Australia for the Genomics Revolution in Health Care. The grant — the second largest in NHMRC history — is being used to fund the Australian Genomics Health Alliance under the leadership of Professor Kathryn North, Director of the Murdoch Children's Research Institute in Melbourne.

Since 2016 the Centre for Cancer Biology (CCB) has been a proud member of Australian Genomics. Professor Hamish Scott, Head of the CCB's Molecular Pathology Research Laboratory, is the lead investigator for Australian Genomics in South Australia. "This grant allows South Australia to provide cutting-edge genomic testing to patients and provides hope for those who are otherwise unable to obtain a diagnosis" said Professor Scott. "Close collaboration between research, diagnostic and clinical services is key to the successful implementation of genomics technology and the size of this grant indicates the Australian government's support for a holistic approach to healthcare."

Australian Genomics is focused on two parallel pilot programs for patients around Australia suffering from cancer or a rare disease. These patients will benefit from access to faster, cheaper and more effective genomics testing. It is hoped that this testing will provide a diagnosis and inform treatment decisions. For cancer patients, this testing also means that researchers can decipher the molecular mechanisms driving tumour growth, allowing for more precise therapy and better monitoring of disease progression. Diagnostic tests based on genomic testing are already making their way to market to allow early diagnosis of at-risk patients. These immediate benefits will also impact future care as genomic testing helps researchers discover new pathways involved in cancer and direct the development of new anti-cancer therapies.

The CCB is proud to be an active member of Australian Genomics and supports genomic medicine as a way of the future for cancer therapy and research. Over the course of 2016, the CCB has worked with Australian Genomics to develop recommendations for the ethical and sustainable implementation of genomics medicine in healthcare. The CCB's Australian Cancer Research Foundation (ACRF) Cancer Genomics Facility will play a key role in Australian Genomics, processing samples from its pilot program and contributing to the development of new genomic assays and approaches for bioinformatics analysis. These activities place the CCB and the State at the forefront of the genomics revolution and establish South Australia as a leading voice in genomic medicine.



Tran Nguyen, Kyaw Ze Ya Maung, Richard D'Andrea, Ian Lewis, Debora Casolari

Saumya Samaraweera, Diana Iarossi, Ka Leung Li, Nur Hezrin Shahrin, Sarah Bray

Acute Leukaemia Laboratory

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

Our 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 with very different prognostic outcomes.

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. The genetic complexity of AML has hampered progress in the field, with the molecular basis for some subtypes still largely unknown. Overall survival for adults with AML is still only 30–40%, however for elderly patients, and some specific subtypes, prognosis is dismal. With the recent advances in genomics, research in this field has been accelerated and we have been using these new technologies to better understand the molecular aberrations responsible for disease initiation, response to treatment, and disease progression.

A significant research focus of our laboratory is the investigation of the mechanisms that control stem and progenitor cell growth and survival, which are commonly deregulated in AML. We have used genetic and epigenetic approaches to characterise novel genes and pathways important in AML pathogenesis. This has led to new biological insights, and novel markers for disease stratification. Our genomics analysis of adult and childhood AML cohorts has identified a role for mutations affecting selected DNA repair genes, and suggests that subtle changes to DNA repair function may be important for risk of developing AML, as well as determining response to anti-cancer therapies. Our continued investigation of these mechanisms will involve testing of novel therapies in selected AML samples, and discovery of new molecularly targeted treatments for high risk AML.

Outcomes for the Community

Our molecular and epigenetic studies will increase fundamental knowledge of AML pathogenesis, disease progression and factors that determine response to therapy. These studies are linked with our efforts to translate laboratory research findings into the clinic, through pre-clinical models, and independent patient cohort studies. For example, the laboratory findings discussed above raise the possibility that AML cases with GADD45A promoter methylation, or specific DNA repair gene mutations, may represent groups that can be targeted with tailored therapies, some of which are already in use for other cancers. The ongoing clinical trials are of direct benefit to patients, providing access to novel therapies that may improve outcome for elderly or high-risk AML patients currently facing dismal prognoses.

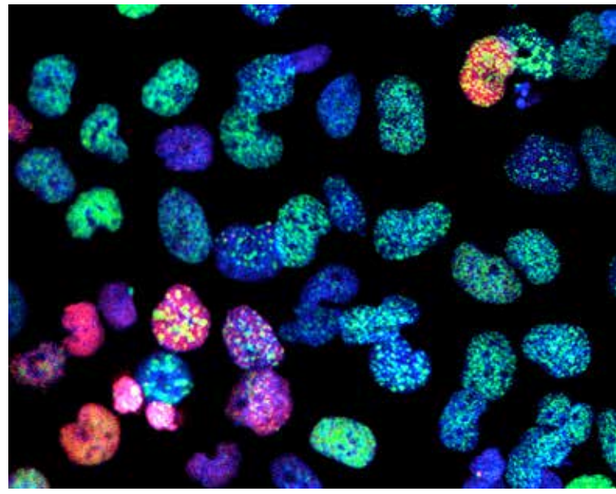
Key discoveries 2016

Epigenetic profiling in AML

It is well established that AML is genetically heterogeneous, and the mutation profile of individual samples at diagnosis is a prognostic factor. Despite findings that changes to DNA and chromatin modification (ie epigenetic changes) occur extensively in AML and are directly linked to pathogenesis, the contribution of epigenetic variability to treatment response and disease progression was previously unclear. In a recently published international collaboration, we have determined the relationship between epigenetic heterogeneity, common AML mutations, and genome-wide gene expression patterns at diagnosis and in relapsed disease samples. This study revealed epigenetic heterogeneity in diagnosis AML samples that evolves through AML progression in a manner that is independent of mutations, thus adding a further layer of complexity to disease evolution, and potentially impacting clinical outcomes. This work was recently published in *Nature Medicine* (Li *et al*, 2016). In a related study we are investigating the prognostic relevance of a specific DNA methylation event in the tumour suppressor gene, GADD45A, a gene also shown to be a key regulator of normal blood stem cell growth and survival. We have previously demonstrated that this increased methylation in the promoter region of GADD45A occurs in 40% of AML samples and is an independent predictor of poor patient outcome for patients treated with chemotherapy. Our current investigations are focussed on dissecting the differences in disease biology between patients with and without this epigenetic mark, and establishing how this highly specific epigenetic event is associated with such a significant difference in patient outcome. Our studies will provide important data regarding the clinical utility of this DNA methylation event, as well as generating new biological insights into the factors that determine disease aggressiveness and response to therapy.

Clinical trials in AML

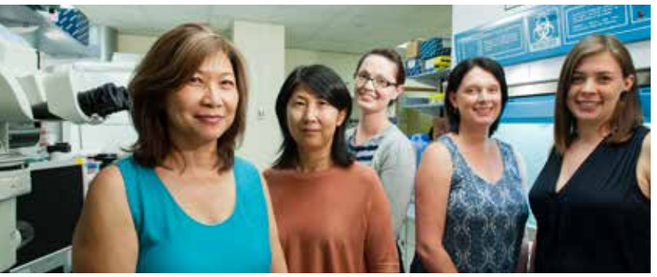
The fundamental research in the Acute Leukaemia Laboratory is complemented by a number of laboratory and clinical studies, which test new therapies for AML, and are carried out in conjunction with the Departments of Haematology at SA Pathology and the Royal Adelaide Hospital. These studies provide AML patients access to clinical trials for a number of novel therapies, and allow parallel laboratory studies investigating the effects of these agents on patient samples. Such studies are critical for understanding the mechanism of these drugs in human AML, and for investigation of the specific molecular factors that affect drug response across a range of AML samples.



Rescue of FANCD2 activity following retroviral transduction of an immortalised fibroblast cell line from a Fanconi Anaemia patient
Nuclear staining for gamma-H2AX (green) and FANCD2 (red) foci, following induction of DNA damage with DNA cross-linking agent. Nucleus is stained blue (DAPI).

Rare DNA repair gene variants in AML

As an approach for discovery of novel mutations in AML, and novel pathways contributing to pathogenesis and treatment response, we performed whole exome sequencing (WES) analysis of tumour DNA for a cohort of 145 AML diagnosis samples obtained (with ethics approval) from the SA Cancer Research Biobank (SACRB) and Princess Alexandra Hospital (Brisbane, QLD). Consistent with other AML genomics studies, we identified a number of aberrations specific to the leukaemia samples in genes that have previously been reported as recurrently mutated in AML. More interestingly however, we identified enrichment in the AML cohort of deleterious mutations in genes associated with DNA repair and the recessive disease Fanconi Anaemia (FA, FANC genes). While FA is caused when both copies of a single FANC gene are affected by mutations, and is associated with an extremely high risk of AML, this sequencing analysis suggests that rare heterozygous deleterious mutations affecting these 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. Recent studies suggest that such mutations are important particularly in the context of certain environmental exposures. To test for functional consequences associated with these mutations we are using highly sensitive assays for DNA damage in engineered cell line models and selected patient samples, with and without these mutations. Our access to patient samples also allows us to test whether it is possible to sensitise AML samples with heterozygous DNA repair gene mutations, to current clinical agents that target tumour cells with impaired DNA repair pathways, as a potential tailored therapy for these AMLs.



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

Cell Signalling Laboratory

Associate Professor Yeesim Khew-Goodall PhD

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

Our main areas of research are:

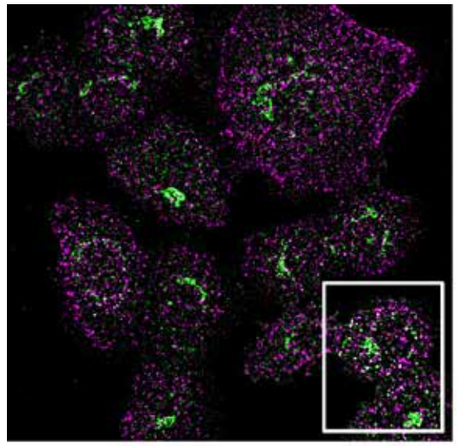
The role of protein trafficking in breast cancer
Dysregulation of cell proliferation is a major driver of cancer. Whether a cell grows and divides, remains quiescent, or dies, is determined in large part by its responses to extracellular growth factors, which bind receptors on the cell surface to activate signalling pathways within the cell.

We study the signalling pathways that control the amount of growth factor receptors that are displayed on the cell surface, and we have identified a major receptor trafficking regulatory pathway that is dysregulated in multiple solid cancers. We have discovered that the protein tyrosine phosphatase PTPN14 (also called Pez) and its substrate PKCδ regulates the amount of growth factor receptors on the cell surface available for ligand binding and signalling. PTPN14 is mutated in multiple cancers, including breast and colorectal cancers and our studies have shown that it is a suppressor of metastasis. Current studies in the Cell Signalling Lab cover understanding the fundamental mechanisms of receptor trafficking regulated by this PTPN14-PKCδ signalling pathway, understanding how dysregulation of this pathway leads to human diseases like cancer, and deciphering how cancers with dysregulation in this pathway and other trafficking abnormalities can be treated.

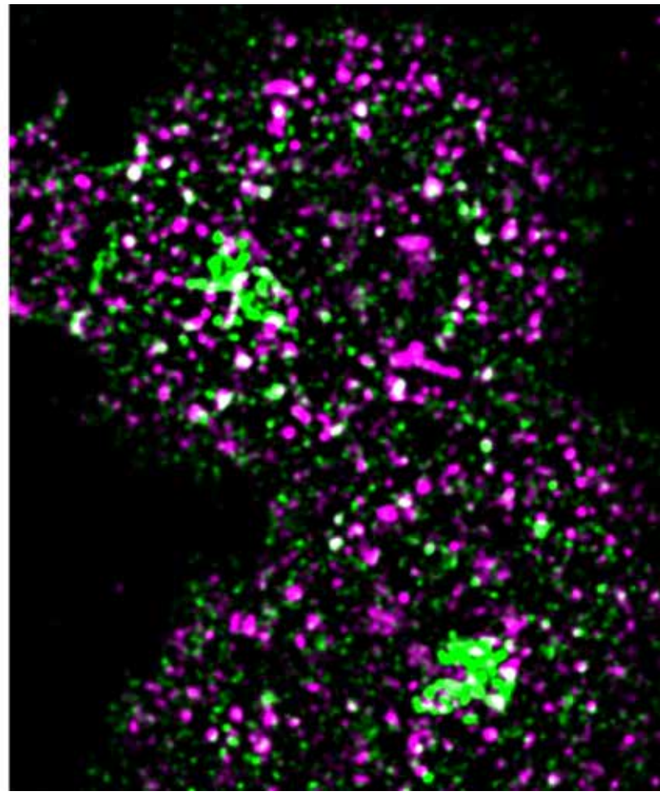
The role of mir-200 in neuroblastoma, in collaboration with the Gene Regulation Unit
Neuroblastoma is a childhood cancer usually affecting children under the age of five, with metastasis being the main cause of death. The ability of cancer cells to invade their surrounding tissue is critical for their spread to secondary organs. We are identifying targets of miR-200 critical for assembly and regulation of the invasive machinery in neuroblastoma, how they act to promote invasion and how they are regulated.

Key discoveries 2016

A particularly exciting development this year is the generation of a new PTPN14 knockout mouse, showing a number of phenotypes that have not been previously reported, but which are consistent with the role of PTPN14 in multiple cancers. With this mouse we were also able to confirm that PKCδ is indeed a physiological substrate *in vivo*.



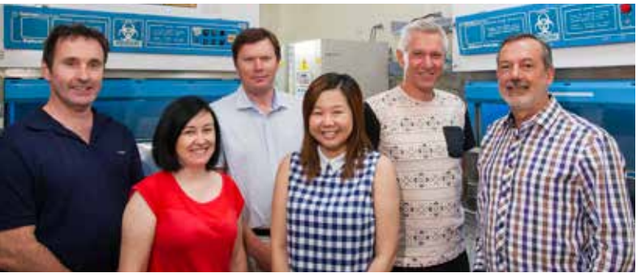
Super-resolution microscopy (STED) image showing colocalisation of protein tyrosine phosphatase PTPN14 (Pez) (green) with an endosomal marker (magenta) following EGF stimulation



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. Current work is 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.



Tim Hercus, Emma Barry, Denis Tvorogov, Winnie Kan, Frank Stomski, Angel Lopez

Rebecca Wright, Melanie Pudney, Hayley Ramshaw, Ceilidh Marchant, Duncan McKenzie, Anna Sapa

Cytokine Receptor Laboratory

Professor Angel Lopez MBBS PhD FRCPA FAA FAHMS

Cytokines are small proteins that act as haematopoietic regulators but also control a range of immune functions and inflammatory responses. Cytokines are typically required to maintain homeostasis until reactive cellular responses are required and act through specific receptors expressed on the surface of responsive cells. Our laboratory is particularly focussed on an important family of cytokines known as the beta common (βc) family, so named because they all utilise a shared receptor subunit, βc.

This family includes GM-CSF, IL-3 and IL-5. Our work is relevant in diseases such as leukaemia that exhibit abnormalities in expression and signalling by βc cytokine receptors, and in allergic disorders, like rhinosinusitis and asthma, where excessive activation of βc cytokine receptors in myeloid cells in the nose or the lung contributes to restricting breathing and causing damage to the nose or the lungs. Our major focus is to understand the how and why of GM-CSF, IL-3 and IL-5 function in both health and disease and to use this knowledge to develop novel therapies. Our research program seeks to determine in atomic detail, the structural and functional properties 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 GM-CSF bound to the alpha subunit of its receptor (GMRα) and identified key interactions between GM-CSF and GMRα that play a major role in GM-CSF signalling. Importantly we also observed conformational changes within GMRα that are necessary for assembly of the GM-CSF signalling, ternary complex, that we previously determined. Excitingly we have now solved the structure of IL-3 bound to the alpha subunit of its receptor (IL-3Rα) as well as the structure of IL-3 in its IL-3 signalling, ternary complex with IL-3Rα and the βc subunit. This structural information has revealed the molecular interactions that allow assembly of the IL-3 receptor complex and has enabled us to probe the functional role played by each of these interactions. Our analysis has already provided a detailed understanding of how IL-3 functions and by comparison with other structures such as those we have already solved for equivalent GM-CSF receptor complexes, is providing clues about the unique and shared biological functions of IL-3 and GM-CSF in health and disease.

Our candidate new drugs have progressed into new clinical trials. There are currently three trials involving our IL-3Rα antibody that are recruiting patients with acute myeloid leukaemia or myeloproliferative diseases running in Germany, USA, France, Netherlands, Belgium and Spain.

In other studies we have been investigating the possible significance of the high expression of the IL-3Rα protein (CD123) on acute myeloid leukaemia stem cells. The over-expression has allowed this protein to become a biomarker for these cells but we have found that it also results in reduced levels of an adhesion molecule (called CXCR4) responsible for keeping these cells in the bone marrow. Cells expressing high CD123 have lower CXCR4 and we believe they are less likely to be retained in the bone marrow facilitating their egress into the blood stream.

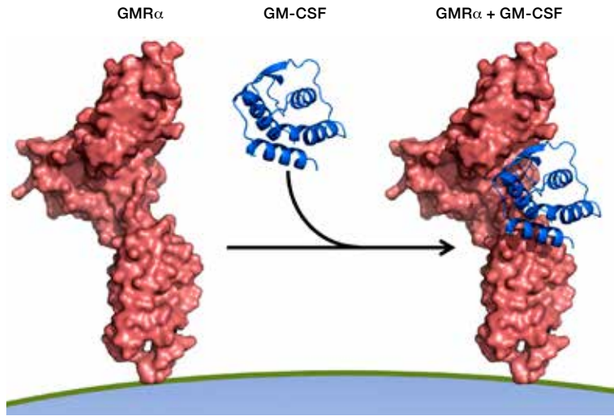
The monoclonal antibody CSL311 that targets the cytokine binding site 2 of βc is being advanced together with CSL Limited and Associate Professor Grimbaldeston's laboratory for the treatment of allergic inflammatory diseases. This is an exciting project aiming at a more personalised medicine without the need for corticosteroids.

In collaboration with Professor Shaun Jackson and Associate Professor Simone Schoenwaelder from the Heart Research Institute in Sydney we have discovered an important role for 14-3-3 in controlling the way platelets can cope with stress and depletion of energy reserves, helping to control their clotting ability. Inhibiting the 14-3-3 protein from the platelet can protect against the development of lethal blood clots, as seen in patients receiving chemotherapy.

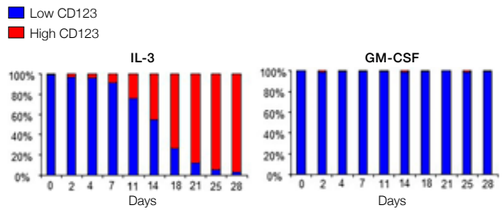
Key discoveries 2016

As the IL-3 receptor is overexpressed in acute myeloid leukaemia as well as in chronic myeloid leukaemia (in collaboration with Professor Tim Hughes, SAHMRI and SA Pathology) 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 and we are evaluating their role in haematological malignancies in collaboration with Professor Tim Hughes and Dr David Ross (SA Pathology). Of these proteins, JAK1 has emerged as an important player in IL-3 signalling. Exploring the roles of JAK1 and JAK2 we have resolved the mechanism of sustained JAK phosphorylation after treatment with a JAK inhibitor. This drug, Ruxolitinib, is approved for treating myeloproliferative neoplasm and a better understanding of its mechanism of action will guide optimal clinical utilisation.

In collaboration with Professor Michael Parker and Dr Sophie Broughton (St Vincent's Institute Medical Research), we solved the structure of human GM-CSF bound to the alpha subunit of its receptor (GMRα) and identified unexpected conformational changes in the receptor that play an important role in GM-CSF signalling (Broughton *et al*, *Structure* 2016). In collaboration with Professor Michael Brown and Dr Tessa Gargett (CCB) we also showed that inhibition of GM-CSF function reduced myeloid-derived suppressor cell function, an observation that could offer therapeutic promise for patients with certain solid tumours (Gargett *et al*, *Clin Trans Imm* 2016). Our collaboration with Professor Shaun Jackson discovered that a protein known to cause cancer is also responsible for life-threatening blood clots, including deep vein thrombosis (DVT), which many people with cancer suffer from. Our novel inhibitors that target this protein are being developed as cancer medications but may have a dual role in both fighting the cancer and the dangerous by-product of cancer therapy, blood clots, at the same time. (Shoenwaelder *et al*, *Nature Communications* 2016).



GM-CSF forms a binary complex with the alpha subunit of its receptor (GMRα)
This is the first step in activating the GM-CSF signalling cascade, a process that is linked to multiple biological outcomes including enhanced myeloid-derived suppressor cell development.



Haematopoietic cells with either low (blue) or high (red) expression of CD123 (IL-3Rα) were cultured in a 99:1 ratio (99% low CD123, 1% high CD123) in low concentrations of (A) IL-3 or (B) GM-CSF
The relative proportion of each population was monitored and, over time, the high CD123 cells outgrew those with lower expression when cultured in IL-3 but not GM-CSF. This demonstrates the specific advantage these cells have when grown in IL-3, similar to the situation of malignant cells outgrowing the normal cells in the bone marrow in leukaemia.

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. As we come up with new leads we collaborate with our pathology and clinical colleagues to accelerate the applicability of our research to our patients.

Abel Anshabo, Qinyong Mao, Sarah Al Haj Diab, Hugo Albrecht, Nishat Khair, Richard Head, Sunita KC Basnet, Mingfeng Yu, Md Saiful Islam, Benjamin Noll, Shudong Wang, Stephen Philip, Yi Long, Matt Sykes, Jasmine Karanjia, Aleks Ochnik, Manjun Li, Ge Zu, Yuchao Yang, Laychiluh Bantie, Robert Milne, Ahmed Magdy Abd El Aziz, Jimma Lenjisa

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 programs at different stages of drug development.

Once we identify a protein target, molecules that can inhibit its oncogenic activity are designed and synthesized 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.

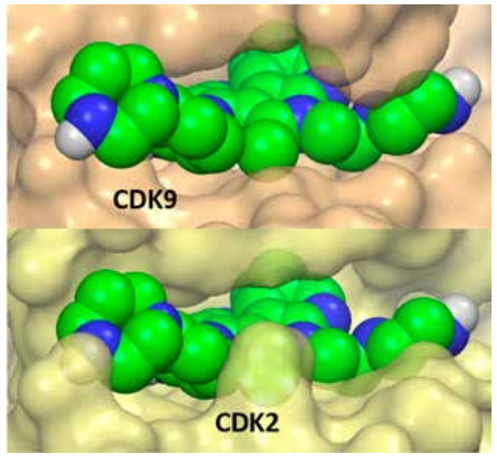
One of our main focuses is drug discovery targeting cyclin-dependent kinases (CDKs). CDKs are key players in cell cycle progression and transcription, but their aberrant behaviour is implicated in cancer progression. For example, > 80% of cancer have CDK4/6 deregulation. CDKs 7/8/9 promote transcription of genes encoding key apoptotic regulators such as Bcl-2 family and onco-proteins such as c-Myc and HDM2. Consequently, CDKs are prime targets in targeted cancer therapy. We mainly focus on CDK4, CDK6, CDK8 and CDK9, and have identified several highly potent and selective CDK inhibitors with impressive safety profiles. Currently we are at the stage of developing them for use in clinical trials for acute myeloid leukaemia, chronic lymphocytic leukaemia, and advanced prostate, breast, colorectal, lung 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 PI3K/Akt/mTOR and Ras/Raf/MEK/ERK mediated oncogenic activities. Inhibition of Mnks effectively blocks the oncogenic activity of eIF4E, while having 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. Concurrently we are also investigating Mnk related cell and structure biology.

Key discoveries 2016

Discovering highly selective CDK9 inhibitors

CDK9 is a key transcriptional regulator and a lucrative target for the treatment of various cancers. 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 identified a highly potent class of CDK9 inhibitors and are tailoring this scaffold to significantly increase the selectivity while maintaining potency. We expect to advance these inhibitors into clinical development and trials.



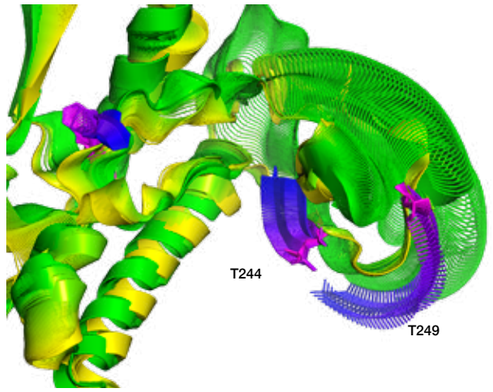
Designing highly selective CDK9 inhibitors

Novel CDK4/6 inhibitors as anti-cancer agents

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 invaluable 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 very high potency and specificity for CDK4/6, against a larger panel of kinases (Tadesse *et al*, *J Med Chem*, 2017; Tadesse *et al*, *Future Med Chem* 2017). Moreover, these compounds possessed favourable drug properties with high oral bioavailability.

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*, *Future 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 site (Basnet *et al*, *Mol Pharm* 2015).



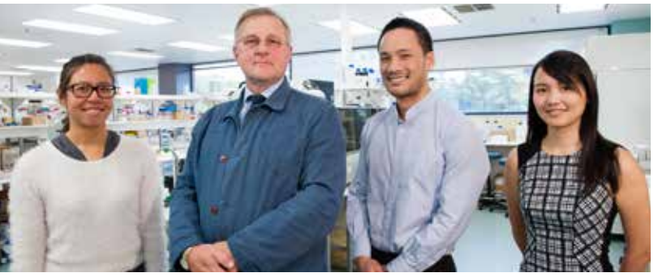
Dramatic conformational changes during Mnk2 activation

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. I-073 is highly efficacious against multiple *ex vivo* and *in vivo* cancer models, including the 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. I-073 offers an exciting therapeutic prospect with excellent potential for progress towards the clinic.

Outcomes for the Community

Cancer remains the most common cause of human mortality. 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 complex diseases or biological puzzles.

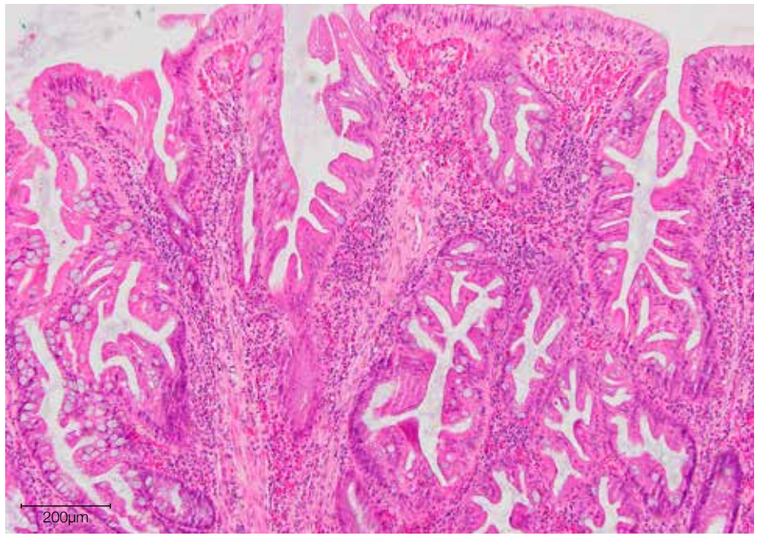


Teresa Tin, Andrew Ruszkiewcz, Vinh-An Phan, Stephanie Wong

Gastroenterology Research Laboratory

Associate Professor Andrew Ruszkiewicz MD FRCPA

The Gastroenterology Research Laboratory focuses on neoplastic diseases affecting the gastrointestinal tract including the oesophagus, colorectum, pancreas and liver. We are particularly interested in developing new methods and diagnostic techniques for early detection of gastrointestinal cancers and its precursors. In colorectal cancer (CRC), we work on non-invasive, blood based tests for detecting sporadic and familial forms of this disease.



Sessile serrated adenomas usually have an intact surface epithelium. As these polyps do not bleed, the faecal occult blood test is ineffective in their detection.

Key discoveries 2016

Serrated polyps as precursors of colorectal cancer

While the majority of CRC is believed to evolve through the conventional adenoma to carcinoma sequence, it has become apparent that as many as 30% of CRCs may arise through an alternate route, known as the 'serrated pathway'. The sessile serrated adenoma/polyp (SSA/P) has been recently recognized as the most common precursor for this pathway and its correct identification in clinical and pathologic practice is of critical importance. The emergence of SSAs as a precursor of CRC, and its morphological similarity to common hyperplastic polyps which are innocuous lesions with no potential for malignant transformation, presents a major challenge for the colonoscopic detection, removal and pathologic identification of these lesions. Realisation of the potential for malignant transformation of SSAs requires detailed characterization of this polyp type in order to improve CRC prevention and early detection. In contrast to conventional adenomatous polyps, sessile serrated adenomas/polyps do not bleed and thus cannot be detected by the faecal occult blood test which is currently used in the National Bowel Cancer Screening Program.

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 CRC and its precursors including conventional adenomas and SSA/P. With CSIRO, we have identified a protein biomarker panel in serum that may diagnose colorectal adenomas with sensitivity of 55% and 58% respectively for advanced precursor adenomas and sessile serrated adenoma at the specificity of 86.4%. This is better than the FOBT which detects advanced precursor adenomas and sessile serrated adenoma at 27% and 16% sensitivity, respectively. Our study of serrated polyps using the next generation sequencing aims to uncover a molecular signature which identifies individuals with underlying genetic predisposition for developing serrated pathway colorectal cancer.

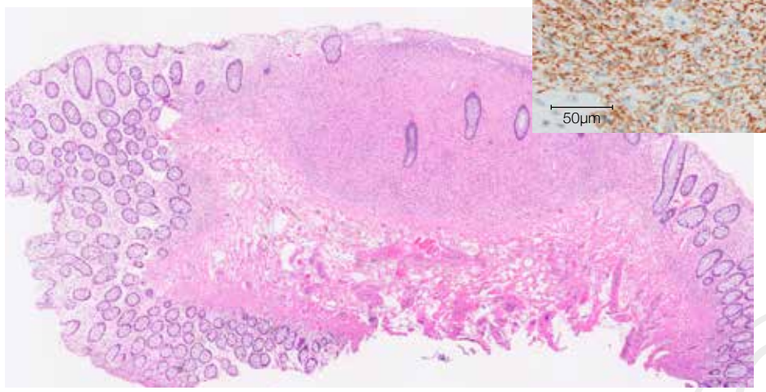
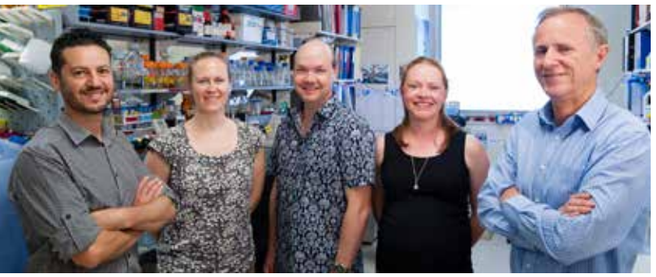


Fig 1 Perineurial-like stromal proliferation occurs in almost 10% of sessile serrated adenomas harbouring BRAF V600E mutation and is a strong indication of epithelial-mesenchymal interactions in serrated polyps.
Fig 2 inset Claudin-1 over expression in these polyps (as shown in one of our studies) may also aid in the diagnosis of these lesions.

Outcomes for the Community

Our work towards a non-invasive blood-based test for conventional adenomas and serrated polyps will result in early detection of the precursors of CRC facilitating their removal and ultimately reducing the morbidity and mortality associated with this deadly disease killing thousands of Australians every year.



John Toubia, Kate Dredge, Andrew Bert, Katherine Pillman, Greg Goodall
Absent: Dawei Liu, Francisco Sadras and Rosemary Sladic

Gene Regulation Unit

Professor Greg Goodall PhD, FAHMS

Our research investigates molecular mechanisms controlling cancer invasion and metastasis. Most deaths from 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, non-coding 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 and circular RNAs 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 (*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 2016 our publications received 1,370 citations.

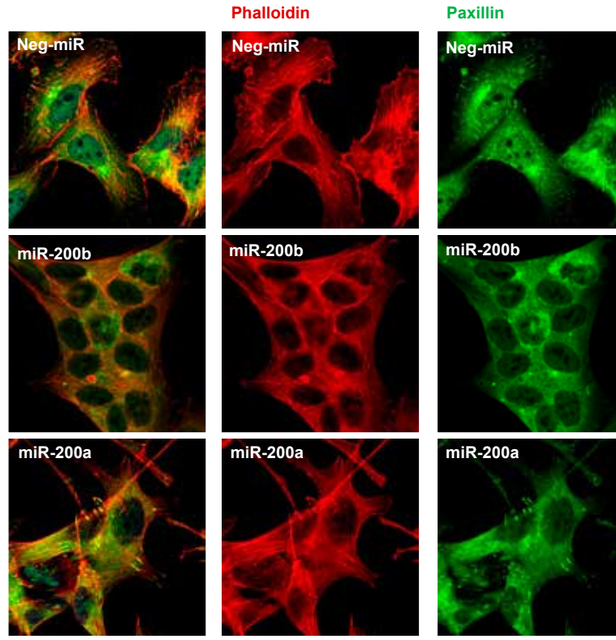
Key discoveries 2016

Functions of circular RNAs in epithelial to mesenchymal transition

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. In addition to pursuing the functions of the many circular RNAs that we have identified to be down-regulated during EMT, due to their control by the RNA-binding protein Quaking (QKI), we have also identified a circular RNA that is regulated in the opposite direction, being expressed in epithelial cells, but disappearing during EMT. This particular circular RNA has interesting properties relating to epithelial cell functions that we are continuing to investigate.

A network-biology perspective of microRNA function and dysfunction in cancer

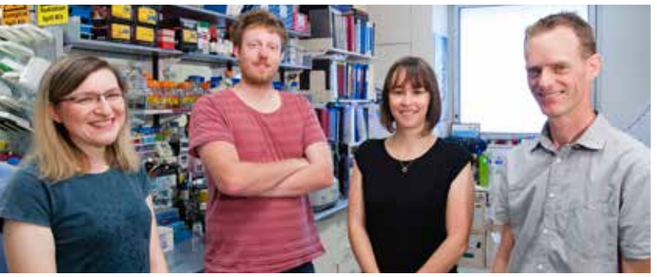
MicroRNAs (miRNAs) participate in most aspects of cellular differentiation and homeostasis, and consequently have roles in many pathologies, including cancer. In recent years, the increased availability of gene expression data and the development of methodologies that profile miRNA targets *en masse* have fuelled our understanding of miRNA functions, and of the sources and consequences of miRNA dysregulation. Advances in experimental and computational approaches are revealing not just cancer pathways controlled by single miRNAs but also intermeshed regulatory networks controlled by multiple miRNAs, which often engage in reciprocal feedback interactions with the targets that they regulate. To provide an up to date perspective on the complexities of regulation of cellular properties by microRNAs, particularly in the cancer context, we have reviewed the operation of individual and co-expressed miRNAs acting at multiple levels in signalling networks (Bracken *et al*, *Nature Reviews Genetics* 2016). We proposed that although miRNAs typically only have a mild effect on individual targets, combinatorial miRNA–target networks have been shaped by evolution to produce profound effects of miRNAs on cellular properties, including their regulation of many processes whose dysregulation leads to cancer. We also propose that the intricate and reciprocal relationship that exists between miRNAs and transcription factors is particularly important. We also considered how miRNA dysregulation underlies cancer progression, arguing for the importance of using genome-wide experimental and bioinformatic tools to examine miRNA function from a network-biology perspective.



The effects of microRNAs on the differentiation state of neuroblastoma cells

A microRNA that has different roles depending on its abundance

In collaboration with Associate Professor Paul Ekert and Dr Nisha Narayan (Murdoch Children's Research Institute), we have investigated the function of a microRNA, called miR-155, that has been previously reported by different groups to have opposing functions during the development of acute myeloid leukaemia, acting in some cases as an oncogene, aiding the development of leukaemia, but in other cases acting as a tumour suppressor. In murine models of the leukaemia developed by our collaborators, it was found that the effect of the microRNA depends on how much is present in the cells, with very high levels suppressing the proliferation of the leukaemia cells, but more modest levels have the opposite effect. This was due to the high levels of the microRNA affecting the expression of additional gene targets that were not regulated by the lower levels of microRNA. These findings collectively describe a novel dose-dependent role for miR-155 in the regulation of AML, which may have important therapeutic implications (Narayan *et al*, *Leukaemia* 2016).



Victoria Arnet, Daniel Neumann, Caroline Phillips, Phil Gregory

Gene Regulation in Cancer Laboratory

Dr Philip Gregory PhD

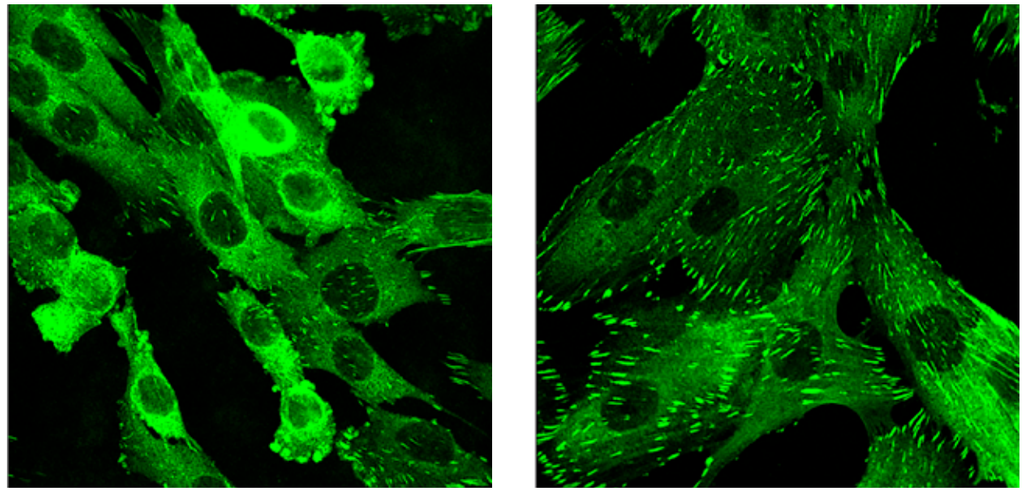
Solid tumours, such as those of the breast, prostate and colon, are composed of epithelial cells. When these cancers spread (or metastasise) they are difficult to treat and ultimately lead to most cancer related deaths.

Our laboratory is identifying the molecular mechanisms which enable epithelial tumour cells to gain invasive and metastatic properties. We focus on the function of non-coding RNAs in the progression of solid tumours towards a metastatic state. The ability of non-coding RNAs, such as microRNAs, to regulate entire programs of gene expression makes them particularly important therapeutic targets. Using *in vitro* and *in vivo* models of cancer cell invasion and metastasis, we have identified microRNAs that directly influence the ability of breast and prostate cancers to progress and metastasise. Our ultimate aim is to determine how the actions of non-coding RNAs may be exploited to limit the spread of epithelial derived cancers.

Key discoveries 2016

MicroRNA-375 regulates prostate cancer progression
In collaboration with Dr Luke Selth and Professor Wayne Tilley at the University of Adelaide, we identified a microRNA which controls epithelial cell plasticity in prostate cancer (Selth *et al*, *Oncogene* 2016 in press). MiR-375 is elevated in the circulation of men with metastatic disease and directly controls the invasive properties of prostate cancer cells. Furthermore, miR-375 levels are regulated by the important EMT-inducing transcription factor ZEB1, and this in turn controls prostate cell invasion through modulating YAP1 levels. This ZEB1-miR-375-YAP1 signature is evident in patient samples demonstrating its clinical relevance in prostate cancer.

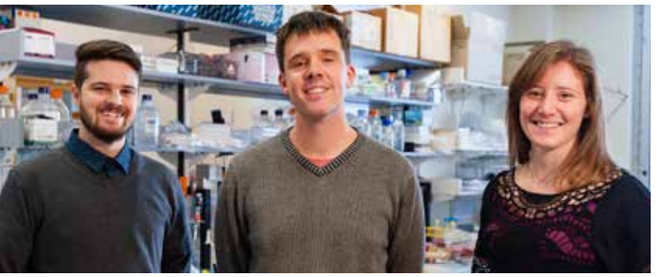
Neuropilin-1 is responsive to androgen deprivation and predicts prostate cancer outcome
In collaboration with Dr Brett Hollier at the Queensland University of Technology, we investigated a role for Neuropilin-1 (NRP1) in prostate cancer. NRP1 expression inversely correlates with the expression of miR-200 (a metastasis suppressing microRNA), and Dr. Hollier's team identified a link between NRP1, androgen deprivation therapy and prostate cancer metastasis – work which was published in the journal Oncogene (Tse *et al,* 2016).



Tumour cells undergoing a dramatic change in focal adhesions after introduction of a microRNA

Outcomes for the Community

Tumour metastasis is the major cause of cancer related death in solid tumours such as the breast, prostate and colon. Our work has identified new avenues through which therapeutic targets may be developed to limit the spread of these epithelial derived cancers, with the aim of improving patient outcomes.



Klay Saunders, Cameron Bracken, Kaitlin Scheer
Absent: Feng Yu

Gene Regulation Networks Laboratory

Dr Cameron Bracken PhD

Understanding how genetic networks become dysregulated in cancer is critical if we are to understand and prevent cancer progression.

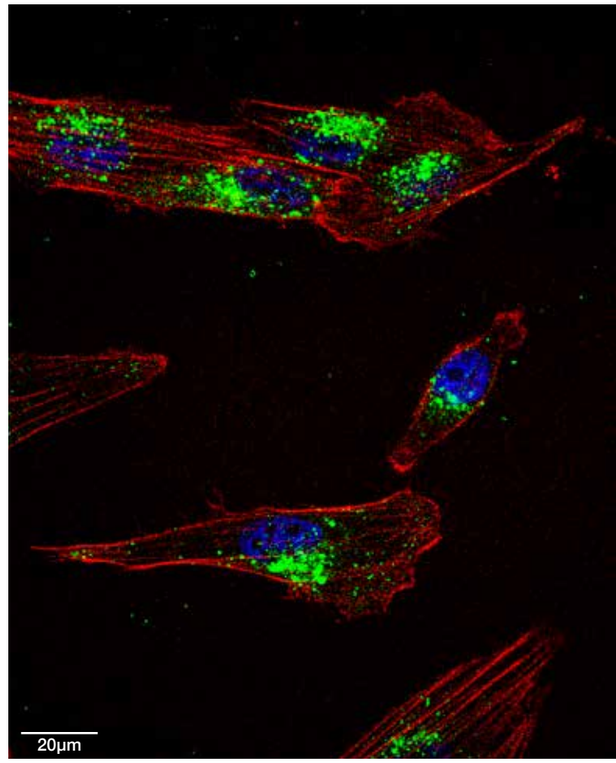
The Gene Regulation Networks Laboratory focuses on important genes called microRNAs which are master regulators of gene expression networks, both in normal physiology and cancer. Utilising cancer cell lines and mass sequencing techniques, we are investigating how microRNAs select and regulate their target genes and how these genes interact to regulate the invasive capacity of cancer cells. This is particularly important as it is the spread of cancer cells (metastasis), which is responsible for most cancer related deaths.

We have identified that different microRNAs act in combination to suppress metastasis and it is only through understanding their combinatorial actions that one can fully understand their functions. In doing so, we hope to identify new genes for use in either diagnosis or future therapeutic targeting. We are also investigating a new role for microRNAs within the nuclei of cells, an area of growing interest where we feel there is compelling evidence to suggest critical, but currently under-investigated, roles.

Key discoveries 2016

Investigating the diversity of microRNA-like molecules
The human genome encodes several thousand different microRNAs, but recent mass-sequencing has indicated that the number of microRNAs may be significantly higher as a wide variety of larger RNA molecules are also naturally chopped up into microRNA-sized fragments. Many of these are themselves dysregulated in cancer and hence, might play important roles as either drivers of cancer or as tumour-suppressors. We have published several studies in 2015 (Thomson *et al*, *Nucleic Acids Research* and Yu *et al*, *Plos One)* where we examine this question. We find that some of these diverse RNA fragments can indeed regulate genes in the same way as traditional microRNAs do, including one specific microRNA that promotes breast cancer progression. Understanding how such microRNAs work will allow us to better understand the genes that control cancer. These genes, or the microRNAs themselves, may be targets of future therapy.

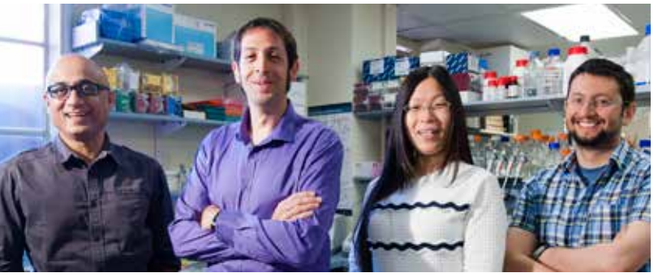
Examining differences between EMT-promoting stimuli
Epithelial-mesenchymal transition (EMT) describes a change in cell state, driven by changes in underlying gene expression, that is used in normal processes to assist cell movement, but that is also commandeered in cancer to promote metastasis. We have extensive expertise investigating this process and the involvement of microRNAs in regulating it. Along with collaborators in Melbourne (Cursons *et al*, *Cell Communication and Signalling*), we have found that different stimuli promote subtly different forms of EMT that will impact upon the effectiveness of different chemotherapy approaches. Understanding and accounting for these differences will be important when selecting therapeutic intervention strategies.



Human neuroblastoma cells
Green fluorescence indicates activated EGF-receptor, an important cancer-associated signalling protein that we work on. Red fluorescence is the actin cytoskeleton. Blue is a DAPI DNA stain indicating cell nuclei.

Outcomes for the Community

Metastasis is a key component of most deaths that result from solid tumours. Our work identifies key genes and new mechanisms that control this process that will improve diagnosis and guide therapeutic choices.



Vinay Tergaonkar, Simon Conn, Feng Yu, Gökhan Cildir

Inflammation and Human Ailments Laboratory

(IMCB Visiting Professor Laboratory)

Professor Vinay Tergaonkar PhD
Associate Professor Simon Conn PhD

Our research group is a collaboration between the Centre for Cancer Biology and the Institute of Molecular and Cell Biology (IMCB) in Singapore, led by Professor Vinay Tergaonkar and Associate Professor Simon Conn.

This laboratory group's focus is on the key role chronic inflammation plays in almost all human diseases, including cancer development. Inflammation is a normal immune system response to infection. However, this process can become unregulated and healthy cells can be damaged in the cross-fire, resulting in disease.

While aging is known to be associated with chronic low-grade inflammation (called Inflammaging) which predisposes the individual to development of disease, cancers in patients of any age can hijack the normal immune system response to facilitate growth and invasion of other areas of the body, resulting in a more highly life-threatening evolution of the disease. Professor Tergaonkar is a global thought-leader in the study of the Nuclear Factor kappa B (NF-kB) pathway as a master regulator of inflammation, but given its pivotal role, it cannot be targeted for chemotherapy. Therefore, our laboratory is working to decipher what is happening at a genetic level downstream of NF-kB that allows the immune system to be hijacked in such a manner.

We utilise cutting-edge genetic strategies, including high-throughput RNA and DNA sequencing to great effect to identify the key players in inflammation. This identification will allow the development of novel and improved targeted therapies for all diseases, especially cancers which have become resistant to chemotherapy. Targeting inflammation specifically will contribute to reducing the side-effects and longevity of current cancer drug treatments.

To complement this approach, we have identified other novel genetic players which act upstream of inflammation and other cellular responses which are hallmarks of cancer. We are implicating these molecules and proteins in new processes and we are confident in our ability to target these Trojan horses of cancer to block the initiation, or relapse of cancer and to resensitise resistant cancers to frontline chemotherapeutics.

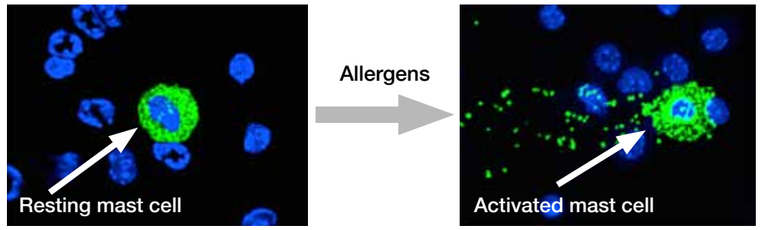
Key discoveries 2016

Mast cell chromatin profiling identifies novel mediators of allergic inflammation

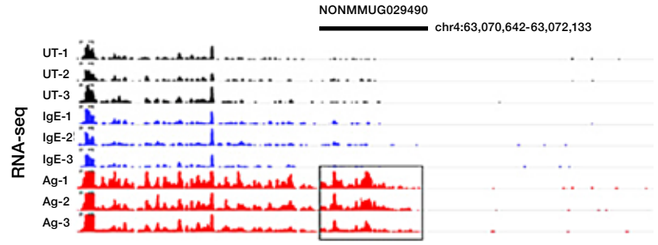
Allergy is one of the least understood immunological responses partly due to the diversity of allergens and the complexity of the immune responses against them. In allergic responses, mast cells are key players with their ability to rapidly degranulate, thereby acutely delivering inflammatory mediators, while also sustaining the inflammatory response through generation of *de novo* transcripts. Although the molecular details of degranulation in mast cells are extensively studied in allergic inflammation, the genome-wide view of chromatin dynamics, enhancer remodeling and transcriptional regulation are largely unexplored. Here, using systems biology approach, we characterized the basal, immunoglobulin E (IgE)-sensitized and antigen (Ag)-induced genome-wide epigenetic and transcriptomic dynamics in mouse and human mast cells. Our results not only suggest extensive reorganization of mast cell chromatin in response to FcεR1 crosslinking but also implicate various disease-associated single nucleotide polymorphisms (SNPs) in mast cell regulatory chromatin domains (Cildir G *et al*, *Trends in Molecular Medicine* 22: 414-29, 2016).

Telomerase promoter reactivation in cancer

Reactivation of telomerase, the chromosome end-replicating enzyme, drives human cell immortality and cancer. Point mutations in the telomerase reverse transcriptase (TERT) gene promoter occur at high frequency in multiple cancers. The Tergaonkar laboratory have illuminated the regulation dynamics of the TERT promoter through NF-kB and long-range chromatin interactions (Tergaonkar V, *Cell Cycle* 15: 156-7, 2016. Akıncılar S *et al*, *Cancer Discovery* 6: 1276-1291, 2016).



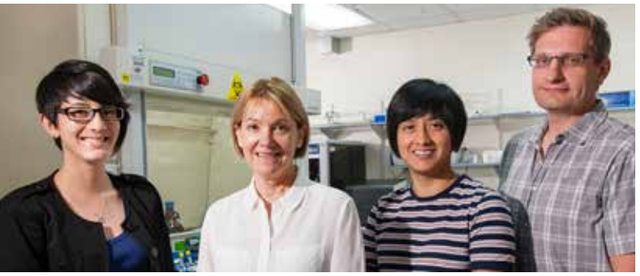
Allergen-induced degranulation of mouse peritoneal mast cells (green: avidin-FITC binding to mast cell granules)



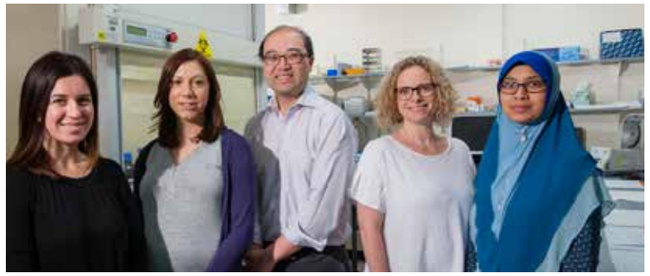
MMUG029490 is a novel lncRNA biomarker of allergic inflammation

Outcomes for the Community

The previous discoveries from Professor Tergaonkar's laboratory on the role of master regulators of inflammation (NF-kB) and cancer (telomerase) have influenced many laboratories. Our current research discoveries indicate new druggable candidates which play key roles in inflammation and chemotherapy resistance of many cancers, offering a beacon of hope for improved cancer treatment.



Zoe Donaldson, Sue Branford, Nathalie Nataren, Adrian Purins



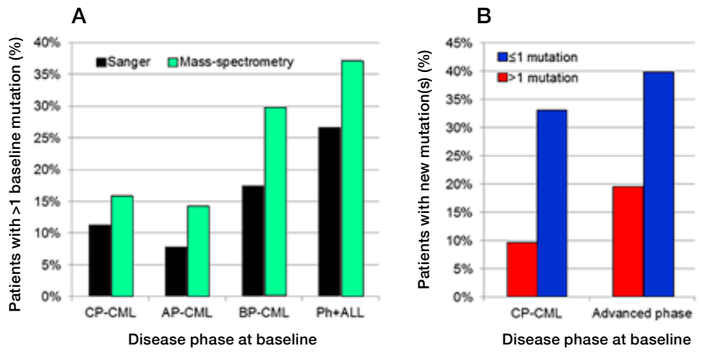
Jodi Braley, Alexandra Yeoman, David Yeung, Bronte Jamison, Nur Hezrin Shahrin

Leukaemia Unit, Genetics and Molecular Pathology

Associate Professor Susan Branford PhD, FFSc (RCPA)

For most patients diagnosed with chronic myeloid leukaemia (CML) today, the life expectancy is high and the development of small molecule drugs to treat CML is one of the great triumphs of cancer research. A small percentage of patients are able to achieve deep responses and eventually stop therapy without relapse, thereby relieving drug-related side-effects that impact quality of life.

However, despite improved survival, ~40% of patients display drug resistance or intolerance and require a change of therapy. More potent drugs can induce higher rates of response and lower rates of transformation to a rapidly fatal acute leukaemia, but are associated with higher toxicity and have not shown a survival advantage. It is not possible to identify patients at diagnosis who are destined for an optimal response and those who will fail therapy early. Therefore, it is not possible to determine which patients may benefit from more potent drugs despite the increased risk of toxicity. Our research aims to understand the molecular basis for the heterogeneity of drug response and to identify biomarkers at diagnosis that will predict response. We and others established that genetic mutations acquired within the BCR-ABL1 gene, which is the causal event of CML, is a major cause of drug resistance and occur in ~50% of resistant patients. New, advanced technology is now allowing us to perform integrative genomics to simultaneously assess all genes to search for other mutations that modify response to therapy. Our initial mutational analysis suggests that BCR-ABL1 expression may provide selective pressure for specific genes/gene family mutations that cooperate with BCR-ABL1 to drive CML progression. A series of *in vitro* functional validation assays are under development to provide a functional proof-of-principal for cooperation of BCR-ABL1 with individual mutations. A more complete understanding of these mutations should advance drug development and allow personalised therapy. We are also investigating biological factors, such as inherited genetic makeup, to determine drug response for individual patients. We aim to translate our work to the clinic by introducing a comprehensive biomarker testing panel at diagnosis that will more reliably predict treatment response and guide appropriate therapeutic decisions.



The association between multiple mutations and acquisition of new mutations for patients treated with ponatinib
A The frequency of patients with multiple BCR-ABL1 mutations detected by standard technique or more sensitive mass spectrometry, according to disease phase at study entry. **B** Rate of new mutations after ponatinib failure/discontinuation, according to the disease phase and number of mutations detected by mass spectrometry at baseline.

Key discoveries 2016

The impact of multiple low-level BCR-ABL1 mutations on response to ponatinib
Ponatinib is a third generation inhibitor of the activated BCR-ABL1 tyrosine kinase that was developed to overcome drug resistance in patients with CML. It is the only drug capable of inhibiting the T315I mutation of BCR-ABL1. This mutation is the most frequently detected mutation and prevents binding of the first and second generation drugs and therefore leads to rapid relapse and, in some patients, progression to a fatal acute leukaemia. We had previously developed a very sensitive technique to detect low levels of BCR-ABL1 mutations using mass spectrometry and demonstrated that some patients can harbour low level mutations that are not detectable by standard techniques. These mutations were associated with rapid relapse if patients were treated with an inhibitor for which the mutation was resistant. Furthermore, we found that if patients had multiple mutations, these were associated with a poor outcome, even if all of the mutations were predicted to be sensitive to subsequent inhibitors. We used the mass spectrometry technique for 363 patients enrolled in an international clinical trial of ponatinib to determine if ponatinib overcomes the risk of poor outcome for patients harbouring low level BCR-ABL1 mutations. The association between multiple BCR-ABL1 mutations and inferior response to second generation BCR-ABL1 inhibitor drugs was not seen with ponatinib therapy (Parker *et al*, *Blood* 127(15) 1870–1880, 2016). However, patients with T315I plus additional mutations did have poorer responses to ponatinib than those with T315I only. The data suggest that ponatinib may prove to be particularly advantageous for patients with multiple mutations detectable by mass spectrometry after drug resistance. However, patients with the T315I mutation plus other BCR-ABL1 mutations may benefit from close monitoring, experimental approaches, or stem cell transplantation to reduce the risk of treatment failure.

BCR-ABL1 quantitation and mutation detection from dried blood spots
Most of the world's CML patients reside in low resource areas, where treatment, diagnostic, and monitoring options are limited by the cost of drug treatment, and access to capable laboratory facilities. Shipping blood to specialised centres for testing is very costly, and test performance can be hampered by sample degradation during transit. These issues frequently preclude the diagnosis of CML for many patients, which denies their access to life saving therapy. We worked with collaborators in the USA, headed by Professor Jerry Radich of the Fred Hutchinson Cancer Research Centre in Seattle, to develop a method to extract RNA from dried blood spots for diagnostic testing for patients with CML (Sala Torra *et al*, *Blood* 127(22) 2773–2774, 2016). Spotted blood can potentially increase the number of CML patients in resource poor areas who can be diagnosed and monitored during therapy. The method could potentially also be used to facilitate and cheapen molecular diagnostic for clinical trials in these areas, which could allow for earlier access of new drugs for CML.

Development of cell-based material for standardised monitoring of treatment response
Molecular monitoring of CML patients using robust tests to measure BCR-ABL1 transcript levels that are standardized to the International Reporting Scale is key to appropriate disease management, especially when treatment cessation is considered. Most laboratories currently utilise a time-consuming sample exchange process with reference laboratories for International scale calibration. Working with multiple international collaborators and the pharmaceutical company Novartis, we developed the first cell-based secondary reference panel that is traceable to and faithfully replicates the World Health Organisation certified reference material (Cross *et al*, *Leukemia* 30(9) 1844–1852, 2016). Importantly, the new material incorporates a level that measures a deep molecular response, which is a critical response level and now a major goal of therapy. The material will provide easier access to standardised methodology, and will act as a tool for assay optimisation, validation and quality assurance to ensure patients receive the correct clinical evaluation of treatment response and appropriate therapeutic intervention.

Outcomes for the Community

Associate Professor Susan Branford, representing the work of our laboratory, was awarded the International CML Foundation (iCMLf) Prize in 2016. The iCMLf is a charitable organisation that aims to improve patient outcomes globally and to improve clinical practice and disease monitoring in CML. The award was in recognition of the critically important work of the laboratory to improve the quality and availability of reliable molecular testing for CML patients globally, and for training and mentoring scientists and clinicians. The iCMLf considered that our research has significantly impacted and improved the management of many CML patients.

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

Lung Research Laboratory

Professor Paul Reynolds MBBS, MD, PhD, FRACP, F Thor Soc

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.

New cancer-related projects in 2016 include the establishment of new models whereby human tumour samples are directly implanted into mice to assess the response to novel anti-cancer therapies, particularly addressing the 14-3-3 protein pathway. New clinical studies are looking at improved biopsy techniques using cryoprobes which obtain larger samples using a freezing technique during bronchoscopy. These samples enable greater molecular profiling of tumours, thereby facilitating the use of newer, targeted therapies.

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 for clinical translation.

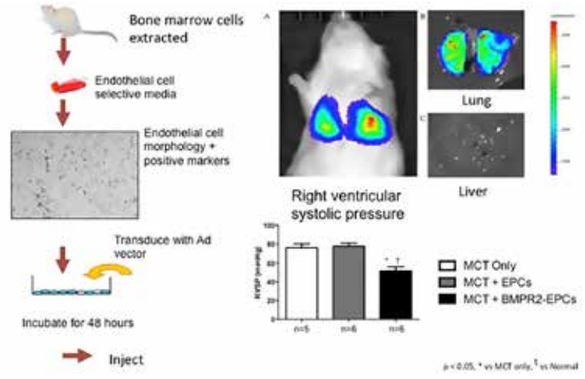
In addition to these major themes, the Lung Research Program also conducts a range of projects looking at markers of lung transplant graft rejection, new therapies in asthma, and interstitial lung disease.

Key discoveries 2016

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. In 2016 we reported that macrophage dysfunction was associated with pathogenic bacteria growth from the airways (Hogge *et al*, *American Journal of Respiratory and Critical Care Medicine* 2016).

Inflammatory mediators and mechanisms in COPD
During 2016 we continued to explore the mechanisms underlying macrophage dysfunction in COPD and have now identified a role for the sphingosine kinase system. Importantly exogenous mediators of sphingosine metabolism could be used to overcome the cigarette smoke-induced defects in macrophage function (Tran *et al*, *J Leukocyte Biol* 2016).

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 (Harper *et al*, *Respirology* 2016; Feng *et al*, *Respirology* 2016). We have used the new EPC approach to achieve a therapeutic outcome in a rat PAH model. Rebecca Harper completed her PhD with this work in 2016 and has been awarded the University of Adelaide Dean's Research Medal. 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 soluble 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 treat 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

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 in the tumour microenvironment in order to gain entry to this vascular highway and spread throughout the body. The focus of our laboratory is to understand how the lymphatic vascular network is constructed during development. We are interested in identifying and characterising genes that are important for lymphatic vessel growth, patterning and maturation. Once we understand how lymphatic vessel growth and development is normally controlled, we will gain new insight into how this process 'goes wrong' in human disease and moreover, will be afforded the opportunity to rationally design novel therapeutics able to block or promote lymphatic vessel growth and/or function and thereby treat human lymphatic vascular disorders.

Outcomes for the **Community**

Lymphatic vessels are of major importance to cancer patients. Cancer cells exploit lymphatic vessels as a route 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 cancer surgery 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 reducing cancer metastasis, while growth promoting agents could provide novel therapeutics for the repair of lymphatic vessels and treatment of lymphoedema.

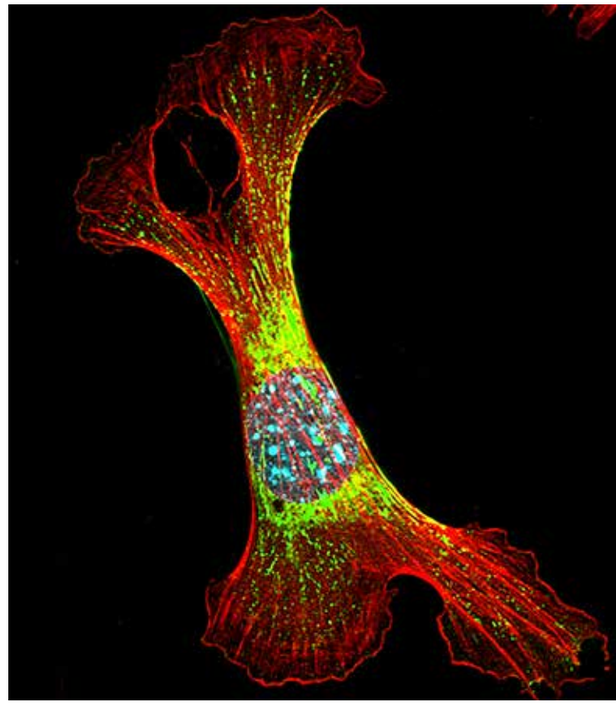
Key discoveries 2016

Understanding how valves are constructed during development

We have had a long-standing interest in understanding how cell identity is programmed during development and in particular, how the identity of the cells that make up our blood vessels and lymphatic vessels is imparted. We have identified a number of molecular switches called transcription factors that are important for this process and in particular, that are important for turning on the identity of the cells that build valves in our vasculature. Valves in our hearts, blood vessels and lymphatic vessels are vital for ensuring that blood and lymph is transported in a unidirectional manner and aberrations in valve development result in human conditions including congenital heart disease, venous disease and lymphoedema. Following our discovery that the transcription factor GATA2 is important for the construction and maintenance of lymphatic vessel valves (Kazenwadel *et al*, *J Clin Invest*, 2015), we have focussed on defining the cellular and molecular mechanisms by which GATA2 orchestrates lymphatic vessel valve development. We have identified several new genes that are regulated by GATA2 and have important roles in valve construction. Ultimately, our goal is to identify new therapeutic targets to which effective therapeutics for the treatment of lymphoedema could be designed.

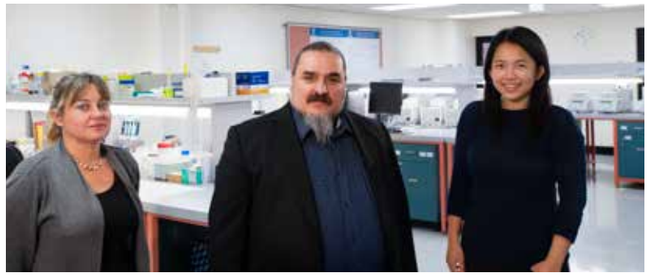
Understanding the genetic and developmental basis of human lymphoedema syndromes

Understanding the genetic underpinnings of human disease teaches us a tremendous amount about normal development, together with the mechanisms by which diseases originate and progress. Work from multiple groups, including ours, in collaboration with Professor Hamish Scott's group at the Centre for Cancer Biology, has uncovered genetic mutations that cause human congenital lymphoedema syndromes. We are now studying a number of these genes in order to understand how they regulate the growth and function of lymphatic vessels during development and how their mutations cause lymphatic vessel dysfunction and lymphoedema.



Dermal fibroblast with nucleus (blue) and cytoskeletal components (red) highlighted

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 in patients. Some of these patients are from families with a history of the disorder while others are isolated cases. 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 genes from the mammalian target of rapamycin receptor pathway (DEPDC5, NPRL2 and NPRL3) in focal epilepsies with or without brain malformations. We also are also working with 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.

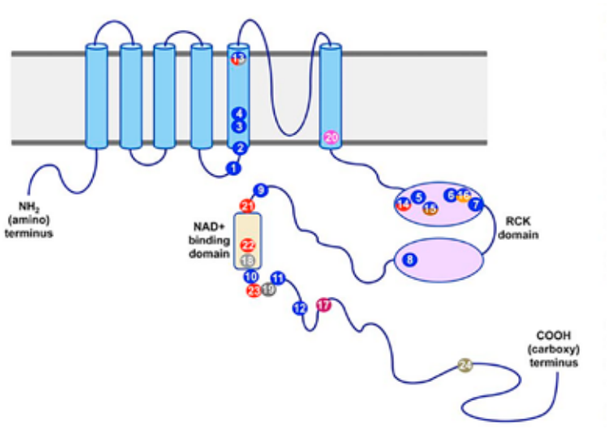


Diagram showing the KCNT1 protein structure and the positions of mutations identified in the gene to date The KCNT1 protein consists of six hydrophobic transmembrane segments (S1–S6) with the pore-loop between S5 and S6. It has a large intracellular carboxy-terminal region containing tandem RCK domains and an NAD+ binding domain. The positions of missense mutations reported by previous studies are indicated, with different colours denoting different phenotypes. Mutations that are associated with more than one phenotype are marked with two or more colours. The numbers in bold type indicate the number of times recurrent mutations have been observed in multiple families and/or patients. ADNFLE, autosomal-dominant nocturnal frontal lobe epilepsy; EOEE, early-onset epileptic encephalopathy; MMFSI, malignant migrating focal seizures of infancy.

Key discoveries 2016

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, this study identified NPRL2 and NPRL3 as two new focal epilepsy genes that also play a role in the mammalian target of rapamycin (mTOR) signaling pathway. Additionally, exome sequencing in two focal epilepsy families with multiple affected members identified NPRL2 and NPRL3 as the top candidate-causative genes. In our cohort of 404 unrelated focal epilepsy patients, 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. It is possible that deregulation of cellular growth control plays a more important role in epilepsy than is currently recognized.

BRAT1-associated neurodegeneration: Intra-familial phenotypic differences in siblings

Recessive mutations in BRAT1 cause lethal neonatal rigidity and multifocal seizure syndrome, a phenotype characterized by neonatal microcephaly, hypertonia, and refractory epilepsy with premature death by age 2 years. Recently, attenuated disease variants have been described, suggesting that a wider clinical spectrum of BRAT1-associated neurodegeneration exists than was previously thought. Here, we report two affected siblings with compound heterozygous truncating mutations in BRAT1 and intra-familial phenotypic heterogeneity, with a less severe disease course in the female sibling. This phenotypic variability should be taken into account when treating patients with BRAT1-associated neurodegenerative disease. Mildly affected individuals with BRAT1 mutations show that BRAT1 must be considered as a cause in childhood refractory epilepsy and microcephaly with survival beyond infancy.

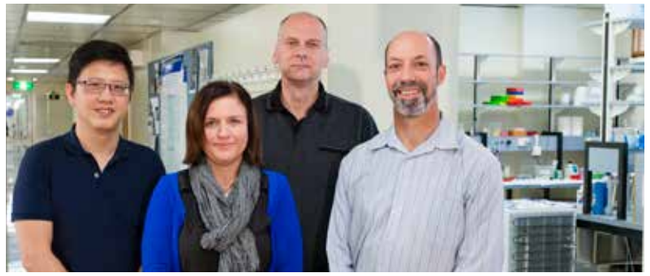
KCNT1 mutations in seizure disorders: the phenotypic spectrum and functional effects

Mutations in the sodium-gated potassium channel subunit gene KCNT1 have recently emerged as a cause of several different epileptic disorders. Our research describes the mutational and the phenotypic spectrum associated with the gene and discusses the comorbidities found in patients, which include intellectual disability and psychiatric features. The gene may also be linked with cardiac disorders. KCNT1 missense mutations have been found in 39% of patients with the epileptic encephalopathy malignant migrating focal seizures of infancy (MMFSI), making it the most significant MMFSI disease-causing gene identified to date. Mutations in KCNT1 have also been described in eight unrelated cases of sporadic and familial autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE). These patients have a high frequency of associated intellectual disability and psychiatric features. Two mutations in KCNT1 have been associated with both ADNFLE and MMFSI, suggesting that the genotype-phenotype relationship for KCNT1 mutations is not straightforward. Mutations have also been described in several patients with infantile epileptic encephalopathies other than MMFSI. Notably, all mutations in KCNT1 described to date are missense mutations, and electrophysiological studies have shown that they result in increased potassium current. Together, these genetic and electrophysiological studies raise the possibility of delivering precision medicine by treating patients with KCNT1 mutations using drugs that alter the action of potassium channels to specifically target the biological effects of their disease-causing mutation. Such trials are now in progress. Better understanding of the mechanisms underlying KCNT1-related disease will produce further improvements in treatment of the associated severe seizure disorders.

Outcomes for the Community

Identifying gene mutations in patients with epilepsy will eliminate the need for further investigative testing to identify a cause, saving them associated costs and hospital visits. Genetic diagnoses allow genetic counselling to be provided to patients and facilitate their optimised clinical care including the selection of drugs for treatment. Together these outcomes will have a large impact on improving the clinical care and the quality of life of patients with epilepsy. In addition, new gene discoveries pave the way for future development of new epilepsy drugs and treatments.

Jesse Cheah, Melina Babic, Hamish Scott, Parvathy Venugopal



Chan Eng Chong, Anna Brown, Peter Brautigan, Chris Hahn

Molecular Pathology Research Laboratory

Professor Hamish S Scott PhD FFSc (RCPA)

Human diseases often have a substantial genetic component giving rise to diversity of presentation, progression and response to treatments. We use state-of-the-art technologies to identify genetic contribution to these disease processes to better understand the pathogenic mechanisms with the aim that targeted treatments that are more efficacious with fewer side-effects can be administered or developed.

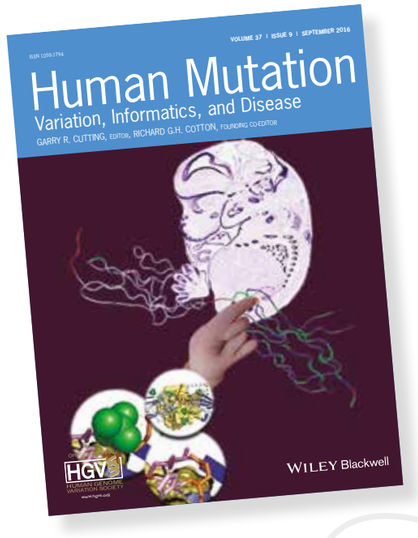
Research in the Molecular Pathology Research Laboratory includes *in vitro*, *in vivo* and *ex vivo* approaches for basic discovery, functional experimentation and translational efforts to benefit the community. Our team is interested predominantly in diseases with severe or catastrophic impact on patients or their families. For many years, we have focussed on inherited blood cell diseases such as leukaemias, lymphomas and autoimmunity (eg arthritis). Since the establishment of the Australian Familial Haematological Cancer Study, >150 families with apparent familial predisposition to leukaemia/lymphoma have been recruited. We have already sequenced the DNA of many individuals by next generation sequencing and for some solved the genetic changes that predispose — we were the first to report *GATA2* mutations (2011) and the second to report *DDX41* mutations (2016) in families with myelodysplastic syndrome (MDS) and acute myeloid leukaemia. We are currently working to understand how *GATA2* and *DDX41* mutations alter their function and the cellular changes that cause cancer. We also are pursuing promising new candidate predisposition genes through collaborations in the USA and Europe. Interestingly, our mutation identification in sporadic cases of MDS has uncovered a germline basis of disease predisposition and progression in >10% of cases.

More recently, we have begun a large 'foetal autopsy' study seeking to identify genetic causes for perinatal deaths or severe birth defects where morphological, biochemical or basic genetic assessment fails. Our first publication has been the identification of a novel autosomal recessive 'ectrodactyly and lethal pulmonary acinar dysplasia syndrome' with mutations in *FGFR2*, where all previous mutations in this gene have resulted in autosomal dominant disease. Other findings have been a novel CASR mutation in autosomal dominant hypocalcaemia and a novel SRY mutation in complete gonadal dysgenesis. We are pursuing promising novel candidate genes for numerous other families.

Key discoveries 2016

Ectrodactyly and lethal pulmonary acinar dysplasia associated with homozygous FGFR2 mutations identified by exome sequencing

Fibroblast Growth Factor Receptor 2 (FGFR2) mutations are seen within the IgIII domain (D3) of the protein. They are heterozygous activating mutations transmitted in an autosomal dominant fashion, and cause Crouzon, Apert, and Pfeiffer syndromes. We have identified a syndrome of ectrodactyly/split hand-foot malformation with acinar dysplasia (a rare congenital lung lesion of unknown aetiology, which is frequently lethal postnatally). To date, there have been no reports of combinations of these two phenotypes. We have identified an infant from a consanguineous union with both ectrodactyly and autopsy confirmed acinar dysplasia. Whole-exome sequencing (WES) analyses identified a novel homozygous FGFR2 (R255Q) mutation in the D3 domain. Expression studies of Fgfr2 mRNA during development in mice show localization to the affected limbs and organs including lungs. Molecular modeling and genetic and functional assays support that this mutation is at least a partial loss-of-function mutation, and contributes to ectrodactyly and acinar dysplasia only in homozygosity. This is the first report of mutations in a human disease with ectrodactyly with pulmonary acinar dysplasia. Hence, homozygous loss-of-function FGFR2 mutations represent a unique syndrome.



Barnett *et al,* 2016 *Human Mutation* cover page

Autosomal dominant hypocalcaemia due to a novel CASR mutation: clinical and genetic implications

We reported a novel in-frame single amino acid deletion in a calcium-sensing receptor (CASR) in a family with autosomal dominantly inherited hypocalcaemia. We described an approach to define pathogenicity of a genetic variation of uncertain significance and postulated that bisphosphonates may have paradoxically increased fracture risk in our patient. We hypothesized that our patient with the CASR mutation produced low bone turnover exacerbated by long-term prednisolone and smoking. The combination of genetic and environmental factors likely attenuated the fracture prevention efficacy of bisphosphonates. This principle might be relevant to others needing glucocorticoids and with another comorbidity associated with low bone turnover (eg renal failure).

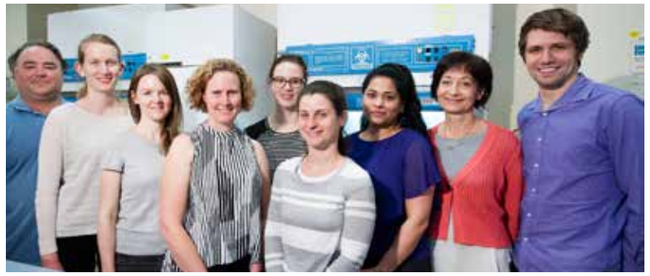
Case report of whole genome sequencing in the XY female: identification of a novel SRY mutation and revision of a misdiagnosis of androgen insensitivity syndrome

We described a 46,XY woman with no evidence of virilisation who was first diagnosed with complete androgen insensitivity syndrome (CAIS) (testicular feminisation) at 18 years. This diagnosis was later questioned due to the presence of intact Müllerian structures (precursors to female reproductive organs). The clinical phenotype suggested several susceptibility genes including SRY, DHH, NR5A1, NR0B1, AR, AMH, and AMHR2. Whole genome sequencing (WGS) was employed to study all candidate genes simultaneously. This revealed a novel missense SRY R130P variant in one of the major genes implicated in complete gonadal dysgenesis (CGD), hence securing this condition over CAIS as the cause of the patient's disorder of sexual development. By performing WGS, rather than just sequencing the AR gene (common cause of CAIS diagnosis), the causal gene was quickly and correctly identified. With the increasing availability, cost-effectiveness, speed and understanding of WGS, we support its use in the clinical evaluation of XY females due to the presence of genetic heterogeneity and oftentimes atypical clinical features in the disorders of sexual development spectrum.

Outcomes for the Community

Our identification of the genetic causes of three very different diseases above enabled a distinctive diagnosis for each of the patients and families. We have reported novel mutations in each case using WES or WGS, and for some the mutation would not have been found without these technologies unless time consuming and expensive studies were performed. A definitive diagnosis has benefits directly to the families involved but also to the wider community where similar situations may be occurring.

Yoon Lim, Loretta Dorstyn, Ammara Farooq, Sharad Kumar, Tianqi Xu, Donna Denton, Andrej Nikolic, Claire Wilson



Ian Nicholson, Shannon Nicolson, Tanya Henshall, Natalie Foot, Kelly Gembus, Jantina Manning, Swati Dawar, Sonia Dayan, Dylan De Bellis

Molecular Regulation Laboratory

Professor Sharad Kumar MSc PhD FAA FAHMS

Our research focuses on the cellular and molecular basis of disease, with an emphasis on cancer research. We study fundamental aspects of programmed cell death and protein ubiquitination, both of which have direct implications for our understanding of the basis of major human ailments including cancer, cardiovascular and inflammatory diseases. Understanding these critical cellular pathways is essential for the early detection and better treatment of human disease.

Programmed cell death is the main mechanism for deleting unwanted cells from the body. It is essential in foetal development and for maintaining cellular homeostasis in the adult organism. In an adult human an estimated 50–70 billion cells die everyday. Therefore, aberrations in cell death can lead to a variety of human pathologies. For example, a key hallmark of cancer cells is losing the ability to die normally. Deciphering the molecular basis of cell death is thus essential for understanding normal functioning of the human body and the disease process. We have made several discoveries to better understand the molecular mechanisms of cell death in normal and cancer tissues, and in animal development. We are now studying the roles of cell death in tumour suppression, metabolism and ageing, as well as defining cell death modes and mechanisms during animal development.

Another major focus of our research is on Nedd4 family of ubiquitin-protein ligases, the enzymes involved in ubiquitination and first discovered in our laboratory. Ubiquitination, a common protein modification system, is best known for its role in protein turnover, but has many (and growing) functions in various aspects of cellular signalling. As such, defects in ubiquitination underlie a large number of human pathologies, including cancer and cardiovascular diseases. For example, several studies, including our own work, have found a critical role for Nedd4-2 in controlling salt homeostasis and hypertension. We are exploring new functions of the Nedd4 family members to better understand their potential as therapeutic targets in pathologies that result from their gain or loss.

Outcomes for the Community

Our research has led to two main outcomes; (i) an understanding of how tumour cells evade normal growth and death signals, fundamental for the development of improved cancer treatment strategies and (ii) a greater insight into the biology of iron metabolism, essential to our understanding of diseases associated with too little iron (anemia) or too much iron (hemochromatosis). Through studying the function of caspase-2 we described a mechanism for suppression of tumour development by killing damaged and potentially cancer causing cells. Our research suggests that lower levels of caspase-2, as observed in many human malignancies, could be a useful prognostic marker. By identifying novel control mechanisms for the primary iron transporter DMT1, our additional studies have described different mechanisms that can regulate iron levels, relevant to the development of novel diagnostic tools and potential therapies for iron-associated diseases.

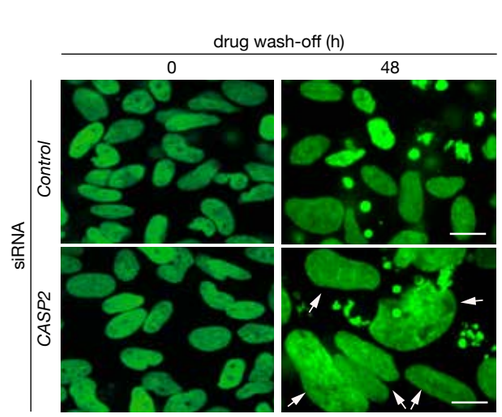
Key discoveries 2016

Caspase-2 kills cells carrying abnormal chromosomes

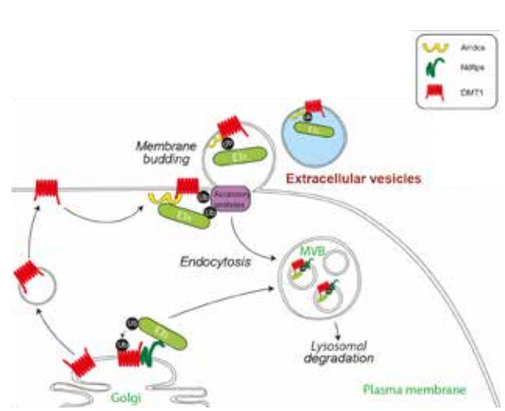
Caspase-2, discovered in our laboratory over 23 years ago, is one of the most evolutionarily conserved members of the caspase family. Our previous work demonstrated that caspase-2 is important in the maintenance of chromosomal stability and in tumour suppression. In further studies published in two recent papers (Dawar *et al*, *Oncogene* 2016 and Dawar *et al*, *Cell Death Dis* 2016) we report that caspase-2 is essential for the efficient removal of cells carrying mitotic aberrations, especially those with abnormal number of chromosomes (aneuploid cells).
We discovered that cells that lack caspase-2 have abnormal cell division 'checkpoints' that normally prevent damaged cells from surviving and becoming aneuploid. As a consequence of this, that mice that are deficient in caspase-2 accumulate aneuploid cells in their bone marrow with ageing (Dawar *et al*, *Cell Death Dis* 2016). In addition, bone marrow from aged caspase-2-deficient mice exhibit enhanced myeloid skewing and features typical of myeloblastic disease. These findings indicate that caspase-2 plays a critical role in preventing the long-term survival and growth of cells that could otherwise become malignant, thus proving a plausible mechanism for tumour suppression by this caspase.

Ubiquitin ligase adaptor proteins are important for regulating protein trafficking

Ubiquitin ligases are important for catalysing the final step in the ubiquitination cascade and contain protein interaction motifs that convey specificity to their target proteins. Some substrates do not contain these interaction motifs, but we have shown that adaptor proteins can link ligases with these substrates. Ndfip2 is one of these adaptors that can link Nedd4 family of ubiquitin ligases with the iron transporter DMT1 and mediate its ubiquitination and degradation. Because of this, mice lacking Ndfip2 show an increase in DMT1 levels and a concomitant increase in iron deposition in tissues (Foot *et al, Sci Rep* 2016), thereby demonstrating a pathological effect of altered protein trafficking.
A second family of adaptor proteins (α-arrestins) also regulate DMT1 by linking the ubiquitin ligases, but instead of internalising the protein and leading to degradation, DMT1 is trafficked into extracellular vesicles and released from the cell (Mackenzie *et al*, *Cell Disc* 2016). These findings present evidence of a non-canonical signal for ubiquitin in protein trafficking.



Caspase-2 deficiency leads to survival of damaged and aneuploid cells
Nuclear staining (green) shows that control cells (Control siRNA) die following anti-mitotic drug treatment, whereas the depletion of caspase-2 (CASP2 siRNA) causes the survival and accumulation of abnormal cells with large nuclei (arrows). Scale bar = 50 μM



Ubiquitin ligase adaptors regulate iron metabolism
Our data have identified two families of ubiquitin ligase adaptor proteins that regulate iron homeostasis; Ndfips mediate the lysosomal degradation of the primary iron transporter DMT1, and Arrdcs act by releasing DMT1 from cells via extracellular vesicles.

Melissa Pitman, Maurizio Costabile, Stuart Pitson, Lorena Davies, Melissa Bennett, Briony Gliddon, Jason Powell

Paul Moretti, Wenying (Layla) Zhu, Alex Lewis, Heidi Neubauer, Houng Taing, Jo Woodcock, Carl Coolen, 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, fibrosis, 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. The sphingosine kinases are key enzymes controlling sphingolipid metabolism, and through this action can regulate central processes such as cell survival and proliferation. Two sphingosine kinases exist in humans; sphingosine kinase 1 and the little studied sphingosine kinase 2. We and others have shown that high levels of sphingosine kinase 1 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 1, which is further supported by findings of elevated sphingosine kinase 1 in a variety of human cancer cells, and inhibition of tumour growth *in vivo* by genetic or chemical suppression of sphingosine kinase.

Recent work in the Molecular Signalling Laboratory has concentrated on identifying the mechanisms regulating the sphingosine kinases, the cellular functions controlled by these enzymes, and in developing small molecule inhibitors as potential anti-cancer agents. In particular we have made several major breakthroughs in understanding how these enzymes are activated, relocalised in the cell, and deactivated, which have provided novel therapeutic targets to control cancer and other diseases.

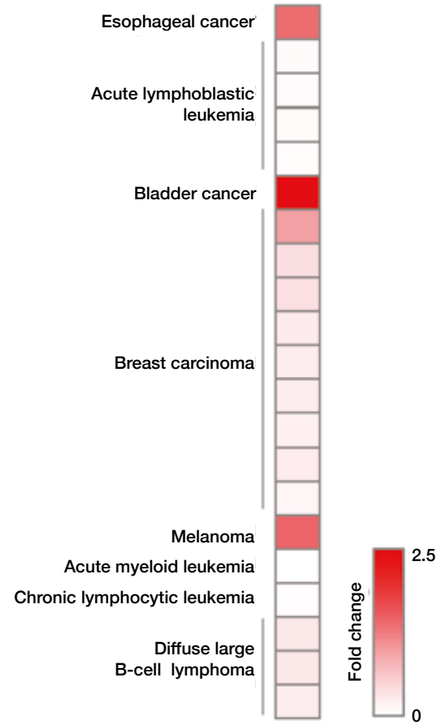
Key discoveries 2016

Sphingosine kinase 2 identified as an anti-cancer target

We and others have established sphingosine kinase 1 as an attractive target in numerous solid and blood cancers. Little has been known, however, about the role and contribution to cancer of the other sphingosine kinase present in human cells, sphingosine kinase 2. We recently identified that levels of sphingosine kinase 2 are increased in a range of human cancers, but only to a slight extent. Using cutting-edge technologies, however, we demonstrated for the first time that even these slight increases in sphingosine kinase 2 can indeed contribute to the development and progression of these cancers. Thus, this work, published in *Oncotarget* (Neubauer *et al*, *Oncotarget*), identifies sphingosine kinase 2 as an important target in cancer and provides impetus for the development of inhibitors to this enzyme for future use as anti-cancer drugs.

Developing inhibitors of dihydroceramide desaturase 1

Dihydroceramide desaturase 1 is another important enzyme, located early in the sphingolipid biosynthesis pathway in cells, that is an emerging target for the control of cancer and a number of other diseases. In collaboration with Associate Professor Bernard Flynn, Monash Institute of Pharmaceutical Sciences, Melbourne, we have developed the first drug-like small molecule inhibitors to dihydroceramide desaturase 1. These inhibitors, published in the *Journal of Medicinal Chemistry* (Aurelio *et al*, *J Med Chem*), open the door to therapeutically targeting dihydroceramide desaturase 1 in cancer and other diseases.



Heat map showing human cancers where significant upregulation of sphingosine kinase 2 mRNA levels have been observed in cancerous tissues compared with corresponding normal tissue

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.

Kimberley Clark, Stephen Fitter, Rosa Harmer, Sally Martin, Kate Vandyke, Jiabin Zhang, Andrew Zannettino, Krzyszof Mrozik, Pawanrat Tangseefa, Jacqueline Noll, Vicki Wilczek

Ankit Dutta, Duncan Hewett, Alanah Bradey, Mara Zeissig, Natasha Friend, Bill Panagopoulos, Khatora Said, Kirsten Smith

Myeloma Research Laboratory

Professor Andrew Zannettino PhD

The Myeloma Research Laboratory studies the molecular and cellular basis for the development of the bone marrow cancer, multiple myeloma. Myeloma is characterised by the clonal proliferation of malignant plasma cells (an immune cell type that normally protects us against infection). Myeloma is the second most common blood cancer, with over 100,000 people diagnosed worldwide each year.

Despite recent advances in treatment, myeloma remains almost universally fatal with a ten year survival rate of approximately 17%. The main clinical manifestations of myeloma are the development of osteolytic bone lesions, bone pain, hypercalcaemia, renal insufficiency, suppressed immunoglobulin production and increased BM angiogenesis (blood vessel formation). Most, if not all, cases of myeloma are preceded by a premalignant (asymptomatic) monoclonal gammopathy of uncertain significance (MGUS) stage. However, the intrinsic genetic factors which trigger the progression from this asymptomatic stage of the disease to overt malignant myeloma remains to be determined. Moreover, recent studies suggest that the bone marrow microenvironment plays a central role in disease progression. Using state-of-the art genomics, *in vitro* models of cancer development and preclinical models of disease, our laboratory is focussed on identifying the key genes which are responsible for disease progression and the role played by the bone microenvironment in disease development and relapse. We believe that these approaches will enable us to identify new molecular markers of disease risk and to design drugs against novel therapeutic targets.

In addition to myeloma-related studies, our laboratory also conducts research in relation to the biology and clinical application of bone marrow-derived mesenchymal stem cell (MSC). Specifically, we study the mechanisms of genetic regulation of MSC self-renewal and differentiation and the way in which this understanding can be exploited to improve cell-based therapies, particularly in the area of cancer-associated bone loss.

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 suffering from the range of paraproteinemias including multiple myeloma, Waldenström's macroglobulinemia, amyloidosis and myeloma-associated bone disease.

Key discoveries 2016

The mesenchymal stem cell marker antibody STRO-1 binds to cell surface heat shock cognate 70

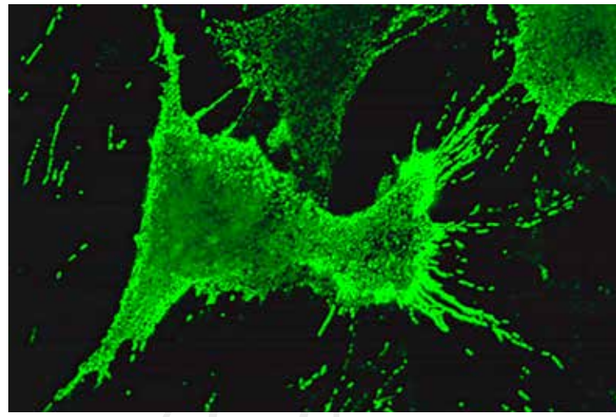
Since its discovery more than 25 years ago, the STRO-1 antibody has played a major role in defining the hierarchical nature of mesenchymal stem cells (MSC) and their progeny. STRO-1 antibody binding remains a hallmark of immature pluripotent MSC. Despite the significance of STRO-1 in the MSC field, the identity of the antigen has remained elusive. Using a combination of two-dimensional gel electrophoresis, coupled with Western blotting and Tandem mass spectroscopy, we identified the STRO-1 antigen as heat shock cognate 70 (HSC70) which is encoded by the HSPA8 gene. STRO-1 binds to immune-precipitated HSC70 and siRNA-mediated knock down of HSPA8 reduced STRO-1 binding. Notably, STRO-1 surface binding was found not to correlate with HSC70 expression. However, sequestration of cholesterol was found to reduce STRO-1 surface binding, suggesting that the plasma membrane lipid composition may be an important determinant in the presentation of HSC70 on the cell surface. The STRO-1 epitope on HSC70 was mapped to the ATPase domain using a series of deletion mutants in combination with peptide arrays and deletion of the first four amino acids of the consensus epitope negated STRO-1 binding. These results provide important insight into the properties that define multipotent MSC and provide the impetus to explore the role of cell surface HSC70 in MSC biology.

Twist-1 enhances bone marrow mesenchymal stem cell support of hematopoiesis by modulating CXCL12 expression

The TWIST-1 gene encodes a basic helix-loop-helix (bHLH) transcription factor important in mediating skeletal and head mesodermal tissue development. We have previously shown that Twist-1 maintains multipotent human bone marrow-derived MSC in an immature state, enhances their life-span, and influences cell fate determination. We found that human MSCs, engineered human to express high levels of Twist-1, expressed elevated levels of the chemokine, CXCL12. Analysis of the CXCL12 proximal promoter using chromatin immunoprecipitation analysis identified several E-box DNA sites bound by Twist-1. Functional studies using a luciferase reporter construct showed that Twist-1 increased CXCL12 promoter activity in a dose dependent manner. Notably, Twist-1 over-expressing MSCs exhibited an enhanced capacity to maintain human CD34+ hematopoietic stem cells (HSC) in long-term culture-initiating cell (LTC-IC) assays. Supportive studies, using Twist-1 deficient heterozygous mice demonstrated a significant decrease in the frequency of MSCs and increased numbers of osteoblasts within the bone. These observations correlated to a decreased incidence in the number of clonogenic MSCs and lower levels of CXCL12 in Twist-1 mutant mice. Furthermore, Twist-1 deficient murine MSC feeder layers, exhibited a significant decrease in CXCL12 levels and lower numbers of haematopoietic colonies in LTC-IC assays, compared with wild type controls. These findings demonstrate that Twist-1, which maintains MSCs in an immature state, endows them with an increased capacity for supporting haematopoiesis via direct activation of CXCL12 gene expression.

Tyrosine kinase receptor c-ros-oncogene 1 mediates TWIST-1 regulation of human mesenchymal stem cell lineage commitment

MSCs express high levels of TWIST-1, which is down regulated during ex vivo expansion. Cultured MSCs engineered to over-express TWIST-1 display decreased capacity for osteogenic differentiation and an enhanced capacity to undergo adipogenesis, suggesting that TWIST-1 is a mediator of lineage commitment. However, how TWIST-1 mediates cell fate determination was not known. In this study, microarray analysis was used to identify a novel downstream TWIST-1 target, tyrosine kinase receptor c-ros-oncogene 1 (C-ROS-1), which was down regulated in TWIST-1 over-expressing MSCs. Chromatin immunoprecipitation analysis showed that TWIST-1 directly bound to two E-box binding sites on the proximal C-ROS-1 promoter. Knock-down of C-ROS-1 in human MSCs and cranial osteoblasts resulted in a decreased capacity for osteogenic differentiation *in vitro*. Conversely, suppression of C-ROS-1 in MSCs resulted in an enhanced capacity to undergo adipogenesis. Furthermore, reduced C-ROS-1 levels led to activation of different components of the PI3K/AKT/mTORC1 signalling pathway during osteogenic and adipogenic differentiation, suggesting that C-ROS-1 is involved in MSC fate switching between osteogenesis and adipogenesis. These findings suggest that targeting C-ROS-1 may represent a novel approach to target disease associated with aberrant bone formation.



Confocal imaging highlighting that HSC70 is localised to lamellipodia like cell protrusions on the surface of human MSCs

Xiangjun Xu, Rachael Lumb, Quenten Schwarz, Sophie Wiszniak

Neurovascular Research Laboratory

Dr Quenten Schwarz PhD

Over 20 children are born with a congenital birth defect within Australia every day. These disorders require medical intervention at birth and treatment throughout life. A significant proportion of these disorders arise from abnormal development of the neuronal and vascular systems.

The driving force behind the research conducted in the Neurovascular Research Laboratory is to identify the cell and molecular mechanisms controlling neuronal and vascular development with the intent of providing novel insight toward the origins and treatment of these debilitating disorders.

During embryonic development multiple different cell types, such as precursors of neurons and blood vessels, communicate with each other to control organ formation. How and why these cell types talk to each other is a major question that the Neurovascular Research Laboratory is trying to answer. Using multiple *in vivo* model systems including mouse, zebrafish and chick, our laboratory is interested in understanding how the precursors of neurons (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 identify 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 fuse high throughput proteomics and genomic 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 affected in schizophrenia and autism, 2) neural crest cells sense their environment to position themselves in appropriate locations to form a functional nervous system, 3) neural crest cells differentiate into bone and cartilage to control craniofacial morphogenesis, 4) blood vessels signal to other cell types to modulate their development, and 5) 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 new 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 using 14-3-3ζ expression as a diagnostic or prognostic test for schizophrenia and autism.

Key discoveries 2016

New insight to the origins of common childhood cancers

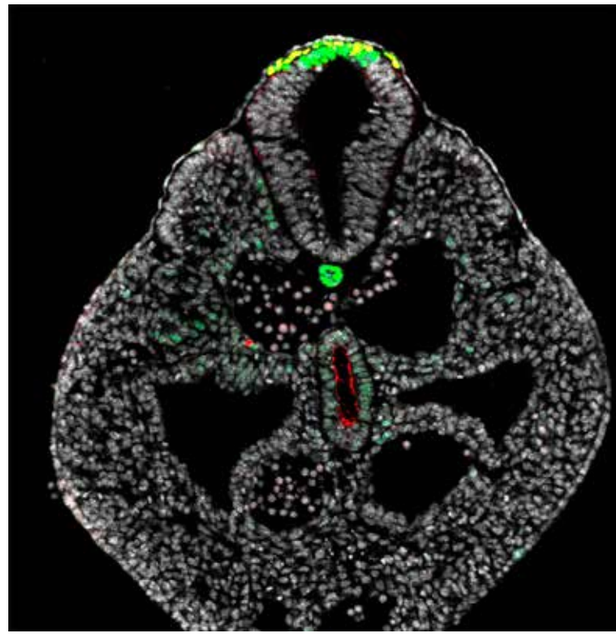
Aberrant development of the peripheral nervous system has significant impact on the bodies fight or flight stress response and forms the basis of several childhood cancers, including neuroblastoma and pheochromocytoma. Using mouse models (Fig 1) our work has elucidated a novel mechanism by which the building blocks of the peripheral nervous system, neural crest cells, are positioned in correct locations within the body. We have found that neural crest cells follow axons to their destinations and that this mechanism drives connections between the central and peripheral nervous systems to control physiological homeostasis. These findings provide new insight to the origins of common childhood cancers.

Blood vessels play an important role in promoting craniofacial development

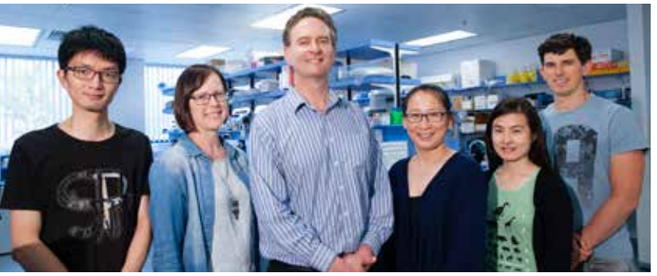
The origins of craniofacial disorders were traditionally thought to arise from developmental defects in neural crest cell development. Our recent publication in PNAS demonstrated that blood vessels play an important role in promoting craniofacial development and that aberrant blood vessel growth may underlie common craniofacial disorders. Moreover, our work suggested that proteins secreted from endothelial cells, the building blocks of the vasculatre, act as angiocrine factors to control growth of the craniofacial skeleton. In the past year we have identified several factors secreted by blood vessels that control craniofacial development. Such factors represent ideal candidates for future therapies to treat craniofacial disorders, but more broadly for the treatment of any defect affecting cartilage such as achondrodysplasia and common sporting injuries. We are currently employing mouse models to address if these factors could be used in a therapeutic setting.

Investigating which cell types within the brain are responsible for the formation of behavioural phenotypes associated with schizophrenia

Over the past 5 years we have identified an essential role for the protein 14-3-3ζ in neuronal development and defined a causal relationship between deficiencies of 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 is an ongoing line of investigation in our laboratory. In the past year we have generated several new lines of mice to address which cell types within the brain are responsible for the formation of behavioural phenotypes associated with schizophrenia. This investigation holds hope of defining how schizophrenia symptoms arise and also to how we may be able to treat them.



Neural crest cells (green) emerge from the dorsal region of the neural tube and begin to express a myriad of genes (yellow) that control their destiny. These neural crest cells migrate toward the gut (red) to seed the peripheral nervous system.



Wenbo (Stanley) Yu, Lisa Ebert, Michael Brown, Yanrui (Judy) Li,
Yann Chan, Alex Staudacher

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, lung cancer, and brain cancer (glioblastoma).

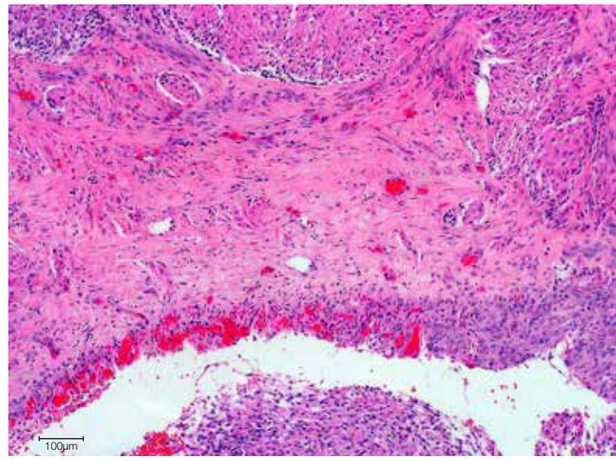
We have safely recruited six metastatic melanoma patients at all three of the planned dose levels into the NHMRC-funded CARPETS phase 1 clinical trial of autologous, GD2-specific, chimeric antigen receptor (CAR) T-cell therapy. No significant adverse events related to the gene-modified T cells were recorded. One of the patients had evidence in his blood of long term persistence of the CAR T cells. This was the only patient to have received lymphodepleting chemotherapy, in order to 'make room' for the GD2-CAR T cells before they were administered to the patient. Hence, we will revise the clinical protocol for the CARPETS study to enrol patients with other GD2-positive malignancies and to improve our methods for growing GD2-CAR T cells in the laboratory so that they last longer in the patient's body.

Gene transfer technologies for therapeutic use often depend on the lentivirus, which has the advantage of being able to integrate into the DNA of non-dividing cells and so make the protein that it encodes. In collaboration with South Australian Health and Medical Research Institute (SAHMRI), we have used lentiviral gene transfer technology to make CAR T cells specific for the myeloid leukaemia antigen, CD123. In addition, we are adopting a different, more advanced lentiviral vector design so that we will make CAR T cells that target more than one glioblastoma antigen at the same time. This will have the advantage of minimising the chances that brain tumour cells will 'escape' from the CAR T cells by losing expression of one of the targeted glioblastoma antigens.

The novel, cancer cell death-specific antibody, APOMAB®, has been coupled to potent cell-killing toxins, to produce a class of anti-cancer drug called an antibody-drug conjugate (ADC). We have shown that APOMAB-ADCs have their most potent anti-cancer activity in animal tumour models if they are coupled to a toxin that targets the DNA in tumour cells. Using a grant awarded by NHMRC to Dr Alex Staudacher, we will be seeking to investigate how APOMAB-ADCs actually work and how they might be used in other cancers such as ovarian cancer. In addition, we have been awarded philanthropic funding to bring a medical imaging version of APOMAB to the clinic. In collaboration with the Metabolic Imaging and Therapy Research Unit at SAHMRI, APOMAB will be coupled to the long-lived positron emitter, Zirconium-89, and a product developed that will be suitable for injection into lung cancer and ovarian cancer patients receiving their first cycle of platinum-based chemotherapy.

Key discoveries 2016

To help understand why there was a relative lack of persistence in the blood of patients who received the GD2-CAR T cells in the CARPETS trial, we studied what happened to the GD2-CAR T cells in the laboratory if they were stimulated with the GD2 antigen expressed by tumour cells. We found that the GD2-CAR T cells died if they were strongly stimulated with the GD2 antigen. One of the main reasons was that the overstimulated CAR T cells made a molecule on their surface called Programmed Death-1 (PD1). If we blocked the PD1 molecule with an anti-PD1 antibody used in the clinic then we could restore the survival and tumour cell killing properties of the GD2-CAR T cells. This result has given us some encouragement that we can use the same clinical antibody in patients who will be subsequently enrolled in the CARPETS trial to see if the CAR T cells might persist longer in their blood (Gargett T *et al*, *Molecular Therapy* 2016).

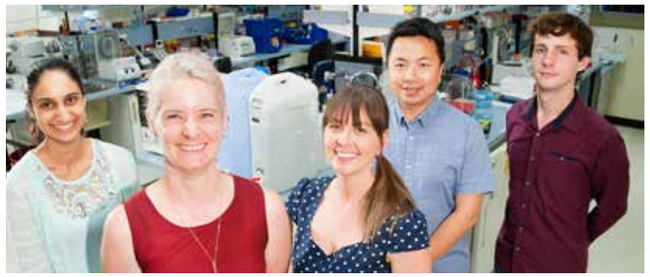


Tumour tissue from a patient with glioblastoma multiforme (GBM)
The tissue was collected, and a thin slice stained with haematoxylin and eosin. These dyes highlight the extreme regional variation which is typical of this cancer (hence its name, 'multiforme'), and likely contribute to the tumours' ability to evade conventional treatments. It is for this reason that we aim to develop new approaches to GBM treatment, based on immunotherapy.

Outcomes for the Community

Our work aims to improve the otherwise poor survival outcomes for patients with melanoma, lung cancer, ovarian cancer, and glioblastoma by using new methods to replace defective components of the patient's immune system that were not useful for fighting cancer. To improve results, we are arming T cells and antibodies with new treatment modalities to do the job.

Zahied Johan, Michael Samuel, Natasha Kolesnikoff-Prizzi



Jasreen Kular, Natasha Pyne, Sarah Boyle, Dave Yip, Brock Le Cerf

Tumour Microenvironment Laboratory

Associate Professor Michael Samuel PhD

Cells of the body exist within a scaffold or matrix of proteins that regulates the way in which the tissue functions. However, the precise molecular mechanisms underlying the interplay between cells and the matrix are not well understood. In cancers, the matrix is abnormally modified, and there is evidence that this promotes tumour growth and spread.

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. We do this in order to identify new targets that could be useful in normalising the tumour micro-environment as a novel approach to cancer therapy.

We have previously shown that signalling through Rho-associated protein kinase (ROCK) promotes epidermal proliferation by increasing ECM production, elevating dermal stiffness and enhancing integrin-mediated signalling. In turn, elevated dermal stiffness further stimulates ROCK activation, initiating a positive feedback loop that promotes skin tumour.

We are working to determine the mechanisms by which ROCK activation 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 working to determine whether 14-3-3ζ inhibition may be useful to accelerate healing of diabetic wounds. We are also employing unbiased screening approaches to identify novel negative regulators of ROCK signalling, which may have utility in accelerating the healing of chronic non-healing wounds.

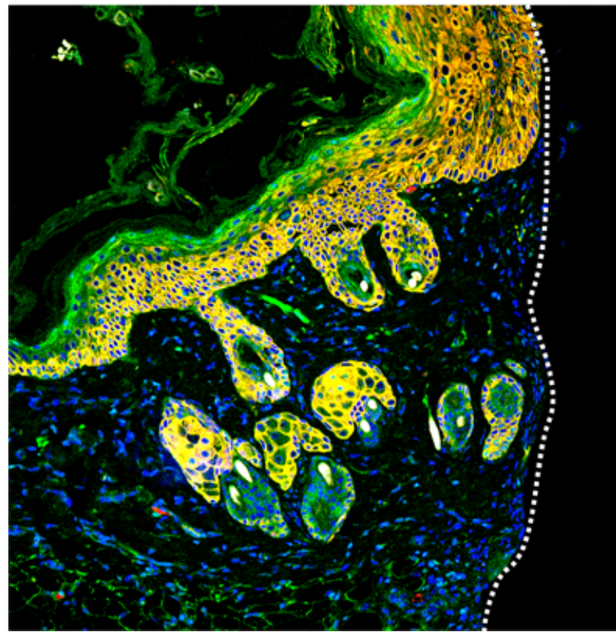
Key discoveries 2016

A novel model permitting tissue-specific, conditional activation of ROCK

We have established a new mouse model in which ROCK can be activated, with precise temporal and spatial control (Samuel *et al*, *Genesis*, 54(12): 636–646). This model will be very useful to identify the function of ROCK in various areas of interest. Importantly, we have evidence that signalling downstream of ROCK is in many different cancers, including cutaneous squamous cell carcinoma, all types of breast cancer and sporadic colorectal cancers. We are currently using this model in order to determine the function of ROCK in normal tissue homeostasis in the skin, breast and gut but also to determine whether activating ROCK in the context of cancers in these tissues promotes tumour progression.

ROCK activation accelerates tumour progression in pancreatic cancer

Both forms of ROCK are over-expressed in pancreatic ductal adenocarcinoma in human patients. There is also evidence that these proteins are hyper-activated in these cancers. In a major collaborative effort with the Olson group in Glasgow, and using the new mouse model described above, we have established that conditional activation of ROCK in a model of pancreatic cancer, promotes invasive tumour growth via a mechanism involving the deployment of matrix degrading enzymes Mmp10 and Mmp13. Pancreatic cancer cells in which ROCK has been activated are able to increase matrix turnover, which promotes invasiveness. Interestingly, survival was increased upon treatment with a ROCK inhibitor and was associated with increased collagen within tumours, illustrating the context-dependent function of ROCK in cancer. Our continuing work therefore seeks to identify the tissue-specific outcomes of ROCK activation.

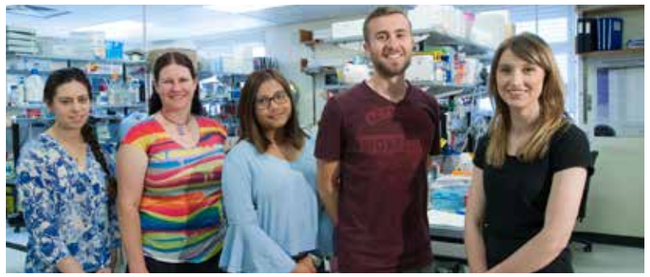


Immunofluorescence staining of a skin wound, showing activation of ROCK (green and yellow) close to the wound margin (dotted line)

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. Our efforts could lead to new therapies to treat both conditions.

Mark DeNichilo, Camille Duluc, Jake Treloar, Claudine Bonder, Natasha Pyne, Lih Tan



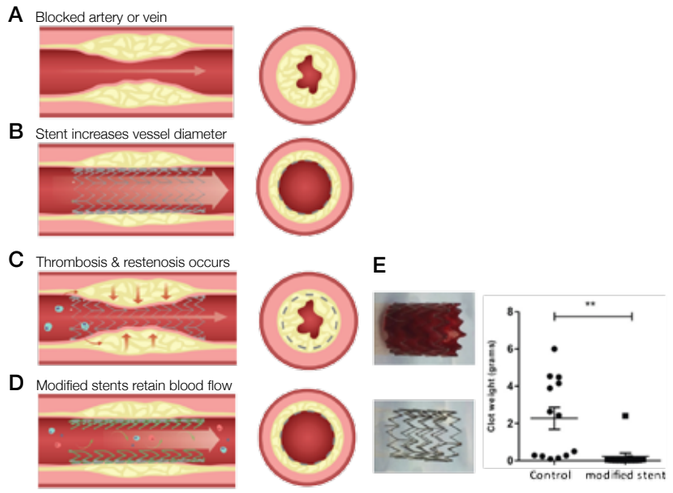
Carmela Martini, Michaelia Cockshell, Kay Khine Myo Min, Eli Moore, Emma Thompson

Vascular Biology and Cell Trafficking Laboratory

Associate Professor Claudine Bonder PhD

Blood vessels make up the vascular system that transports cells, oxygen and nutrients to support all tissues and organs throughout the body. 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), promises to provide new treatment options for the most deadly and debilitating diseases.

With an overall focus on blood vessels in disease, our laboratory has three main areas of interest. The first, *vasculogenic mimicry* (VM), a process whereby cancer cells themselves form vascular-like structures to increase the blood supply to tumours for growth and metastasis. It is well documented that increased VM is associated with poor clinical outcome and we have identified novel elements in the VM associated with breast cancer and melanoma. Second, *endothelial progenitor cells* (EPCs) contribute directly to blood vessel formation (vasculogenesis) and can be used to support organ transplantation or revascularise denuded vessels. We are developing EPC capture biomaterials to revolutionise the metal stents which are inserted into blocked arteries and veins. 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 attenuating this debilitating disease.



In (A), schematic of vascular occlusion which is corrected surgically in (B) via angioplasty with insertion of metal stents. In (C), thrombosis and restenosis block stented vessels which may be overcome in (D) with our modified stents which (E) demonstrate reduced clot formation *in vitro*.
n=13 individual experiments **p<0.05

Key discoveries 2016

Vasculogenic mimicry:
a key contributor to cancer progression

The growth and spread of solid tumours (eg breast cancer and melanoma) is dependent on an ability to access the blood supply. To meet this demand, 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 tumours is tightly linked to increased metastasis and poor survival, suggesting that targeting VM in the clinic holds enormous therapeutic potential.

In 2016 we published in the journal *Angiogenesis* that desmoglein-2 (DSG2), an adhesion molecule belonging to the desmosomal cadherin family, is ectopically expressed by EPCs and some ECs and that it mediates cell:cell adhesion as well as migration. Of greater interest, we published in the journal *Oncotarget* that DSG2 is significantly increased in some patients with melanoma and that it correlates with poor patient outcome. We revealed that DSG2 plays a critical role in regulating melanoma VM (*in vitro* and *in vivo*) and current work with a blocking peptide to DSG2 may reveal a new treatment option for patients with melanoma.

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) and that it correlates with poor patient outcome. In collaboration with Professor Angel Lopez (CCB) we have identified that IL-3 and its receptor (IL-3R) promotes VM by IDC breast cancer cells *in vitro*. With inhibition of IL-3R shown to prevent VM formation and tumour growth *in vitro* and *in vivo*. Current work now focuses on targeting the IL-3/IL3R axis to develop new treatment options for patients with aggressive breast cancer.

Revolutionizing vascular devices

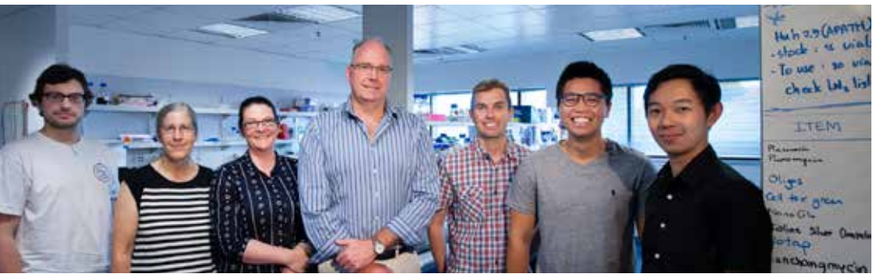
Vascular occlusions are a major contributor to cardiovascular disease (CVD) and are a leading cause of death worldwide. Overcoming these blockages requires insertion of stents or artificial vascular grafts to maintain vessel diameter and has become a multi-billion dollar industry. Despite recent advances in device technology and post-operative care, clotting and scarring remain a significant health concern which can be life-threatening. Unfortunately, more often than not, anti-clotting medications are required long term and/or more surgical intervention is required. As part of the Cell Therapy Manufacturing Co-operative Research Centre, our team is testing an innovative concept where modified stents (first coated with a low-fouling surface (patent application PCT/2016/901008) and then topped with ournovel peptides to specifically capture EPCs/ECs (patent US13/882806; PLoS ONE 7: e46996, 2012)) to provide the rapid revascularisation of implanted devices long sought by surgeons to treat vascular occlusions with minimal intervention and medication.

Identification of a new target to treat allergic inflammation

Rapid recruitment of neutrophils to a site of inflammation is associated with allergic diseases, such as asthma and anaphylaxis. Although anti-histamines and steroids are the mainstay of treatment for symptomatic relief, their effectiveness is varied; thus, a better understanding of acute allergic reactions is required. In 2016, and together with Professor Stuart Pitson (CCB), we published in the *Journal of Immunology* a role of sphingosine kinase (SK) in neutrophilic inflammation. These studies identified that histamine- and allergen-induced neutrophil recruitment *in vitro* and *in vivo* is SK-1 dependent. Of greater interest, we showed that topical application of Fingolimod (an approved pro-drug for treatment of multiple sclerosis) significantly reduced skin inflammation in two independent mouse models as well as the 'skin prick test' in humans. Future studies include collaborative work with Professor Robert Heddle (Chief Pathologist, SA Pathology and Head, Clinical Immunology Unit, Royal Adelaide Hospital).

Outcomes for the Community

Our expertise in blood vessels, and the endothelial cells which form their inner lining, allows us to critically interrogate diseases such as cancer, cardiovascular disease and allergic inflammation. Our ultimate aim is to provide new treatment options to, on the one hand, ablate blood vessel development (including vasculogenic mimicry) in cancer patients and on the other hand, augment blood vessel function in patients with blocked arteries and veins.



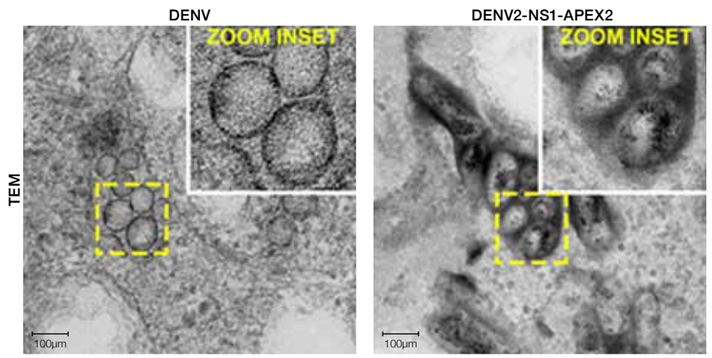
Colt Nash, Cathy Scougall, Kylie Van der Hoek, Michael Beard, Nick Eyre, Byron Shue, Chuan Lim

Viral Pathogenesis 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 *Flaviviridae* family, which include Dengue virus, West Nile virus and the emerging Zika virus (ZIKV) as well as 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, Dengue and ZIKV 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 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.



Analysis of NS1 protein localization in DENV-infected cells by APEX electron microscopy revealed localization of NS1-APEX2 both to the membrane and interior of viral replication factories

Key discoveries 2016

Regulation of HCV replication complex biogenesis and function

Like all positive strand RNA viruses, HCV infection induces cytoplasmic membrane rearrangements that support and compartmentalise the replication of its genome. Recent studies have indicated that the NS5A protein, a non-enzymatic phosphoprotein plays essential roles in replication compartment biogenesis and virus assembly. Through the use of genetically engineered viruses that encode reporter or epitope insertions within NS5A we have employed high resolution proteomics and imaging techniques to definitively identify NS5A phosphorylation sites and demonstrate that one of these phosphorylation sites (pSer235) is essential for HCV genome replication. Using a combination of host kinase siRNA screening, and advanced imaging techniques, including 'APEX' electron microscopy and pulse-chase fluorescent imaging of NS5A biosynthesis we have determined that pSer235 is important in the formation of viral induced membrane rearrangements and the cellular localisation of NS5A. Furthermore, we show that phosphatidylinositol-4 kinase III alpha (PI4KIIIα) is important for Ser-235 phosphorylation. Thus Ser-235 phosphorylation of NS5A is essential for HCV RNA replication and normal replication complex formation and is regulated by PI4KIIIα. This work was published in the journal *Virology*.

Mapping the Dengue virus genome

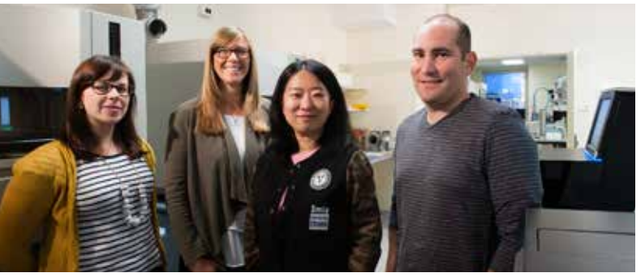
Dengue virus (DENV) is the major mosquito-borne virus that affects humans. Globally it is estimated to infect approximately 400 million people and cause 25,000 deaths each year. An improved understanding of the molecular details of the DENV life cycle will enable the development of desperately required and effective antivirals to combat DENV. Using high-throughput random insertion mutagenesis coupled with next-generation sequencing we have identified 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.

Host response and factors that regulate Flavivirus replication

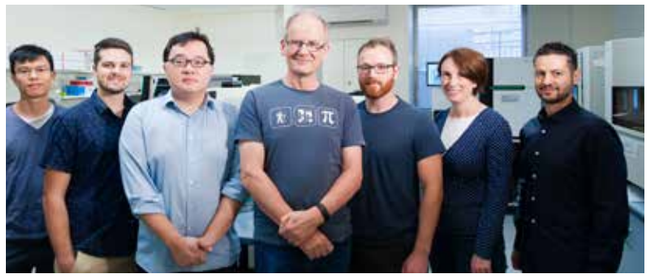
Viruses in the *flaviviridae* family utilise and exploit numerous host factors in the viral lifecycle. Genome-wide CRISPR/Cas9 KO screens represent a unique method to selectively delete cellular genes and determine their impact on virus biology. We have used a GecKO CRISPR/Cas9 genome-wide KO approach to identify cells that have survived *flaviviridae* infection due to knockout of a host factor critical for viral replication. Using a number of screening techniques to select for cells that have lost viral replication and hence loss of a critical cellular factor, we have used NGS technology to identify the cellular gene in question. Using this genome-wide approach we have identified key cellular factors involved in *flavivirus* replication and are further evaluating their impact on the virus life cycle. This work will greatly improve our understanding of the dynamics of the *flaviviridae* life cycle and may help direct development of new antiviral targets.

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.



Rosalie Kenyon, Wendy Parker, Ming Lin, Joel Geoghegan



Jinghua (Frank) Feng, Klay Saunders, Paul Wang, Andreas Schreiber, David Lawrence, Emily Hackett-Jones, 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

The ACRF Cancer Genomics Facility is an integral part of the cutting-edge research occurring within the CCB. With an emphasis on translating innovative research into tangible results for patients, the CCB's partnership with SA Pathology has enabled the efficient application of genomic technologies in a diagnostic setting.

Research and Diagnostics

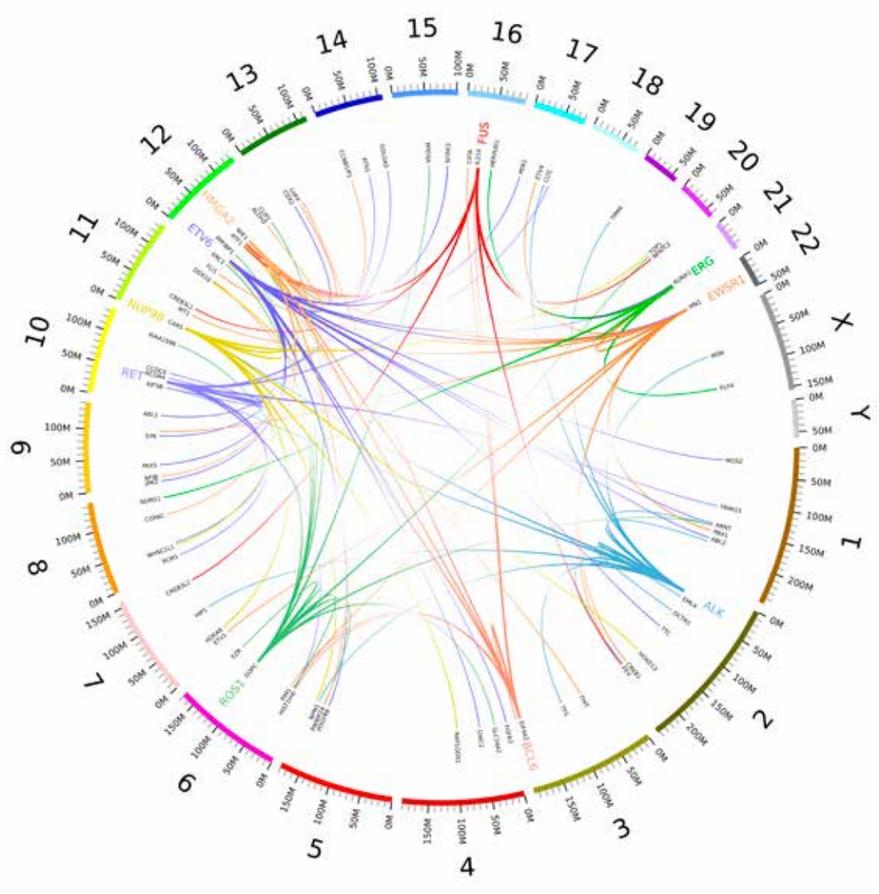
Working in close collaboration with the Genetics and Molecular Pathology Directorate, three new technologies have been implemented in diagnostics in the past three years and in some cases research results have been turned into diagnostic tests before publication. Development and testing continues on new assays to detect gene fusion events that drive haematological malignancies, somatic mutation detection in solid tumours and molecular barcoding techniques to improve the accuracy and sensitivity of next-generation sequencing based tests. In 2016, the Genomics Facility also acquired new digital droplet PCR technology that is ideal for liquid biopsy testing and monitoring minimal residual disease.

In addition to working with diagnostics, the Genomics Facility has processed over 4000 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, and bacterial and viral genomes. Bridging the gap between research and diagnostics is an exciting development for the Genomics Facility.

Bioinformatics

A core activity of the Cancer Genomics Facility is our next generation sequencing program, for which we are continuously improving and driving advancements in wet-lab and bioinformatic protocols. The primary motivation is to improve the sensitivity of existing technology so that we can use it in new domains, such as for the detection of mutations in cell-free and circulating DNA as well as for ultra-precise mutation detection in DNA and RNA. We are addressing these aims through a program of testing and development of molecular barcoding techniques of DNA and RNA fragments, prior to PCR amplification. We are now routinely using these barcodes in most of our sequencing experiments and new bioinformatic algorithms, which we are developing, will soon translate this into substantial improvements in sensitivity and accuracy of many of our sequencing applications.

Technological developments like this are often motivated by the major impacts they have on research outcomes, but an additional driver for us is the direct and immediate impact they have on diagnostic applications. Being embedded in the South Australian Health system the CCB, and the Genomics Facility in particular, are in the enviable position of being intimately involved in translating protocols and techniques directly from research to diagnostic applications. Bioinformatic algorithms, tools and analysis pipelines that we develop, including those developed as part of the molecular barcoding project, as well as our much-used variant interpretation and reporting tool VariantGrid, can be quickly taken up by our diagnostic bioinformaticians. This integration of the research and diagnostic bioinformatics is so complete that sometimes it's hard to define where one begins and the other stops. It results in significant cost and time savings in translating research activities to practice.

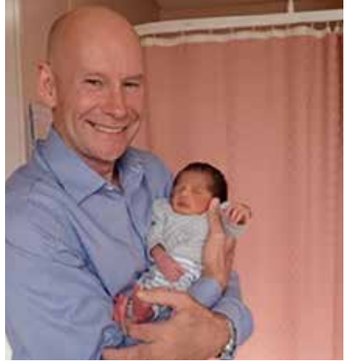


Circos plot demonstrating possible gene fusion events detectable by cDNA capture technologies when combined with next-generation sequencing

Outcomes for the Community

With NATA accreditation and the subsequent implementation of cytogenetic microarrays, next-generation sequencing panels and clinical whole exome sequencing, we are ensuring new technologies improve the standard of healthcare for South Australians. These new tests are cheaper, more informative and for some patients may even suggest new treatment options. This personalized approach will give patients and their doctors alternative therapeutic options when conventional therapies have failed. In 2017 we will continue to support both researchers and clinicians in basic research, translational research and diagnostics.

Bioinformatics analyses performed in our group are an essential component of the Centre for Cancer Biology's leading role in developing high throughput sequencing capabilities for South Australia, providing researchers an evermore 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.



Vijay Mahalingan and Sharmila Vijayakumar and Associate Professor Chris Barnett proudly showing off 'their' healthly baby in May 2016 as a result of our project (Case Two). Photographs by Associate Professor Chris Barnett and the parents.

Dr Saumya Samaraweera using the Agilent Seahorse XFp Analyzer. The patented technology of the Seahorse Analyzer allows sensitive real-time measurement of cellular bioenergetics, providing insights into metabolic reprogramming of cancer cells.

Outcomes for the Community

A basic research project with immediate clinical outcome and longterm significance. This NHMRC funded grant awarded to the Molecular Pathology Research Laboratory was entitled 'Genetic autopsy of perinatal death: diagnosis and discovery by Genome Sequencing.' We are working in close collaboration with Paediatric and Reproductive Genetics of the SA Clinical Genetics Services, the Deptartment of Surgical Pathology at the Women's and Children's Hospital as well as the many developmental biologists at the Centre for Cancer Biology.

We are looking for genetic causes of perinatal death such as stillbirth and miscarriage, a surprisingly common and obviously emotional problem. What do genes involved in fetal disease have to do with cancer? We are finding genes involved in developmental programs of differentiation and proliferation, the same broad biological pathways disturbed in cancer. The question of whether these genes will be important in cancer will be the subject of future studies. But as described below, our findings are of immediate practical use to the families involved, helping them have healthy children with preimplantation genetic diagnoses.

Case One

A young couple were seen by the SA Clinical Genetics Service as they had had three pregnancies affected by suspected Meckel-Gruber syndrome, a rare autosomal recessive lethal disorder characterised by abnormal kidney function and central nervous system malformations.

An expensive standard test panel performed overseas found no mutations or no abnormalities in the genes they screened. An expanded test referred to as whole exome sequencing performed as part of the Genomic Autopsy Study also found no abnormality on a standard bioinformatics pathway.

Manual analysis of the data by Professor Hamish Scott and PhD candidate Alicia Byrne from the CCB identified two mutations or changes in a gene associated with Meckel-Gruber syndrome, a 32 base pair deletion and a second mutation, neither of which were identified by the overseas commercial laboratory or our standard bioinformatics.

Review of literature by the CCB team in association with highly trained medical staff revealed that the 32 base pair deletion is actually a mutation that has been reported many times before. Without the good relationship between referring doctor, Dr Barnett, and the laboratory, and particularly Professor Scott's manual review of the data, the molecular diagnosis would remain unknown. Without this collaboration between diagnostic and research groups the chance of a child with this condition is a 25% risk. The couple are currently undergoing IVF treatment with the prospect of preimplantation genetic diagnosis for this condition.

Case Two

A consanguineous couple with two infants affected by apparent autosomal recessive polycystic kidney disease was seen by the SA Clinical Genetics Service. Standard commercial testing for autosomal recessive polycystic kidney disease did not detect any abnormality. To further investigate the disorder in this family a research genome (Genomic Autopsy Study) was performed.

In a research setting where additional genes can be interrogated, a homozygous variant was identified in a transmembrane gene which explained the condition found in the children. To demonstrate the mutation or change found by the researchers, the same change was produced in a mouse model. An affected mouse with CRISPR-CAS9 created homozygous mutations/ change in the same gene identified by Professor Scott and this has solved this case for this family.

After years of turmoil around their pregnancies, the couple had a healthy newborn last year using preimplantation genetic diagnosis for our newly discovered gene.

Both of these cases have been solved by a combination of good clinical phenotyping, good clinician-patient relationships, good communication between clinician and laboratory, good technology, good laboratory work, and good old-fashioned data trawling.

Associate Professor Christopher Barnett MBBS FRACP FCCMG
Clinical Geneticist
Head, Paediatric and Reproductive Genetics
SA Clinical Genetics Service, Women's and Children's Hospital

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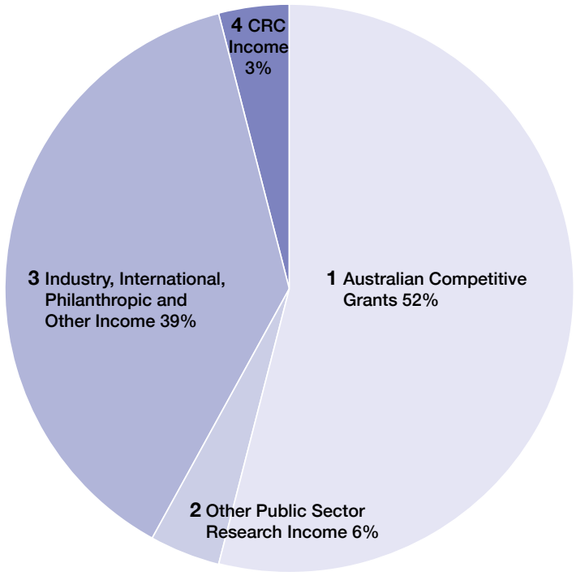
Zysk A, DeNichilo MO, Panagopoulos V, Zinonos I, Liapis V, Hay S, Ingman W, Ponomarev V, Atkins G, Findlay D, Zannettino A and Evdokiou A. Adoptive transfer of ex vivo expanded Vγ9Vδ2 T cells in combination with zoledronic acid inhibits cancer growth and limits osteolysis in a murine model of osteolytic breast cancer. *Cancer Lett*. 2016.

Financial Highlights

Research Income 2016 Calendar Year

1	Australian Competitive Grants	6,014,712
2	Other Public Sector Research Income	667,640
3	Industry, International, Philanthropic & Other Income	4,597,052
4	Cooperative Research Centre (CRC) Income	400,000
	Total	AUD 11,679,404



New Grants and Fellowships

The Centre for Cancer Biology has been fortunate to receive around $9,000,000 in grant funding from the NHMRC and ARC to fund critical research into areas such as lung cancer, perinatal death and childhood cancers including neuroblastoma. Professor Greg Goodall and Associate Professor Yeesim Khew-Goodall were among the CCB researchers who won major grant funding for their research.
Photograph by Naomi Jellicoe

New Grants and Fellowships

Investigator	Title	Granting Body
Bardy, Hahn, Schreiber, Moore, Scott, D'Andrea, Ross	Whole genome sequencing of 'triple-negative' myeloproliferative neoplasms	Contributing Haematologists Committee: Research Project 2016
Branford S	NHMRC Fellowship: Defining genomic mechanisms associated with treatment response, drug resistance and early blast crisis in chronic myeloid leukaemia	NHMRC
Bonder, C	Anti-fouling properties of proprietary-coated bare-metal stents	Cell Therapy Manufacturing CRC
Bonder, C	Increasing the patency of prosthetic grafts: a smart surface approach	Medvet
Boyle, S	2017 Early Career Fellowship	Royal Adelaide Hospital Research Committee
Brown MP, Lopez AF	Advancing T-cell therapy for leukaemia and glioblastoma	SAHMRI Beat Cancer Hospital Research Package
Brown MP, Staudacher A	APOMAB: a new way to find out which patients benefit from chemotherapy	HSCGB and Hospital Research Foundation
Brown MP	CARPETS: A Phase I open label study of the safety and immune effects of an escalating dose of autologous GD2 chimeric antigen receptor-expressing peripheral blood T Cells in patients with metastatic BRAF-mutant and GD2-positive melanoma	NHMRC
Brown MP	Data Manager funding	Beat Cancer Project
Brown MP	Nanodrop and plate reader	Royal Adelaide Hospital Research Infrastructure Block Grant for Equipment
Conn S	ARC Future Fellowship: The molecular interactome and functions of circular RNAs	ARC
Conn S	circRNAs as Trojan horses of oncogenesis	Ray and Shirl Norman Cancer Research Trust
D'Andrea R, Wang S	CDK9 as a target for Acute Myeloid Leukaemia (AML) treatment	BioSA Innovation
Dibbens L	The identification of new epilepsy genes by whole genome sequencing	NHMRC
Ebert L, Brown MP, Bonder C	Checkpoint blockade immunotherapy in melanoma: getting tumour-killing T cells to their site of action	Royal Adelaide Hospital Clinical Project Grant
Eyre NS, Beard MR	Identification and development of inhibitors of the Zika virus NS2B/3 protease	Channel 7 Children's Research Foundation (CRF)
Gargett, T	Investigation of the phenotype and function of chimeric antigen receptor (CAR) T cells in RAH metastatic melanoma patients enrolled on the CARPETS study	RAH Research Foundation
Gronthos S, Zannettino A, Anderson P	Tyrosine kinase receptor c-ros-oncogene 1 mediates Twist-1 haploinsufficiency induced craniosynostosis in children: a novel therapeutic target	NHMRC
Goodall G, Preiss T	Functions of circular RNAs	NHMRC
Goodall G	NHMRC Fellowship: Discovering how microRNAs and circRNAs control cancer metastasis	NHMRC
Goodall G, Khew-Goodall Y, Samuel M, Bracken, C	Using miR-200 to find new therapeutic targets for neuroblastoma	NHMRC
Gregory P, Goodall G	Characterising novel alternative splicing networks that promote tumour cell plasticity	NHMRC
Hiwase S, Hahn CN, Scott HS, Brown AL, Schreiber AW, Lewis ID	Germline variants collaborate with somatic mutation so initiate and/or drive disease in primary myelodysplastic syndrome (MDS) and therapy-related myeloid neoplasms (t-MN)–APP1108964	RAH Research Committee NHMRC Near Miss Grants 2016
Jankovic T, Van der Hoek K, Jolly LA, Eyre NS	The impact of Zika virus infection on placenta and neural development during early gestation	Robinson Research Institute (RRI) Innovation Seed Funding Program
Kumar S, Mathivanan S	Exploring the role of Arrcd4 in extracellular vesicle biogenesis and its implications in tissue homeostasis	NHMRC
Kumar S, Denton D, Baehrecke E	Hormone-dependent autophagy and growth signalling in developmental cell death	NHMRC
Kumar S, Webb A	Cell death by self-eating: understanding autophagy-dependent tissue removal	ARC
Lewis I, D'Andrea R, Samaraweera S	Characterising the metabolic changes associated with mutations affecting oxidative phosphorylation in AML	Royal Adelaide Hospital Research Fund
Li J, Liu L, Wu X, Goodall G	Efficient causal discovery from observational data	ARC
Lopez AF, Grimbaldeston M	Novel approaches to control mast cell function in allergic inflammation	NHMRC
Lopez AF, Geoghegan J, Scott HS	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 Grant
North K, Sinclair A (SA CIs: Scott HS, Fletcher J, Gecz J, White D, Wesselingh S, Lopez AF; SA AIs: Barnett C, Kassahn K)	Preparing Australia for genomic medicine: a proposal by the Australian Genomics Health Alliance	NHMRC
Oehler M, Pitson P, Pitman M	Defining the CIB2/SK1 axis as a prognostic indicator and chemosensitizing target in ovarian cancer	Royal Adelaide Hospital Research Grant
Parker W, Geoghegan J, Moore S, Yeung D, Schreiber A, Thean T, Scott H	Development of an accurate and sensitive RNA-based test to detect clinically actionable fusion genes for the molecular diagnosis of cancer	Royal Adelaide Hospital Research Grant
Pitson S	Liquid handling robot and plate reader	Neurosurgical Research Foundation
Pitson S	Multi-channel pipettes	Hallett Cove Districts Lions Club
Pitson S	Modulating sphingolipid signalling to enhance wound healing	NHMRC
Pitson S, Powell J, Pitman M	Targeting sphingosine kinase to improve glioblastoma therapy	Neurosurgical Research Foundation
Reynolds P, Bonder C, Voelcker N	Engineered cell therapy for pulmonary hypertension	Royal Adelaide Hospital Research Grant
Rajak S, Geoghegan J, Kearney D, Kokavic D, Selva D	The genetics of periocular sebaceous gland carcinoma	Royal Adelaide Hospital Research Grant
Robertson S, McColl S, Zannettino A	Adelaide GSEx Flow Cytometry Facility	ARC
Scott HS	Genetic autopsy of perinatal death: diagnosis and discovery by genome sequencing	NHMRC
Scott HS	Research Fellowship extension	NHMRC
Scott HS, Hahn CN, Brown AL, Tergaonkar V, Schreiber AW, D'Andrea R, Godley LA	Using familial haematological malignancies and germline variants to identify new haematopoietic and pan-cancer genes	Cancer Council Project Research Project Grant
Staudacher A	Investigating novel antibody drug conjugates for treating lung cancer	NHMRC
Tergaonkar V, Conn S	Circular RNAs in leukaemia	RNA Biology Center, Singapore
Whitfield R, Kochetkova M	eEF2K as a novel target for combination therapy with anti-angiogenic agents in breast cancer	Royal Adelaide Hospital Research Grant
Wiszniak S	Tom Simpson Trust Fund Equipment Grant	National Heart Foundation
Woodcock J, Lopez AF, Reynolds P	Developing new therapies for lung cancer	Royal Adelaide Hospital Research Grant
Zannettino A, Revesz T, Fitter S, Sutton R	The role of novel paediatric B-cell Acute Lymphoblastic Leukaemia (ALL) blast cell-derived factors on blast cell and stromal cell biology	Women's and Children's Health Foundation

Seminar Program

Dr Daniel Thomas
Institute of Stem Cell & Regenerative Medicine, School of Medicine, Stanford University, San Francisco, USA
MiSL: a tool for rapid discovery of synthetic lethal targets in cancer 21/01/2016

Associate Professor Kevin Morris
School of Biotechnology and Biomedical Sciences, University of NSW, Sydney; Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California
Genomic dark matter; the complexities of Non-Coding RNA from mechanism to therapeutic 17/03/2016

Dr Michael Piper
ARC Future Fellow, Group Leader, School of Biomedical Sciences and The Queensland Brain Institute, University of Queensland, Brisbane
Transcriptional control of neural stem cell biology in development and disease 24/03/2016

Mr Luke Hickey
Senior Director of Human Biomedical Marketing, Pacific Biosciences, Walter and Eliza Hall Institute for Medical Research, Melbourne
Human genome sequencing in the era of long reads 31/03/2016

Professor John Mariadason
Head, Oncogenic Transcription Laboratory, Olivia Newton-John Cancer Research Institute, Melbourne
Insights into the anti-tumour activity of histone deacetylase inhibitors 7/04/2016

Associate Professor Margaret Hibbs
Head, Leucocyte Signaling Laboratory, Department of Immunology and Pathology, Monash University, Melbourne
Defining mechanisms underlying chronic lung inflammation 14/04/2016

Dr Emma Josefsson
Laboratory Head, Walter and Eliza Hall Institute of Medical Research, Cancer and Haematology Division, Melbourne
Platelets promote tumour progression in Eμ-myc driven lymphoma 21/04/2016

Professor Peter Gunning
Head, School of Medical Sciences, University of New South Wales, Sydney
Targeting the architecture of the cancer cell: from basic cell biology and first-in-class therapeutics to synergy with standard-of-care agents 28/04/2016

Dr Marco Herold
Molecular Genetics of Cancer, Walter and Eliza Hall Institute for Medical Research, Melbourne
Using CRISPR/Cas9 technology to identify and validate novel cell death regulators in vitro and in vivo 5/05/2016

Professor Andreas Strasser
Joint Division Head, Molecular Genetics of Cancer Division, Walter and Eliza Hall Institute for Medical Research, Melbourne
How does the tumour suppressor p53 protect us from developing cancer? 12/05/2016

Professor Geraldine O'Neill
Focal Adhesion Biology Group Leader, Paediatrics and Child Health, Children's Hospital, Westmead, New South Wales
Space invaders: how invading cancer cells negotiate tissue barriers 19/05/2016

Professor Ryan Lister
Plant Energy Biology, ARC Centre of Excellence, The University of Western Australia, Perth
Natural and artificial regulation of the DNA methylome 26/05/2016

Professor Sally Dunwoodie
Head, Chain Reaction Program in Congenital Heart Disease, Developmental and Stem Cell Biology Division, Victor Chang Cardiac Research Institute, and Professor, Faculty of Medicine, University of New South Wales
Identifying genetic and environmental factors causing developmental defects in humans and mice 2/06/2016

Professor Sean M Grimmond
Director and The Bertalli Chair in Cancer Medicine, University of Melbourne Centre for Cancer Research
Decoding the root causes and therapeutic opportunities in recalcitrant cancers 9/06/2016

Professor Robert Vink
Pro Vice Chancellor, Division of Health Sciences, University of South Australia
Increased intracranial pressure: a basic scientist's perspective on a clinical problem 16/06/2016

Dr Marie-Liesse Asselin-Labat
Laboratory Head, ACRF Stem Cells and Cancer division, Walter and Eliza Hall Institute of Medical Research, Melbourne
Differential DNA repair mechanisms in lung stem cells participate in lung carcinogenesis 23/06/2016

Dr Enzo Porrello
Research Fellow, School of Biomedical Sciences, The University of Queensland, Queensland
A neonatal blueprint for cardiac regeneration 7/07/2016

CCB Annual General Meeting
Invited Speaker: Professor Suzanne Cory
Honorary Distinguished Professorial Fellow, Molecular Genetics of Cancer Division, Walter and Eliza Hall Institute of Medical Research 14/07/2016

Professor James Whisstock
Director, ARC Centre of Excellence in Advanced Molecular Imaging, NHMRC Senior Principal Research Fellow, Dept of Biochemistry and Molecular Biology, Monash University, Victoria
Atomic resolution insights into pore formation by perforin-like immune effectors 26/07/2016

Dr Andrew Nash
Senior Vice President, Research CSL Limited
Biologics R&D at CSL: new therapies for rare diseases 28/07/2016

Professor Rob Parton
Group Leader, Cell Biology and Molecular Medicine Division; Investigator, Centre for Rare Diseases Research; Investigator, Breakthrough Science Program in Mechanobiology, University of Queensland
Cave exploration at the nanoscale: new insights into the structure and function of caveolae 4/08/2016

Professor Clare Lloyd
Wellcome Senior Research Fellow in Basic Biomedical Sciences; Professor of Respiratory Immunology; Head, Inflammation, Repair and Development Section; Head, Division of Respiratory Sciences, National Heart and Lung Institute, Imperial College, London
Living on the edge: regulation of pulmonary immunity by epithelia 15/08/2016

Dr Lan K Nguyen
Senior Research Fellow, Head, Network Modelling Laboratory, Department of Biochemistry and Molecular Biology, School of Biomedical Science, Monash University
Quantitative and predictive modelling: an integrated approach to understand cancer signalling and cell-fate determination 25/08/2016

Professor Stephanie S Watowich
Professor, Department of Immunology, Division of Basic Science Research, The University of Texas MD Anderson Cancer Center, Houston, USA
Innate immune regulation in inflammation and cancer 30/08/2016

Professor Michael F Good
Head, Laboratory of Vaccines for the Developing World, NHMRC Senior Principal Research Fellow Institute for Glycomics, Griffith University, Queensland
Natural and vaccine-induced immunity to group A streptococcus 1/09/2016

Associate Professor Jeff Holst
Head, Origins of Cancer Program, Centenary Institute; Conjoint Associate Professor, Sydney Medical School, University of Sydney, New South Wales
Regulation of nutrient uptake controls cancer cell growth and metabolism 8/09/2016

Professor Steve Webb
Clinical Professor, School of Population Health, University of Western Australia, Perth
Replacing random care with randomised care 15/09/2016

Dr Susan Woods
Senior Research Fellow, University of Adelaide/SAHMRI, South Australia
Modelling the alternate pathway to colorectal cancer using genome engineered organoids: CRISPrs with that? 22/09/2016

Professor Keith M McLean
Adjunct Professor, Australian Regenerative Medicine Institute, Science, Technology, Research and Innovation Precinct (STRIP), Monash University, Victoria
Implantable materials for medical devices, tissue engineering and cell therapies 13/10/2016

Dr Tri Phan
Laboratory Head, Intravital Microscopy, Garvan Institute of Medical Research, Sydney
Insights from intravital imaging of cancer cells in mice with intact immune systems 20/10/2016

Professor Oliver Mühlemann
Professor of Biochemistry, Director of the NCCR RNA Disease, University of Berne, Switzerland
Trying to make sense in nonsense-mediated mRNA decay 27/10/2016

Dr Timothy R Mercer
Laboratory Head, Transcriptomic Research, Garvan Institute for Medical Research, Sydney
Representing the human genome with synthetic controls 3/11/2016

Dr Bryan Day
Team Head, Translational Brain Cancer Research Laboratory (QIMR Berghofer) and Sid Faithfull Fellow, Royal Brisbane Hospital, Queensland
EphA3: A valid specific *therapeutic target in brain cancer* 10/11/2016

Dr Eija Korpelainen
CSC-IT Centre for Science Ltd, Espoo, Finland
Enabling life scientists to analyze their own sequencing data 11/11/2016

Dr Susanne Heinzel
Immunology Division, Walter and Eliza Hall Institute for Medical Research, Melbourne
Ticking away: regulation of division progression of T and B cells 17/11/2016

Associate Professor Elgene Lim
Laboratory Head, Connie Johnson Breast Cancer Research, Garvan Institute for Medical Research, Sydney
New insights into Endocrine resistance in Breast Cancer 24/11/2016

Associate Professor Tamas Revesz
Senior Haematologist-Oncologist, SA Pathology, Women's and Children's Hospital, South Australia
First steps towards personalized medicine in childhood leukaemia 1/12/2016

Dr Guillermo Gomez
Senior Research Officer, Institute for Molecular Bioscience, University of Queensland, Queensland
Mechanochemical control of collective cellular responses in epithelial tissues 8/12/2016

Associate Professor Janni Petersen
Associate Professor, Flinders Centre for Innovation in Cancer, Flinders University, South Australia
Target of Rapamycin (TOR) integrates environmental signals to control cell growth and division 15/12/2016

Invited Presentations

Acute Leukaemia Laboratory

Associate Professor Richard D'Andrea

Invited Speaker

Healthy Development Adelaide Meeting. Adelaide, Australia. April

13th One-Day Symposium of the HGSA-SA Branch. Adelaide, Australia. September

Peter MacCallum Cancer Centre Cancer Networking Meeting. Melbourne, Australia. November

Molecular Studies of AML. Centenary Institute, Sydney, Australia. November

Mr Kyaw Ze Ya Maung

Invited Speaker

Rare variants affecting the Fanconi Anaemia DNA repair genes associate with increased risk for AML. HSANZ 19th Scientific Weekend Meeting, Victor Harbor, Australia. September

Cell Signalling Laboratory

Associate Professor Yeesim Khew-Goodall

Invited Speaker

FASEB Protein Phosphatase Conference. Steamboat Springs, Colorado, USA. July

Lorne Cancer Conference. Lorne, Australia. February

Hunter Systems and Cell Biology. Hunter Valley, Australia. March

Invited Speaker and Session Chair

ComBio 2016. Brisbane, Australia. October

Cytokine Receptor Laboratory

Professor Angel Lopez

Invited Speaker

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

Session Chair

Garvan Institute, 2016 Leaders in Science and Society Seminar, Sydney, Australia. April

Signalling by the βc family of cytokines. Peter MacCallum Research Institute, Melbourne, Australia. March

Gastroenterology Research Laboratory

Associate Professor Andrew Ruszkiewicz

Invited Speaker

OMICS, World Congress on Human Genetics. Barcelona, Spain. August

Australasian Gastrointestinal Pathology Society Annual Meeting. Perth, Australia. October

Inflammation and Human Ailments Laboratory

Professor Vinay Tergaonkar

Invited Speaker

Lorne Cancer Conference. Australia. February

Merck invited lecture. University of Mainz, Germany. June

IFOM, Milan, Italy, June

Yale University, Dept of Immunobiology, USA. June

German Cancer Center (DKFZ). Heidelberg, Germany. June

8th Garvan Signaling Symposium. Sydney, Australia. October

National Centre for Biological Sciences. Bangalore, India. November

ICSAF-2016. Sastra University, India. December

World Cancer Congress. Miami, Florida, USA. November

Leukaemia Laboratory, Genetics and Molecular Pathology

Associate Professor Susan Branford

Session Chair

American Society of Hematology CML Education Session. San Diego, USA. December

Satellite meeting, Haematology of Australia and New Zealand Conference 2016. Melbourne, Australia. October

Human Genetics Society of Australasia Meeting, SA Branch. Adelaide, Australia. October

Australian Society of Medical Research (ASMR) Meeting. Adelaide, Australia. July

South African CML Pathology Advisory Board. Cape Town, South Africa. March

Invited Speaker

American Society of Hematology CML Education Session. San Diego, USA. December

China Global Opinion Leaders Summit. Chengdu, China. November

Molecular Monitoring Steering Committee Meeting 2016. Taipei, Taiwan. October

18th Annual John Goldman Meeting on CML. Houston, USA. September

Glivec, Exjade, Nilotinib National Meeting on Haematologic Malignancies. Sydney, Australia. August

Peter MacCallum Cancer Cencer Journal Club. Melbourne, Australia. June

Royal Brisbane Hospital Journal Club. Brisbane, Australia. June

Australian Leukaemia Foundation Patient and Carers Education Day. Perth, Australia. February

BCR-ABL1 lab excellence workshop. Gold Coast, Australia. May

South African CML meeting. Cape Town, South Africa. March

Fiona Stanley Hospital Journal Club. Perth, Australia. February

Lymphatic Development Laboratory

Associate Professor Natasha Harvey

Invited Speaker or Session Chair

9th Australasian Society for Stem Cell Research Meeting. Bunker Bay, Australia. December

5th Australian Network of Cardiac and Vascular Developmental Biologists Meeting. Sydney, Australia. November

1st Lipedema Foundation Scientific Retreat. New York, USA. October

8th Garvan Signalling Symposium. Sydney, Australia. October

Asia Pacific Lymphology Conference. Darwin, Australia. May

Centenary Institute Symposium: Imaging the Endothelium in Health and Disease. Sydney, Australia. May

The Hunter Cell and Developmental Biology Meeting. Hunter Valley, Australia. April

Gordon Research Conference: Lymphatics. Ventura, CA, USA. March

Invited Seminars

University of Melbourne Department of Anatomy and Neuroscience. Melbourne, Australia. October

Uppsala University Department of Immunology, Genetics and Pathology. Uppsala, Sweden. September

St George's University London Department of Clinical Genetics. London, UK. September

University of Cambridge Department of Physiology, Development and Neuroscience. Cambridge, UK. September

Molecular Pathology Research Laboratory

Dr Hamish Scott

Invited Speaker

American Society of Hematology 58th Annual Meeting and Exposition, Scientific Workshop on Inherited Hematopoietic Malignancies. San Diego, USA. December

Australian Centre of Blood Diseases and Central Clinical Schools Scientific Meeting. Melbourne, Australia. August

HGSA SA Branch symposium, Adelaide, Australia. September

Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG) annual scientific meeting, Cairns, Australia. June

Invited Speaker or Session Chair

Royal College of Pathologists of Australasia (RCPA): Pathology Update 2017, Melbourne, Australia. February

Royal College of Pathologists of Australasia (RCPA): Pathology Update 2016, Melbourne, Australia. February

HGSA 40th Annual Scientific Meeting, Hobart, Australia. August

Dr Christopher N Hahn

Invited Speaker

ComBio 2016, Cancer Genomics Symposium, Brisbane, October.

Dr Anna L Brown

Invited Speaker

New Directions in Leukaemia Research Conference. Sunshine Coast, Queensland, Australia. March

American Society of Hematology Annual Meeting, San Diego, USA. December

Friday workshop on inherited hematopoietic malignancies. American Society of Hematology Annual Meeting, San Diego, USA. December

Session Chair

Friday workshop on inherited hematopoietic malignancies. American Society of Hematology Annual Meeting. San Diego, USA. December

Haematology Society of Australia and New Zealand State Branch 19th Scientific Weekend Meeting. Victor Harbor, Australia. September

Ms Alicia Byrne

Invited Speaker

37th Annual Lorne Genome Conference, Lorne, Victoria, Australia. February

University of South Australia School of Pharmacy and Medical Sciences 2016 Symposium, Adelaide. June

Dr Parvathy Venugopal

Invited Speaker

Haematology Society of Australia and New Zealand State Branch 19th Scientific Weekend Meeting. Victor Harbor, Australia. September

Molecular Regulation Laboratory

Professor Sharad Kumar

Plenary Speaker

ANZSCDB President's Medal Lecture, ComBio 2016. Brisbane, Australia. October

Invited Speaker

Cold Spring Harbor Asia Conference: Ubiquitin Family, Autophagy and Disease. Suzhou, China. April

FASEB Research Conference: Ubiquitin and cellular regulation. Big Sky, Montana, USA. June

Gordon Conference on Cell Death. Girona, Spain. July

AusFly2016, Australian Fly Meeting, Victoria, Australia. September

CCB-A*STAR Strategic Meeting. IMCB, Singapore. December

Invited Lecture

Peter McCallum Cancer Institute. Melbourne, Australia. May

Institute of Immunology, University Medical Center. Mainz, Germany. June

Anatomy and Neuroscience, Melbourne University. Melbourne, Australia. August

The University of Tokyo. Tokyo, Japan. December

Dr Donna Denton

Invited Speaker

AusFly2016, Australian Fly Meeting, Victoria, Australia. September

Dr Natalie Foot

Session Chair

Cell Biology Session: ASMR SA Conference. Adelaide, Australia. June

Australia and New Zealand Society for Cell and Developmental Biology, 6th Annual Meeting. Adelaide, Australia. November

Dr Tanya Henshall

Session Chair

Australia and New Zealand Society for Cell and Developmental Biology, 6th Annual Meeting. Adelaide, Australia. November

Dr Jantina Manning

Selected Speaker

Australia and New Zealand Society for Cell and Developmental Biology, 6th Annual Meeting. Adelaide, Australia. November

Ms Shannon Nicolson

Invited Speaker

AusFly2016, Australian Fly Meeting, Victoria, Australia. September

Selected Speaker

Autophagy in Stress, Development & Disease, Gordon Research Seminar. Ventura, CA, USA. March

Australia and New Zealand Society for Cell and Developmental Biology, 6th Annual Meeting. Adelaide, Australia. November

Dr Claire Wilson

Selected Speaker

Animal Model session: ASMR SA Conference. Adelaide, Australia. June

Session Chair

Australia and New Zealand Society for Cell and Developmental Biology, 6th Annual Meeting. Adelaide, Australia. November

Molecular Signalling Laboratory

Professor Stuart Pitson

Invited speaker

12th Indo-Australian Biotechnology Conference: Biotechnology interventions in human health. Bhubaneshwar, India. August

3rd Australian Lipid Meeting. Melbourne, Australia. November

ComBio 2016. Brisbane, Australia. October

Royal Adelaide Hospital Research Fund Luncheon. Adelaide, Australia. May

Neurosurgical Research Foundation. Adelaide, Australia. June

Fay Fuller Foundation. Adelaide, Australia. November

2017 Lightsview Ride Like Crazy Sponsors Night. Adelaide, Australia. November

Dr Maurizio Costabile

Session Chair

Clute Institute International Science Education Conference, Venice, Italy.

Invited speaker

ComBio 2016. Brisbane, Australia. October

Dr Jason Powell

Selected Speaker

New Directions in Leukemia Research, Noosa, Queensland, Australia. March

Myeloma Research Laboratory

Professor Andrew Zannettino

Invited speaker

New Directions in Leukaemia Research meeting. Noosa, Australia. March

Inaugural National Myeloma Workshop. Melbourne, Australia. September

Neurovascular Research Laboratory

Dr Quenten Schwarz

Plenary Chair

8th Australian Developmental Biology Workshop. Mornington Peninsula, Australia. December

Evo-Devo session at the 8th Australian Developmental Biology Workshop. Mornington Peninsula, Australia. December

Invited Speaker

Neural stem cells at the 8th Australian Developmental Biology Workshop. Mornington Peninsula, Victoria. December

Dr Sophie Wiszniak

Invited Speaker

Agile X 4 Morphogenetic Prototyping Workshop, UniSA, Adelaide, Australia. November

ComBio 2016. Brisbane, Australia. October

Ms Reem Hasaneen

Invited Speaker

Australian Society for Medical Research (ASMR) SA Scientific Meeting short talk. Adelaide, Australia. June

Invited Presentations continued

Translational Oncology Laboratory

Professor Michael P Brown

Invited Speaker

Korea Opdivo Melanoma Launch Symposium. Seoul, South Korea. June

Korea Opdivo NSCLC Launch Symposium. Seoul, South Korea. June

Multi-National Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) Annual Meeting on Supportive Care in Cancer. Adelaide Convention Centre, Adelaide, Australia. June

Joint Cancer Science Institute of Singapore/ National University Cancer Institute, Singapore (CSI-NCIS) Lung Cancer Symposium 2016. National University of Singapore, Singapore. July

National University of Singapore Centre for Translational Medicine. Singapore. January

Institute of Molecular and Cellular Biology. Singapore. January

Miltenyi Biotec. Bergish-Gladbach, Germany. September

24th NSW Stem Cell Network Workshop. Sydney, Australia. April

Royal Australasian College of Physicians Congress. Adelaide Convention Centre, Adelaide, Australia. May

Medical Oncology Group of Australia Annual Scientific Meeting. Gold Coast, Australia. August

Bellberry Education Weekend 2016. The Science Exchange, Adelaide, Australia. August

Locoregional Melanoma 2016.Peter MacCallum Cancer Centre, Melbourne, Australia. August

International Congress of Immunology (Melbourne, Australia. August

International Society for Cell Therapy: Australia and New Zealand (ISCT-ANZ) Regional Meeting. Melbourne, Australia. November

Hudson Institute Seminar. Monash Health, Melbourne, Australia. April

Session Chair and Judge

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

Plenary Session Chair, Cancer Immunotherapy: translating science to patients. The 14th Annual Haematology and Oncology Targeted Therapies (HOTT) Symposium. Sydney, Australia. April

Dr Tessa Gargett

Invited Speaker

International Congress of Immunology, The CARPETS Trial: GD2-specific CAR T cell therapy for Advanced Melanoma. Melbourne, Australia. August

CAR Network Meeting. Miltenyi Biotech Headquarters, Germany. September

Cell Therapy Manufacturing CRC Workshop. Adelaide, Australia. September

Adelaide Blood Club Breakfast Meeting. Adelaide, Australia. August

Tumour Microenvironment Laboratory

Dr Michael Samuel

Invited Speaker

Annual Scientific Meeting of the Matrix Biology Society of Australia and New Zealand (MBSANZ), Camden NSW, Australia. November

ComBio 2016, Tissue Architecture and Cell Migration Symposium (Cell Biology Stream), Brisbane, Australia. October

16th Hunter Meeting and 9th Imaging Workshop, Pokolbin NSW, Australia. April

Olivia Newton-John Cancer Research Institute Seminar Series, Melbourne. May

Dr Sarah Boyle

Invited speaker

6th Adelaide ANZSCDB Cell and Developmental Biology Meeting. Adelaide, Australia. November

Australian Society for Medical Research (ASMR) Annual Adelaide Meeting, Ross Wishart Memorial Award presentation. Adelaide, Australia. June

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

Vascular Biology and Cell Trafficking Laboratory

Associate Professor Claudine Bonder

Chair

South Australian Breast Cancer Study Group. Adelaide, Australia. March

Invited Speaker

Cardiac Society of Australia and New Zealand. Adelaide, Australia. August

Basil Hetzel Institute, University of Adelaide. Adelaide, Australia. September

Division of Pharmacology, Monash University. Victoria, Australia. October

Western University. London Ontario, Canada. October

Australian Physiological Society. Adelaide, Australia. December

Australian Vascular Biology Society. Hobart, Australia. December

Viral Pathogenesis Laboratory

Associate Professor Michael Beard

Chair

Innate Immunity Session, International Symposium on Hepatitis C Virus and Related Viruses. Kyoto, Japan. October

Invited Speaker

University of Sydney. Sydney, Australia. June

National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID). Rocky Mountain Laboratories. Montana, USA. March

Dr Nicholas Eyre

Chair

The Frank Fenner Viral Pathogenesis Session, Australian Virology Society Scientific Meeting. Hunter Valley, Australia. December

ACRF Cancer Genomics Facility

Dr Andreas Schreiber

Invited Speaker

Taking the confusion out of fusions: structural mutation detection in cancer research and diagnostics. ABACBS 2016, QUT, Brisbane, Australia. November

Dr Katherine Pillman

Invited Speaker

Alternative splicing: one cell's trash is another's treasure. BioInfoSummer 2016, University of Adelaide, Adelaide, Australia. November

Swimming in circles, AGTA 2016, Auckland, New Zealand. October

Centre for Cancer Biology 2016 Awards

Associate Professor Claudine Bonder won the 2016 Winnovation (Women in Innovation) Award in the 2016 Emerging Innovator category. Claudine was recognised for her work leading a team investigating how blood vessels contribute to disease progression, particularly where blocked blood vessels are the leading cause of cardiovascular disease. Claudine's team is translating this research into treatments which will overcome the current clinical hurdles of cardiovascular disease and save thousands of lives world-wide.

Photograph by Brenton Edwards

Awards

Acute Leukaemia Laboratory

Mr Kyaw Ze Ya Maung

ASH Abstract Achievement Award, 58th American Society of Hematology Annual Meeting and Exposition

Mr Mahmoud Bassal

WA/SA Semi-Finals Champion and People's Choice Award, 2016 FameLab 3MT, Perth

Inflammation and Human Ailments Laboratory

Associate Professor Simon Conn

2016 Simpson Cancer Research Prize, Prime de récherche, National Science Research Centre, France

Leukaemia Laboratory, Genetics and Molecular Pathology

Associate Professor Susan Branford

2016 International Chronic Myeloid Leukemia Foundation (iCMLf) Award

Lymphatic Development Laboratory

Dr Genevieve Secker

Best PostDoc Poster, 5th ANZSCDB Meeting, Adelaide, Australia

Ms Jan Kazenwadel

Best Student Poster Award, 5th Australian Network of Cardiac and Vascular Developmental Biologists Meeting, Sydney, Australia

Dr Drew Sutton

Runner-Up Best Postdoctoral Poster Award, 5th Australian Network of Cardiac and Vascular Developmental Biologists Meeting, Sydney, Australia

Molecular Pathology Research Laboratory

Ms Alicia Byrne

Maurice de Rohan International Scholarship

Co-op High Achiever Research Grant

Gould Experimental Science Grant

Best Oral Presentation, University of South Australia School of Pharmacy and Medical Sciences 2016 Symposium, Adelaide, Australia

Travel Grant, 37th Annual Lorne Genome Conference

Molecular Regulation Laboratory

Ms Swati Dawar

Outstanding PhD Student Poster, 5th ANZSCDB Meeting, Adelaide, Australia

Professor Sharad Kumar

The Australia and New Zealand Society for Cell and Developmental Biology (ANZSCDB) President's Medal

Molecular Signalling Laboratory

Ms Heidi Neubauer

Outstanding Student Oral Presentation Prize, 6th ANZSCDB Adelaide Meeting, Adelaide, Australia

Joint Winner, Royal Adelaide Hospital Medical Staff Society Research Prize for Best Student Oral Presentation, Medical Grand Round, Adelaide, Australia

Ms Melissa Bennett

2016 MF & MH Joyner Scholarship in Medicine

RAH Dawes top-up PhD scholarship

UniSA Vice Chancellor and President's Scholarship

Ms Wenying Zhu

Joint Winner, Royal Adelaide Hospital Medical Staff Society Research Prize for Best Student Oral Presentation, Medical Grand Round, Adelaide, Australia

Beat Cancer Travel Grant

Dr Maurizio Costabile

Online Learning Consortium Effective Practice Award, *Improving student learning of College Biochemistry using simulations*, New Orleans, USA

Best Presentation, Clute Institute International Science Education Conference, Venice, Italy

Myeloma Research Laboratory

Mr Krzysztof Mrozik

Plenary Speaker (selected from abstract), Inaugural National Myeloma Workshop, Yarra Valley, Australia

Executive Dean Prize, Faculty of Health and Medical Sciences, University of Adelaide, Australia

Dr Chee Man Cheong

Awarded the John Barker Prize for Medical Research

Translational Oncology Laboratory

Dr Tessa Gargett

Beat Cancer Travel Grant 2016

Australian Society for Immunology Travel Bursary to attend International Congress of Immunology Melbourne

Best Early Career Researcher Presentation, ASMR SA Scientific Meeting, Adelaide

Tumour Microenvironment Laboratory

Ms Sarah Boyle

Ross Wishart Memorial Award 2016, Australian Society for Medical Research

Vascular Biology and Cell Trafficking Laboratory

Associate Professor Claudine Bonder

2016 Emerging Innovator Award, 2016 Winnovation (Women in Innovation) 2016, University of South Australia, Division of Health Sciences, One Team Award

Dr Eli Moore

2016 CCB Early Career Researcher (ECR) Award

Ms Lih Tan

University of South Australia, Three Minute Thesis (3MT) Runner-up, Grand Final, People's Choice Award

Viral Pathogenesis Laboratory

Dr Nick Eyre

Oral Poster Award, Australian Virology Society Scientific Meeting, Hunter Valley, Australia

HCV2016 Travel Fellowship, International Symposium on Hepatitis C Virus and Related Viruses, Kyoto, Japan

Associate Professor Claudine Bonder, Ms Monica Oliphant AO and Dr Philip Gregory present the Oliphant Trophy to Ms Alexandra Stephenson (centre right), Adelaide Hills Home School Group, for Most Outstanding Scientific Content Entry by a South Australian High School Student

Professor Suzanne Cory AC presents Dr Eli Moore with the 2016 CCB Early Career Researcher Award

Dr Sophie Wiszniak presents Dr Gen Secker with ANZSCDB award for Best Postdoc Poster

Dr Emma Parkinson-Lawrence (left) and Associate Professor Claudine Bonder (right) present the Cancer Biology prize to Ms Brittany Cole (centre) for the highest grade in the third year Cancer Biology course at the University of South Australia

Dr Sophie Wiszniak presents Ms Heidi Neubauer with ANZSCDB award for Runner-up Student Oral

Professor Suzanne Cory AC and Dr Helle Christophersen (Millennium Science) present the award for Best Publication to Professor Greg Goodall on behalf of Associate Professor Simon Conn

Service to the Community

Cytokine Receptor Laboratory

Professor Angel Lopez

Australian Cancer Research Foundation (ACRF) Medical Research Advisory Committee

Australian Academy of Health and Medical Science (AAHMS) Selection Committee

Viertel Medical Advisory Board (MAB) member

Australian Academy of Science (AAS) Sectional Committee member

Peter MacCallum Cancer Centre, Scientific Advisory Panel member

Dr Hayley Ramshaw

Cancer Australia Grant Review Panel

Gastroenterology Research Laboratory

Professor Andrew Ruszkiewicz

Examiner for the Royal College of Pathologists of Australasia

Gene Regulation Section

Professor Greg Goodall

NHMRC Assigners Academy

Cancer Australia Grant Review Panel

NBCF Grant Review Panel

Associate Editor *Oncogene*

Associate Editor *Oncogenesis*

Leukaemia Unit Molecular and Genetic Pathology

Associate Professor Susan Branford

QIAGEN's European Scientific Advisory Board for Haematology/Oncology

Novartis Molecular Steering Committee

International Chronic Myeloid Leukemia Foundation (iCMLf) Scientific Advisory Committee

Member of the Molecular Diagnostics RCPA Quality Assurance Program Executive for Australia

Deputy Facilitator of the Genomics, Genetics and Druggable Targets pillar, South Australian Comprehensive Cancer Consortium

Lymphatic Development Laboratory

Associate Professor Natasha Harvey

Member, NHMRC Assigner's Academy

Member, Australian Academy of Science National Committee for Cell and Developmental Biology

Member, Australia and New Zealand Society for Cell and Developmental Biology Committee

Vice-President, The Hunter Meeting Organising Committee

Member, 8th Australian Developmental Biology Workshop Organising Committee

Chair, RAH Scholarships and Fellowships Committee

Member, RAH Research Committee

Member, CCB Mentoring Committee

Molecular Pathology Research Laboratory

Professor Hamish Scott

Centre for Cancer Biology, SA Pathology representative to the National Genomic Healthcare Alliance

Facilitator of the Genomics, Genetics and Druggable Targets pillar, South Australian Comprehensive Cancer Consortium

South Australian Cancer Research Biobank Executive Committee

Co-Director, the ACRF Cancer Genome Facility

Scientific Advisory Board, for the BLACKSWAN Foundation, a Foundation for Research in Orphan Diseases

Editorial Board of PLoS Genetics

Communicating editor on the Editorial Board of Human Mutation

Ad hoc program and project grant reviewer for the NHMRC, ARC and DEST

Molecular Regulation Laboratory

Professor Sharad Kumar

UniSA Research Leadership Committee

Editorial Board and Triage Editor, Cell Death and Differentiation

Editorial Board, Frontiers in Cancer Molecular Targets and Therapeutics

Editorial Board, Oncotarget (Cell Death and Autophagy Section)

Editorial Board, ScienceOPEN

Editorial Board, Cell Stress

Associate Editor, Molecular & Cellular Oncology

Member, Faculty of 1000

President-Elect, ANZSCDB

Co-Convenor, Hunter Cellular Biology Meeting

Member, NHMRC Assigners Academy

Molecular Signalling Laboratory

Professor Stuart Pitson

Member of the NHMRC Grant Assigner Academy

Member of Research Fellowship Selection Committee, Victorian Cancer Agency

Member of Priority-driven Young Investigator Project Grants Review Committee, Cancer Australia

Editorial Board member, Cellular Signalling

Editorial Board member, Prostaglandins and Other Lipid Mediators

Editorial Board member, Journal of Bioenergetics and Biomembranes

PhD Thesis Examiner, University of New South Wales

SA State Representative, National Association of Research Fellows of the NHMRC (NARF)

Myeloma Research Laboratory

Professor Andrew Zannettino

Committee Member, Medical and Scientific Advisory Group, Australian Myeloma Foundation

NHMRC Assigners Academy, National Health and Medical Research Council

Board of Directors, Colgate Australian Clinical Dental Research Centre, University of Adelaide

Advisory Board, Robinson Research Institute (RRI), University of Adelaide

Subject Matter Expert and Assessor, Science and Industry Endowment Fund (SIEF), CSIRO

Bioscience Pillar Committee Member, South Australian Comprehensive Cancer Centre

Member, Cell Reprogramming Australia (CRA)

Scientific Advisory Committee, Bone Health Foundation

Translational Oncology Laboratory

Professor Michael P Brown

Medical Research Advisory Committee, Australian Cancer Research Foundation

NHMRC Development Grant Review Panel

Victorian Cancer Agency: Selection Panel, Clinician-Researcher Fellowships

Industry Consulting

Member, Scientific Advisory Board, Cartherics Pty Ltd

Tumour Microenvironment Laboratory

Associate Professor Michael Samuel

NHMRC Grant Review Panel 2016

Member of Panel, Cycling Health Forum, Santos Tour Down Under 2016

Appeared on SCOPE (children's science program, Network Ten) to present a segment on wound healing

Committee Member, CCB Consumer Advocacy Group

Dr Sarah Boyle

SA State Representative for ANZSCDB

Committee member of CCB Consumer Advocacy Group

Instigator and Administrator of the CCB Twitter account (@CCB_Research)

Representative of CCB at the University of South Australia "Here's Health. Research" student postgraduate information and networking evening

Representative of CCB at SAHMRI Academic Health Science and Translation Centre Student Open Night

Volunteer for Cancer Council Daffodil Day

Dr Zahied Johan

Volunteer, UniSA Open Day

Vascular Biology and Cell Trafficking Laboratory

Associate Professor Claudine Bonder

Grant Review Panel for the NMHRC

SA Tall Poppy Selection Committee

UniSA Division of Research Management Committee

Leadership Group of University of South Australia, Cancer Theme

ABC Radio 891, Evenings with Peter Goers

National Breast Cancer Foundation

Tea Tree Gully Legacy Group

Science in Schools, North Adelaide Primary School

MC for Oliphant Science Awards, South Australian Science Teachers Association Student Awards

ACRF Cancer Genomics Facility

Dr Andreas Schreiber

Introduction to RNA-seq analysis workshop, BioInfoSummer 2016. University of Adelaide, Adelaide, Australia. November

CCB Bioinformatics Workshop. Adelaide, Australia. August/September

Organising Committee, BioInfoSummer 2016. University of Adelaide, Adelaide, Australia. November

Mr David Lawrence

Genomics in Python Workshop, BioInfoSummer 2016. University of Adelaide, Adelaide, Australia. November

Dr Katherine Pillman

Organising Committee, ABACBS 2016, QUT, Brisbane, Australia. November

Dr Paul Wang

Genomics in Python Workshop, BioInfoSummer 2016. University of Adelaide, Adelaide, Australia. November

Research Staff and Students

Acute Leukaemia Laboratory
Professor Richard D'Andrea
Associate Professor Ian Lewis
Dr Sarah Bray
Dr Debora Casolari
Dr Saumya Samaraweera
Dr Nur Hezrin Shahrin
Ms Diana Iarossi
Ms Tran Nguyen
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Mr Mahmoud Bassal (PhD)
Mr Ka-Leung Li (PhD)
Mr Kyaw Zeya Maung (PhD)

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Dr Leila Belle
Dr Xiaochun Li
Dr Ana Lonic
Ms Freya Gehling
Students
Mr James Paltridge (PhD)

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Dr Tim Hercus
Dr Winnie Kan
Dr Duncan McKenzie
Dr Hayley Ramshaw
Dr Frank Stomski
Dr Denis Tvorogov
Dr Nicole Witter
Dr Dave Yip
Ms Emma Barry
Ms Mara Dottore
Ms Ceilidh Marchant
Ms Melanie Pudney
Mrs Anna Sapa
Mrs Rebecca Wright

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Dr Sarah Al Haj Diab
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Mr Aik Wye Goh (PhD)
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Ms Theodosia Teo (PhD)
Ms Tai Cheuk Ying (Hons)

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Mr Matthew Gartner (Honours)

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Professor Hamish Scott
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worldwide cancer research, formerly known as AICR

Australian Government, Cancer Australia

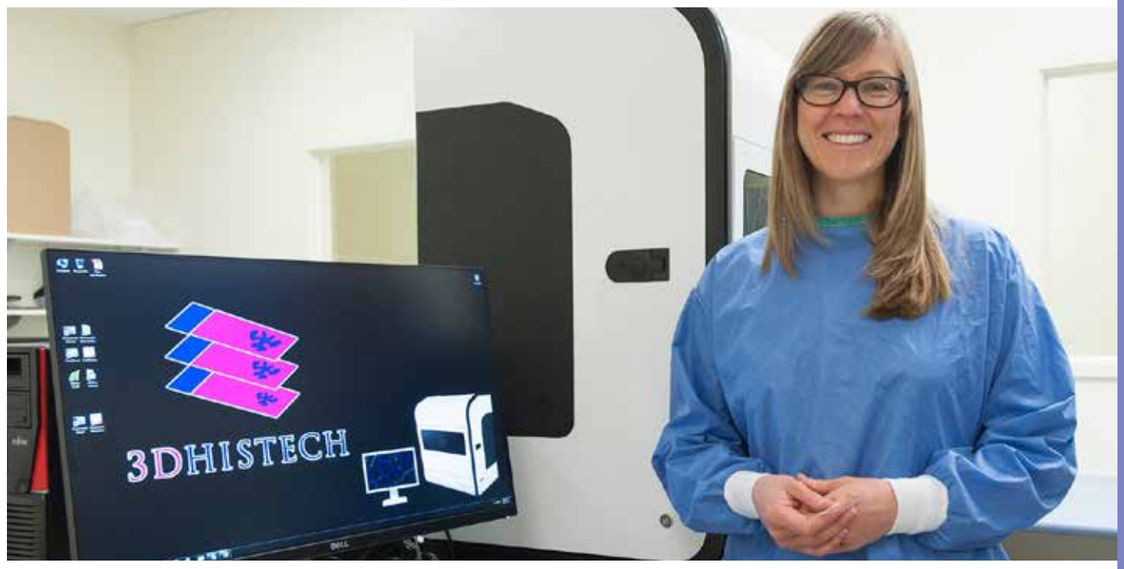
Australian Government, Australian Research Council

Research Australia, An alliance for discoveries in health

NCRIS, National Research Infrastructure for Australia, An Australian Government Initiative

The Hospital Research Foundation Team raises funds for the Centre for Cancer Biology
Nardia Frank, Maria Phuong, Jerry Witkowski, Abbey Flanagan
Paul Flynn (CEO), Kate Rushforth, Sarah Avramidis, Antonia Costa

Supporting Our World Class Research



The Panoramic 3DHISTECH is the first of its kind in Australia and performs automated, high resolution imaging of fluorescently labelled or histologically stained tissue samples using structured illumination. Associated software enables quantification of features or labelled cells and the three dimensional reconstruction of imaged tissue.

The Centre for Cancer Biology relies on grants awarded to our researchers and the generous support of individuals and organisations to carry out our vital research.

Make a donation

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.
All donations are greatly appreciated and are fully tax deductible. 100% of your donation will make a significant difference to the lives of thousands of people, now and into the future.

Make a donation in memoriam and in honour

Make a gift to the Centre for Cancer Biology in lieu of flowers to honour a loved one who has passed away, or to mark special occasions such as birthdays, weddings and anniversaries.
A personalised plaque may be affixed to any equipment bought.

Build a corporate partnership

The Centre for Cancer Biology welcomes the support of the business community. Please contact us to discuss how we might partner with your organisation.

Sponsorship

Companies or individuals may wish to sponsor a research project or individual.

Fellowships

These can be from one to five years and can be named after a family, a family member, or a company.

Ways you can donate

Secure online donations can be made via the CCB website
100% of your donation will support cutting edge research and facilities at the Centre for Cancer Biology.
www.centreforcancerbiology.org.au

The Hospital Research Foundation
The Hospital Research Foundation is committed to raising vital funds to support world-class medical research undertaken at the Royal Adelaide Hospital and it's research arms which includes the Centre for Cancer Biology.

The Hospital Research Foundation
Locked Bag 1, Regency Park South Australia 5010

Office: 60 Woodville Road, Woodville South Australia 5011

Telephone +61 8 8244 1100
Email: contactus@hospitalresearch.com.au

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Thank you

Notes