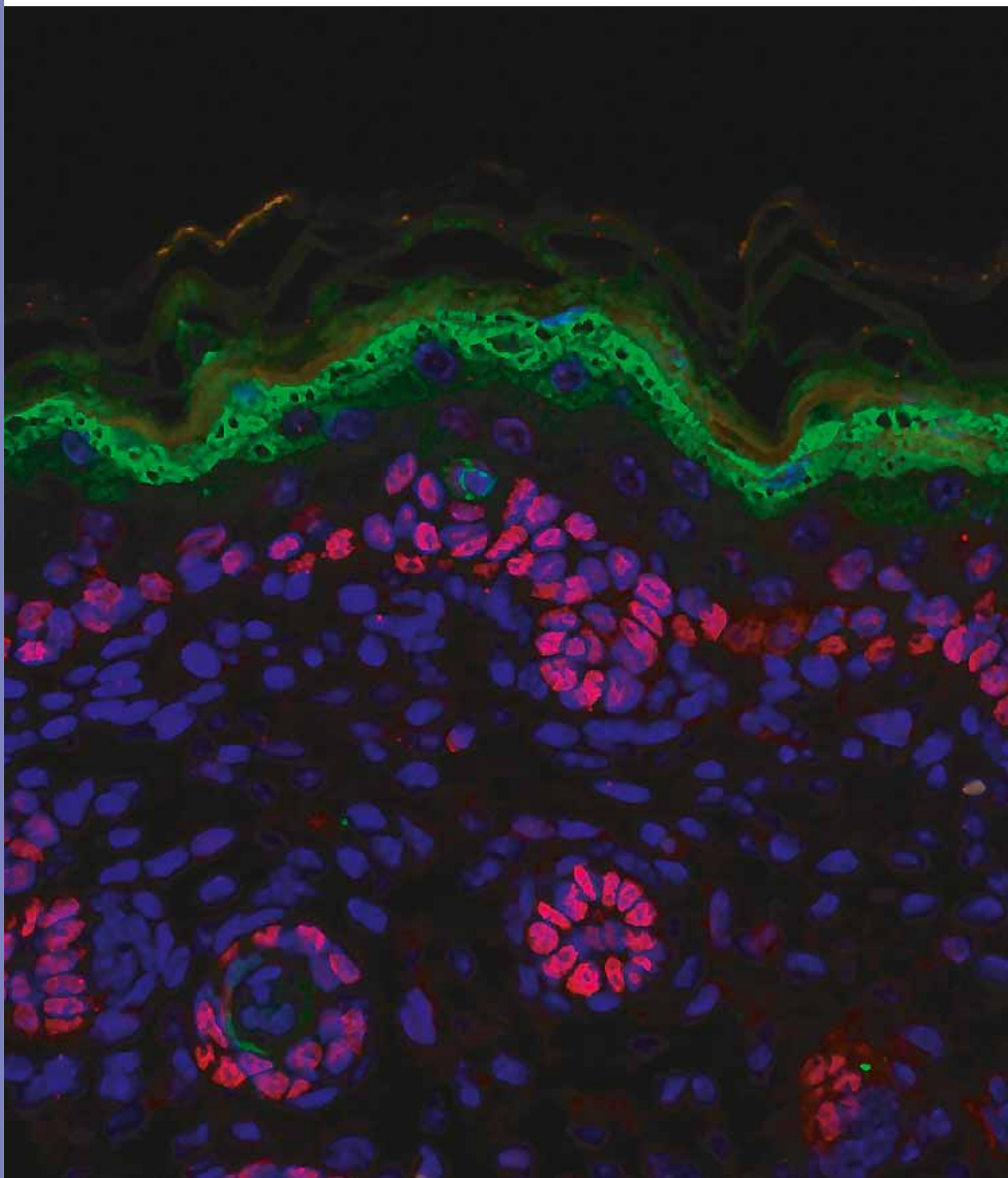
2011
Annual Report

Centre for Cancer Biology



Centre for Cancer Biology

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Cover image

Skin analysis in mice deficient for the *Nedd4-2* gene

Skin sections from wild-type and *Nedd4-2* knockout mice stained for DNA (blue), p63 (red) and the epithelial marker involucrin (green). Adapted from Boase N *et al.* 2011 (Courtesy of Eleanora Candi)

2011
Annual Report

Centre for Cancer Biology

Executive Director's Report

I am pleased to reflect on the progress of SA Pathology's Centre for Cancer Biology since its establishment in 2009.

The concept behind the CCB was to concentrate our best cancer research into a cohesive centre which achieves critical mass and a spectrum of research from basic biology to patient treatment that powers the concept of translational research.

This Annual Report demonstrates the success of the CCB in multiple ways. I want to highlight the success of the CCB research teams in attracting nationally and internationally competitive funding, the success of individual researchers in attracting highly competitive fellowships which bring in their own salaries, and the range of scientific publications in top-tier scientific and medical journals.

SA Pathology spends $8 million a year in support of research. Even in hard economic times we are pleased to do this because it gives substance to our mantra 'Supporting Training and Medical Research' because it makes SA Pathology a stimulating environment for our pathologists to work in, and because it keeps us in the front line of the delivery of pathology services. The researchers bring in over $18 million of competitive research funding, making SA Pathology a major force in medical research in South Australia.

Over the last year SA Pathology has been pleased to work with the developing South Australian Health and Medical Research Institute (SAHMRI) to foster the development of high quality translation of research in South Australia. Again, the CCB has been a major contributor. Whilst the CCB is already too large to become an integral unit of SAHMRI's cancer theme, it will work closely with the Institute to ensure synergies and avoid duplication. We envisage that the CCB will continue to be the powerhouse in basic cancer biology, while translation of the CCB's discoveries to practice will be done in close collaboration with SAHMRI's cancer theme.

As I prepare to move back to my home state of Victoria I look back at what I have been able to achieve in South Australia. The formation and development of the Centre for Cancer Biology will certainly be one of my proudest achievements.

Ruth Salom
Executive Director, SA Pathology

Professor Angel Lopez

Professor Sharad Kumar

Directors' Report

Discovery and translation continue to be the two main pillars of the Centre for Cancer Biology. It is the fundamental discoveries that provide a much needed understanding of the causes of cancer. And it is armed with this understanding that we can begin to imagine and innovate to come up with new breakthroughs in the diagnosis and treatment of cancer.

We are delighted with the progress of the CCB during 2011. Our researchers have made important discoveries that were published in some of the best international scientific journals. Overall 105 scientific papers were published in 2011 with exciting new findings in the areas of metastasis, cancer genetics, leukaemia cell growth, protein structure and function, apoptosis, new blood and lymphatic vessel formation, inflammation and cancer stem cells. Of note, Professor Hamish Scott led an international collaboration in identifying the inherited gene defects which predispose some people to develop acute myeloid leukaemia and myelodysplastic syndrome, a finding of high diagnostic and prognostic value. Attesting to the significance of this work, it was published in the prestigious journal *Nature Genetics*.

Signs that the research of the CCB is making an impact are visible and most pleasing. The work of many of our members is rapidly accumulating a high number of citations by our colleagues, with a highlight being the manuscript in *Nature Cell Biology* by Professor Greg Goodall and Dr Yeesim Khew-Goodall on the molecular regulation of metastases by microRNA's. In the short time since its publication in 2008, this work has now been cited over 700 times and is in the top 15 most quoted papers on cancer in general and number one, most cited paper, in the specific field of microRNA and cancer since 2008.

The translation of our work into better health care has continued with the work of the Hughes laboratory improving on the timing and dosage of drugs for chronic myeloid leukaemia patients, and of the Lopez laboratory in collaboration with CSL Ltd in taking a drug discovered in this Centre all the way to clinical trials in acute myeloid leukaemia patients.

A culture of cancer research excellence is an important thrust of the CCB and one that can be measured by publication quality, citation and public health outcomes. A clear sign that the CCB is on the right path can be seen in the significant number of research grants, fellowships and awards that CCB members obtained during 2011. In the latest round of the highly competitive NHMRC Project Grants scheme, CCB researchers won 16 new grants and three fellowships for Professor Hamish Scott (PRF), Professor Greg Goodall (SRF) and Dr Daniel Thomas (CJ Martin). We were delighted to see not only our senior and established researchers obtaining new grants (Professor Sharad Kumar, two four-year grants), but also our young Fellows succeed, in particular Dr Claudine Bonder and Dr Natasha Harvey who were awarded two grants each.

Further fellowships were obtained by Dr Philip Gregory and Dr Loretta Dorstyn (three-year SA Cancer Collaborative Senior Research Fellowships), and Dr Natasha Harvey (four-year Heart Foundation Career Development Fellowship). Our new recruit from the Beatson Institute, Dr Michael Samuel, was successful in obtaining his first NHMRC Project Grant and a three-year Florey Fellowship. Dr Lisa Ebert, recently arrived from Melbourne, has also won a three-year Florey Fellowship.

We are very proud of the achievements and recognition that our CCB members continue to receive: Assoc Professor Stuart Pitson was awarded the 2011 ASBMB Merck Research Excellence Medal, Dr Quenten Schwarz was awarded the 2011 SA Young Achiever Award by BioInnovation SA, and Dr Phil Gregory a 2011 Tall Poppy Award by the Australian Institute of Policy and Science.

We are well aware that to maintain and foster a culture of research excellence, we need not only the brightest and most dedicated minds, but also the conditions that allow them to flourish. A key ingredient for this to happen is state-of-the-art technological platforms that allow the rapid advance of our research. We are pleased to report that the establishment of the CCB's Cancer Genome Facility, with support of the Australian Cancer Research Foundation, Minister Hill, Medvet and the University of Adelaide is well under way. Experienced bioinformaticians have been recruited, the latest genomics equipment has been purchased, and the refurbishment needed to accommodate the Genome Facility is well advanced. We look forward to it becoming fully operational, now only a matter of a few months away.

Assoc Prof Stuart Pitson is presented with the 2011 ASBMB Merck Millipore Research Excellence Award by Mr Mark Kraschnelfski from Merck Millipore

The Cancer Genome Facility will be invaluable for our research into the causes of cancer and for developing more useful diagnostic and prognostic tools for the management of cancer patients, in effect enabling us to perform better forms of personalized medicine.

The multidisciplinary nature of our research needs several technological platforms and we are pleased with the support of the Super Science program and the CRC for Biomarker Translation that together have allowed the purchase of a 2-photon microscope, an invaluable tool in the visualization of cell migration and new blood vessel formation.

We had the Inaugural CCB Annual General Meeting on 16 June 2011. We are grateful to the Minister for Health and Ageing, the Rt Hon John Hill, for his strong support and presenting prizes. Special thanks to our keynote speaker, Professor Joseph Trapani, Executive Director, Cancer Research, Peter MacCallum Cancer Centre, who highlighted the benefits and long term importance of cancer research and its impact on patients.

This is also an opportunity for both of us to thank Professor Ruth Salom and Professor Heddy Zola. We are grateful to Professor Salom for her continued support of our cancer research and Professor Zola who has greatly facilitated the overall work of the CCB and in particular our own work, helping us to lead the CCB in a largely undistracted way.

This year we have made the special effort of communicating our exciting results and their significance to the community at large through the printed media, radio and television. We are grateful to the media for making this possible. Thanks also to the RAH Research Fund, led by Mark Goldsmith, who are reporting our scientific successes and raising awareness of our cancer research to the South Australian community. The interest and support of the community is growing, as manifested by the increase in donations and bequests. We are very grateful for this material benefit and for the strong encouragement that this represents for the CCB in its pursuit of cancer research excellence and better health outcomes.

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

Dr Michele Grimbaldeston being presented with the Medvet Special Research Initiative Project funds by the Hon John Hill MP and Medvet Chairman, Mr Terry Evans

Dr Philip Gregory being presented with the 2011 SA Young Tall Poppy Award by the Governor for South Australia, His Excellency Rear Admiral Kevin Scarce AC

Dr Quenten Schwarz (2nd from right) was awarded the BioSA 2011 Young Achiever award by BioInnovation SA's Dr Jurgen Michaelis (1st left) and Mr Dennis Mutton (1st right)

5th Barossa Meeting

On the 21–24 November 2011, we hosted the 5th Barossa Meeting on the theme of Cell Signalling and Molecular Medicine. The Meeting covered the most topical aspects of cell signalling, highlighting their versatility and their impact in disease.

We were privileged to count with a stellar group of overseas colleagues: Facundo Batista, Zhijian 'James' Chen, Ivan Dikic, Vishva Dixit, Mukesh Jain, Shigekazu Nagata, Andras Nagy, Tony Pawson, Juan Rivera, Frank Slack, Sarah Spiegel, John Schrader and Henning Walczak, and 18 interstate colleagues whose stature ensured the meeting was fully booked well before the opening day. The Meeting was opened by Professor Don Bursill, SA Chief Scientist, and was conducted in a convivial yet critical atmosphere with vigorous questions and discussions.

A meeting report, published in *EMBO Reports* 13: 178-180, 2012, was kindly written by Roger Daly and Ivan Dikic who remarked that 'the combination of outstanding science, the location and the superb food and wine led to a meeting that was extremely stimulating to both the intellect and the senses'.

As is customary at these meetings, we presented the Clifford Prize for Cancer Research which on this occasion was awarded to Professor Vishva Dixit of Genentech, San Francisco, for his outstanding work on the cellular machinery that controls cell death. The Prize comprises a perpetual trophy, superbly crafted by Nick Mount, and a magnum of Grange Hermitage donated by Penfolds. Professor Dixit now joins a growing list of distinguished Clifford Prize awardees that include John Dick (Toronto), Tony Hunter (San Diego) and Axel Ullrich (Munich).

Three and a half days of intense science were interspersed with gastronomic delights. We enjoyed the wonderful culinary skills of Elli Beer and the oenological knowledge of Michael Hill Smith, backed by some of South Australia's best viticulturists who generously donated their products.

These meetings are ideal for students mixing with world-class scientists, to showcase the excellent science in South Australia and for the development of collaborations with outstanding colleagues. The strong support we continue to receive from the Australian scientific community ensures the Barossa Meetings are firmly entrenched in the Australian scientific calendar.

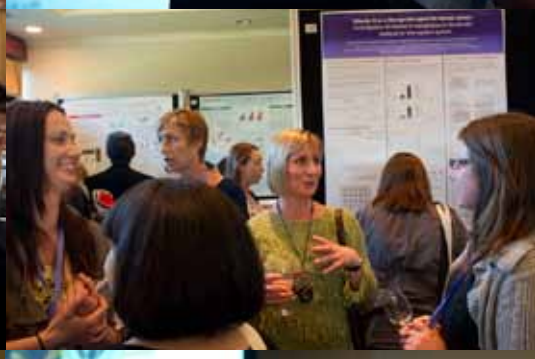
Prof John Schrader, Director of the Biomedical Research Centre, Vancouver unwinds with Professor Heddy Zola Research Director SA Pathology

Hon John Hill MP awarded Prof Vishva Dixit the Clifford Prize for Cancer Research

Hon John Hill MP

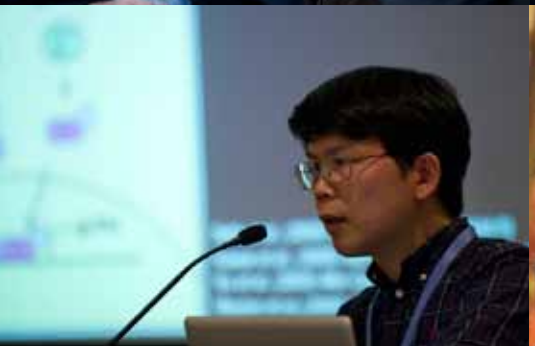


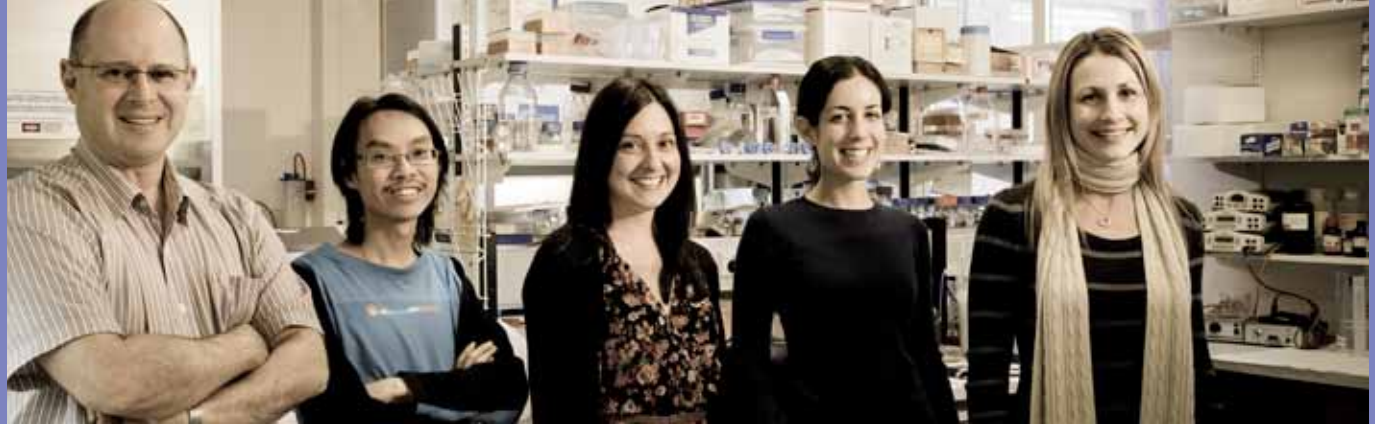








Richard D'Andrea | Chung Kok | Diana Salerno | Teresa Sadras | Sonya Diakiw

Acute Leukaemia Laboratory

Professor Richard D'Andrea PhD

Associate Professor Ian Lewis MBBS PhD FRACP FRCPA

Our major focus is to understand the mechanisms underlying normal blood cell growth and differentiation, and the changes associated with the initiation and progression of myeloid haematological malignancies.

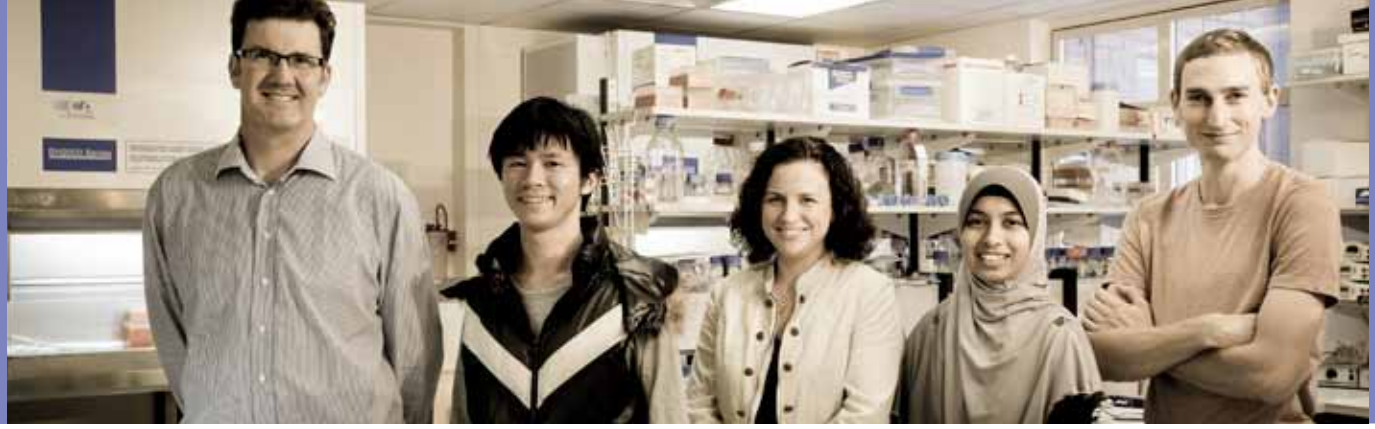
We are using a number of *in vitro* systems and animal models to dissect the pathways that control cell survival, proliferation, differentiation and self-renewal in the myeloid lineage in response to GM-CSF and IL-3. These studies have led to a major focus on the role of β-catenin activation in response to these two cytokines. To study gene function in the myeloid system we are using myeloid cell lines as well as engineered mouse models with targeted gene ablation or conditional gene knock-out. In the last 12 months we have had a significant focus on the role of *TCF4* (Brown *et al*, *Differentiation*, Epub 2011), *KLF5* (Diakiw *et al*, *Leukaemia Research*, Epub 2011) and *GADD45A*. In collaboration with other groups we are also exploring the role of a number of genes in myeloid leukaemia, including the genes for *GATA2* (*Nature Genetics* 43: 1012-7, 2011), *VENTX* (*PNAS* 107: 16946-51, 2010) and *EVI1* (*PNAS* 109: 2168, 2012).

We have performed molecular genetic analysis of patient samples from our large Bio-bank with the aim of defining molecular characteristics associated with response and survival. We are investigating the role in AML of tumour suppressor gene silencing by DNA methylation. In particular our studies have shown that CpG methylation in the regulatory region of two tumour suppressor genes, *GADD45A* and *KLF5*, is associated with a poor patient outcome in selected AML subtypes. Through molecular and genetic cohort studies of patients with MPN we have characterised roles for *DNMT3A* (Rao *et al*, *British J Haematology*, Epub 2011) and *RUNX1* (*British J Haematology* 153: 672-5, 2011) in pathogenesis of this disease. In addition we have focused on a number of somatically acquired molecular changes that we have identified through an exon capture and Next-generation sequencing approach using Polycythemia vera patient samples.

Finally, we have reviewed the latest information on the mobilisation of haemopoietic stem cells for transplantation, with the focus on what is the current best practice and how understanding of the bone marrow stem cell niche provides new insights into optimising mobilisation regimens (*Pathology* 43: 547-65, 2011).

Outcomes for the Community

A number of the studies described impact directly on classification and treatment of AML patients where selection of treatment options is critical. For example, the *GADD45A* methylation mark defines a group of elderly patients for which first-line treatment with demethylating agent may be considered. We are now collaborating to explore this further in clinical trial cohorts receiving de-methylation agent therapy. Our MPN studies suggest a role of c-Met receptor activation in MPN pathogenesis and the existence of a number of c-Met inhibitors that are in clinical use means that the approach of targeting these pathways in MPN can be rapidly tested and translated to clinical trial.



Ian Lewis | Nick Ka Leung Li | Anna Brown | Nur Hezrin Shahrin | Grant Engler

Key discoveries 2011

Roles for β-catenin in GM-CSF and interleukin-3 (IL-3) receptor signalling

GM-CSF promotes growth, survival, differentiation and activation of normal myeloid cells. The GM-CSF receptor (GMR) activates multiple pathways, however the mechanism by which these modulate the differentiation of myeloid progenitors is unclear. We have utilised activated mutants of the GM-CSF receptor with non-overlapping signalling (*Blood* 115: 3346-3353, 2010) to explore the signals promoting granulocyte and macrophage differentiation. Our analysis of a mutant that promotes monocyte differentiation at the expense of granulocyte differentiation (see Brown *et al*, *Differentiation*, Epub 2011) revealed that stabilisation of β-catenin is regulated through GM-CSF receptor via a specific pathway, and this acts in concert with TCF4 to modulate the activity of key monocyte genes.

Aberrant stabilisation of β-catenin is observed in AML and is associated with a poor prognosis and overall survival. We speculated that increased levels of β-catenin in AML cells may be linked to high levels of IL-3 receptor alpha subunit (CD123) which is up-regulated on AML LSC. Our studies have shown that IL-3 can modulate β-catenin activity in murine myeloid progenitor cell line models and β-catenin is required for IL-3 induced growth and survival. In addition, we have found that increased levels of β-catenin activity can increase the sensitivity of cells to IL-3, and we propose that this may contribute to the leukaemic transformation by providing an aberrant survival signal.

Novel tumour suppressor genes which mark poor prognosis in AML

In 2009, (*Leukaemia* 23: 729-738, 2009), we identified the stress induced tumour suppressor gene *Growth Arrest and DNA Damage inducible 45A* (*GADD45A*) is a down-regulated gene in AML, and we have shown that *GADD45A* displays promoter hyper-methylation associated with gene silencing in 42% of AML patients. This hypermethylation is an independent predictor of poor survival in AML overall, and in normal karyotype and elderly (>60 years) patient subgroups. Treatment of AML cell lines and patient samples with demethylating agent results in demethylation of the GADD45A promoter, increased GADD45A expression and increased sensitivity to daunorubicin suggesting that some AML patients may benefit from treatment with demethylating agent.

The *KLF5* gene is also down-regulated and methylated gene in AML (Diakiw *et al*, *Leukaemia Research*, Epub 2011) and recently we have shown that a single nucleotide polymorphism (SNP) in the promoter of KLF5 also confers reduced expression in AML. Our analysis of patient samples has shown that 6% of AML patients display this SNP genotype together with CpG methylation of KLF5, and this combined molecular signature is an independent predictor of poor outcome. This is an important example of how inherited and acquired changes at tumour suppressor loci combine to affect the outcome of cancer patients.

Identifying new targets in myeloproliferative neoplasms

Whilst JAK2 mutation has been demonstrated to be a feature of Ph-MPN, recent studies indicate that additional, JAK2-independent events contribute to the MPN phenotype, and treatment with JAK2 inhibitors has shown little evidence of disease-modifying effect. Thus it is important now to identify pathways that can be targeted in conjunction with JAK2 to develop effective therapy that may improve patient quality of life and survival rates.

Using an exon-capture and a Next-generation sequencing approach we have isolated a somatic cancer-associated mutation in c-Met in chronic phase MPN samples. As other evidence is accumulating to support a role for Hepatocyte Growth Factor (ligand for c-Met), via several mechanisms in clonal expansion in MPN, this suggests that targeting this receptor tyrosine kinase in MPN may be beneficial. To test this we are targeting c-Met signalling in a mouse model of PV and using the established Ba/F3 cell line model of JAK2V617F signalling to characterise the c-Met somatic mutation identified in MPN patient samples.

Mark Guthridge | Daniel Thomas | Nhan Truong

Cell Growth and Differentiation Laboratory

Dr Mark Guthridge PhD

Cells in the body are able to accomplish an impressive range of functions within their lifetime. Underlying this diversity in cellular functions are a number of fundamental responses that include cell survival, cell proliferation (growth) and cell differentiation (commitment to a more mature cell identity).

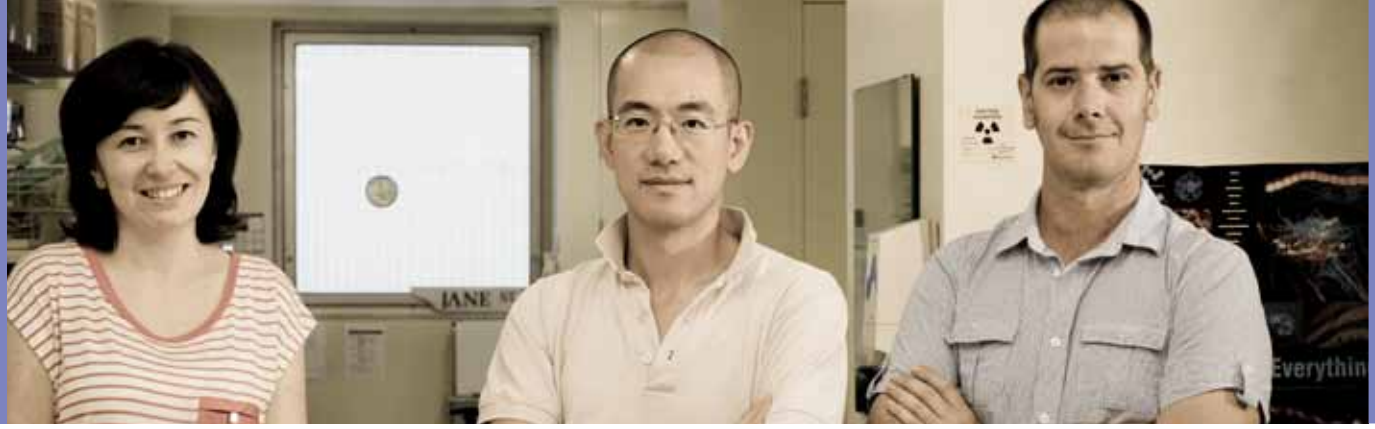
Growth factors and cytokines are central regulators of these cellular responses through their ability to bind and activate specific cell surface receptors.

The overall focus of the Cell Growth and Differentiation Laboratory work lies in understanding the fundamental molecular mechanisms by which growth factors and cytokines regulate specific cell functions and what goes wrong in the regulation of these mechanisms in pathologies such as inflammatory disorders, developmental disorders and cancer.

We have identified a new 'switch mechanism' by which growth factors are able to control cell survival, proliferation and differentiation. This mechanism involves site-specific serine phosphorylation of cytokine and growth factor receptors, such as the Granulocyte Macrophage Colony Stimulating Factor receptor (GM-CSF receptor) and Fibrobast Growth Factor Receptor. These site-specific serine phosphorylation events allow the activated receptors to couple to specific intracellular signalling pathways and control diverse cellular responses.

Cancer is a disease in which the normal pathways controlling cell survival and proliferation become corrupted. We have identified signalling components within normal cells that are highly susceptible to 'short-circuits' that lead to deregulation of cell survival and proliferation resulting in the development of cancer. By identifying and characterizing these short-circuits, we hope to find new therapeutic approaches for the selective targeting of cancer cells.

Our work has identified specific serine residues in growth factor and cytokine receptors that selectively and independently promote cell survival. Importantly, these serine residues embedded in the cytoplasmic tails of cell surface receptors are subject to deregulation in cancers such as acute myeloid leukaemia (AML) and glioma. Global analysis of these phosphoserine regulated cell survival programs has identified a number of potential therapeutic targets including serine-threonine kinases and lipid kinases (eg phosphatidyl inositol 3-OH kinase) as well as stomal factors (eg osteopontin). Importantly, several of these potential therapeutic targets also represent prognostic factors that are associated with poor overall patient survival. Thus, our work now provides a framework for the pre-clinical and clinical validation of these targets in diseases such as AML.



Emma Barry | Yang Kong | Jason Powell

Key discoveries 2011

Phosphatidyl inositol 3-kinase (PI3K) is a dual specificity kinase with the ability to phosphorylate both lipids (phosphatidyl inositols) and proteins. PI3K is a pivotal regulator of both cell survival and proliferation and constitutive activation of the PI3K pathway represents one of the most common oncogenic events in cancer. By comparing the cell survival pathways in normal non-transformed cells to those in leukaemic cells, we have identified a 'PI3K cell survival network' that is deregulated in human AML.

In collaboration with Dr Andew Wei (ACBD and Alfred hospital) and Dr Paul Ekert (Walter and Eliza Hall Institute), biochemical and functional mapping of this network has led to the identification of key targets that govern cell survival in AML cells. Importantly, blockade of key components of this survival network leads to the induction of apoptosis (programmed cell death) in AML cells but not normal bone marrow cells. We are developing strategies to target these deregulated cell survival networks in an effort to find new therapeutic approaches for the treatment of AML.

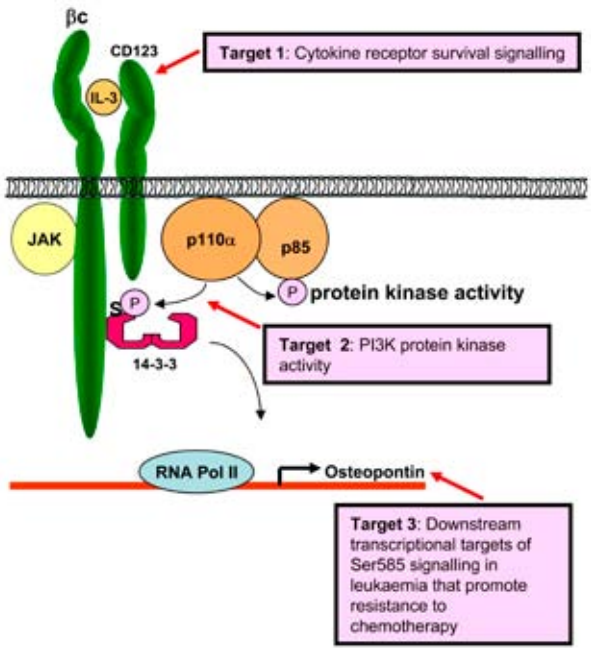


Diagram sumarizing novel targets for therapy in acute myeloid leukaemia studied in the Cell Growth and Differentiation Laboratory

Outcomes for the Community

Leukemia remains a major cause of cancer deaths. In adults, despite 30 years of substantial progress in conventional chemotherapy and bone marrow (BM) transplantation, overall survival (OS) remains dismal. For example, the five year OS for acute myeloid leukemia (AML) patients is 20-30%. If long-term durable cures are to be obtained for the treatment of leukemia, new therapeutic approaches that allow the selective targeting of leukemic cells will be required. Our work has identified key kinase-driven pathways that underpin leukemic transformation and paves the way toward the pre-clinical and clinical development of new approaches that seek to improve outcomes for AML patients.

Yeesim Khew-Goodall | Lesley Crocker | Xiaochun Li | James Paltridge

Cell Signalling Laboratory

Dr Yeesim Khew-Goodall PhD

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

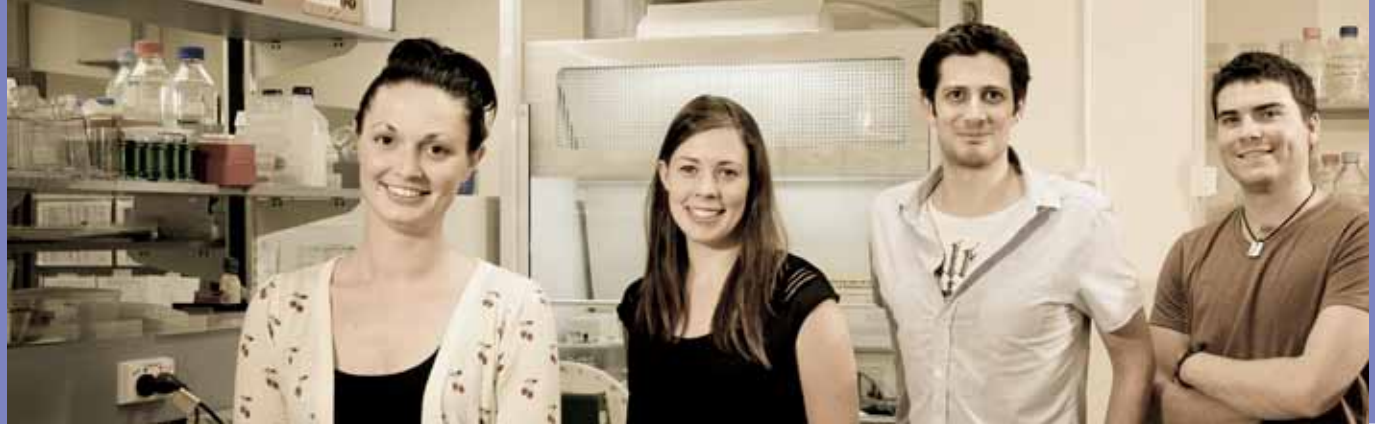
Our disease model is breast cancer metastasis and our long term focus is to understand what turns a benign cancer cell which remains local and treatable into a malignant cell capable of spreading to multiple organs. In solid tumours, which make up ~80% of human cancers, metastasis is the main cause of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

An ongoing interest of the Cell Signalling Laboratory is the interactions of the cancer cell with its microenvironment. Cells secrete factors that can act upon themselves or on other cells for normal maintenance or homeostasis. Cancer cells, through mutations, can have an altered composition of secreted factors which can act to alter their immediate microenvironment, turning it from one that suppresses cancer progression to one that supports metastasis and resistance to chemotherapy. Recent studies have shown that the cancer 'secretome' can also prepare a metastatic niche in secondary organs to facilitate their ability to embed in those organs. To date, however, little is known about the mechanism(s) by which the cellular secretome is regulated or how this regulation might be altered in cancer cells. We have shown that the protein tyrosine phosphatase Pez, a protein which we have studied for many years, regulates TGFβ secretion. In some cells, increased Pez expression resulting in TGFβ secretion can cause them to undergo an epithelial-mesenchymal transition, an early step deemed necessary for the dissemination of breast cancer cells. Recent highlights include elucidation of new functions for the protein tyrosine phosphatase Pez, whereby its expression in breast cancer cells, in addition to its cell autonomous actions, may lead to alterations in the local microenvironment to promote or retard metastasis.

A new area which we have begun investigating is the role of Pez in regulating glucose uptake and insulin signalling in adipocytes. Adipose tissue is the richest source of Pez expression and its expression in this tissue is regulated upon differentiation. New data from the laboratory suggest that it may play a role in modulating glucose uptake and insulin resistance.

MicroRNAs are relatively newly discovered small non-coding RNAs. Recognition of their roles in regulating cellular functions have increased enormously in the last few years. Using a cell culture model of epithelial-mesenchymal transition developed in our laboratory, in a collaboration with the Goodall Lab, we previously discovered a family of microRNAS (the miR-200 family) that are crucial inhibitors of epithelial cell motility and invasiveness, thus making them crucial regulators of metastasis. Bolstered by our success with this previous discovery, the Cell Signalling Laboratory has embarked on a search for other microRNAs whose dysregulation may drive breast cancer metastasis. To this end, we have also identified microRNAs that may be altered during cancer progression to bring forth changes to the microenvironment to facilitate metastasis. In ongoing collaborations with the Goodall (Gene Regulation) and Anderson (Peter MacCallum Research Institute, Melbourne) Laboratories, we have established mouse models to assess the roles of various proteins and microRNAs in metastasis.

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



Ana Lonic | Freya Gehling | Sam Dyer | Nick Hauschild

Key discoveries 2011

1 We identified novel functions for the protein tyrosine phosphatase Pez that would help us understand the normal physiological functions of this protein. Importantly, these findings could be a key to understanding how mutations in this protein that have been identified in breast and colon cancers may facilitate metastasis or oncogenesis.

2 We have identified a number of microRNAs whose expression are altered upon transdifferentiaion of fibroblasts to myofibroblasts, a process that has been shown to occur in the stroma of breast cancers and thought to play a role in enhancing metastasis and chemoresistance. These microRNAs therefore have potential roles in altering the stroma of breast cancers to promote cancer progression.

3 A new area which we have begun investigating is the role of Pez in regulating glucose uptake and insulin signalling in adipocytes. New data from the laboratory suggest that it may play a role in modulating glucose uptake and insulin resistance.

Outcomes for the Community

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

Anna Sapa | Emma Barry | Angel Lopez | Rebecca Krake | Mara Dottore | Hayley Ramshaw

Cytokine Receptor Laboratory

Professor Angel Lopez MBBS PhD FRCPA

Cancer arises as the result of dysregulation of certain signalling pathways. At the apex of many of these are cytokine receptors which control the extent and the quality of cellular responses. Deciphering the structural and dynamic requirements of cytokine receptors and their downstream signalling apparatus will allow us to understand and ultimately control many types of cancer as well as certain inflammatory diseases.

Our research focus is the understanding of the molecular basis of cancer and chronic inflammation and the interplay between these conditions. The cytokines interleukin-3 (IL-3) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are key regulators of hemopoietic cell growth and function as well as being important contributors to chronic inflammation. We aim to define their mechanism of action and to exploit our breakthroughs to generate new tools for the better management of cancer.

A key regulator of multiple hemopoietic lineages is IL-3 and in some diseases such as acute myeloid leukaemia or AML, the receptor for IL-3 is upregulated. We are seeking to understand the biological significance of this phenomenon and how it contributes to AML development and progression in collaboration with Associate Professor Ekert of the WEHI in Melbourne and Associate Professor Richard D'Andrea of the CCB. We are also targeting the IL-3 receptor with a monoclonal antibody we originally developed as a means to attack stem/progenitor cells in human AML and chronic myeloid leukaemia, both approaches in collaboration with CSL Ltd and with Professor Tim Hughes of the Melissa White Memorial Laboratory in the CCB.

An important aspect of our studies is the determination of the 3-dimensional structures of GM-CSF and IL-3 bound to their cognate receptors, a long term aim supported by our NHMRC Program Grant with Professor Michael Parker of St Vincent's Institute of Medical Research, Melbourne. Following our determination of the structure of GM-CSF bound to its receptor that revealed a new mechanism of cytokine receptor activation, we are now generating IL-3 receptor complexes to ascertain their structure, the intermediate stages in their full assembly, and the functional role that each complex plays in generating the full gamut of biological activities.

Downstream of cytokine receptors we are analysing the signosome to identify the main participants in the cytokine receptor signalling apparatus and their role in disease. In collaboration with Associate Professor Paul Ekert from WEHI, we have identified an IKK-mediated pathway (see below) and in collaboration with Associate Professor Stuart Pitson and Dr Joanna Woodcock from the CCB, we documented the significance of the 14-3-3 family of adaptor proteins. In collaboration with Dr Tetyana Shandala and Dr Doug Brooks, we have also characterized the role of 14-3-3 in innate immunity (*Journal of Cell Sciences* 124: 2165-74, 2011).

One of the important aspects of cell signalling is that signalling nodes do not exist in isolation, and may not necessarily be specific to a biological system. As such we have explored, in collaboration with Dr Quenten Schwarz of the Neurovascular Research Laboratory, CCB, the role of the 14-3-3 signosome in neuronal development. We found the 14-3-3 signalosome that we have characterized to be an important node in GM-CSF signalling, plays an essential role in the migration and synapsis formation of hippocampal neurones. Significantly, the deletion of 14-3-3 zeta leads to anatomical, functional and behavioural defects in mice analogous to human schizophrenia (*Molecular Psychiatry* 17: 451-466, 2012). The analysis of highly conserved signalling nodes across diverse biological systems has the power to reveal unsuspected non-redundant roles in disease.

Sue Heatley | Tim Hercus | Barbara McClure | Nichole Chrislie | Natasha Pyne | Frank Stomski | absent: Phillip Nguyen and Karthik Venkataraman

Key discoveries 2011

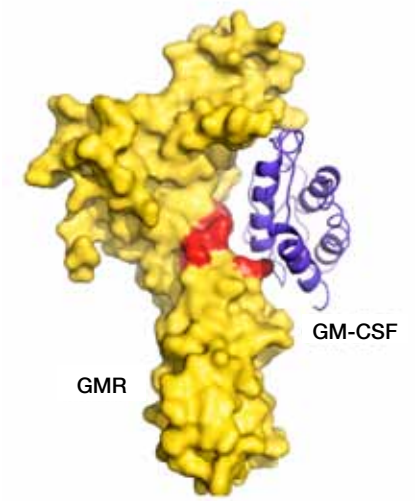
A new signalling pathway activated by the IL-3 cytokine receptor

In collaboration with Associate Professor Paul Ekert, we found that the IL-3 receptor triggers a new signalling pathway that mediates cell survival in hemopoietic cells. This pathway involves the phosphorylation of a pro-apoptotic member of the Bcl-2 family PUMA on serine 10 which targets this protein for proteasomal degradation. We identified IKK1/IKK2/Nemo as the kinase complex that interacts with and phosphorylates PUMA, for the first time revealing the involvement of this kinase complex in IL-3-mediated survival functions. This novel pathway controlling the balance of hemopoietic cell survival vs death is likely to play a role in hematological malignancies.

Monoclonal antibody (MAb) 7G3 against the IL-3 receptor (CD123) mediates killing of human leukaemic stem cells by a natural killer cell mechanism

We originally generated the MAb 7G3 which recognizes the IL-3 receptor (CD123) and blocks the binding of IL-3. We are collaborating with CSL who are developing this antibody as a possible therapy in acute myeloid leukaemia based on its ability to selectively recognize CD123 on leukaemic stem cells and to block the stimulatory effect of IL-3.

In collaboration with CSL and Prof Richard Lock of the Lowy Institute, NSW, we have studied how human acute myeloid leukaemia stem cells can be better targeted by MAb 7G3 that has been engineered by CSL for optimal binding to the Fc receptor of human NK cells. The engineered antibody, CSL362, is an efficient mediator of killing by human NK cells, in a short time period and at low effector to target cell ratios. Importantly, MAb CSL362 mediated antibody-dependent cell cytotoxicity (ADCC) of leukaemic stem cells which are resistant to the original MAb 7G3. This optimized ADCC mechanism is likely to be very important for the eradication of CD123 positive leukaemic stem cells in future clinical trials.



Molecular model of the GM-CSF receptor binary complex showing GM-CSF (in blue) bound to the extracellular portion of GMRα (in yellow), the GM-CSF-specific subunit of the GM-CSF receptor complex.

This model was generated from X-ray crystallographic data using crystals of the soluble GM-CSF:sGMRα binary complex. The surface of GMRα is shown in yellow with GM-CSF contact residues in red, while GM-CSF is shown as a blue ribbon.

Outcomes for the Community

Many cancers, particularly some types of leukaemia are difficult to treat. Many patients show promising responses after initial treatment with chemotherapy only for the cancer to come back. Understanding the causes of relapse in leukaemia is essential for the development of more effective forms of therapy and ideally a cure. At least in leukaemia, there seems to be a mother cancer cell (Leukaemia stem cell) that gives rise to many daughter cancer cells and which is difficult to eradicate. Our aim is to test whether we can specifically target and kill the leukaemia stem cell with our MAb 7G3 and its modified forms to prevent patients from relapsing.

Andrew Bert | Natasha Kolesnikoff | Phil Gregory | Joanne Attema | Cameron Braken | Suraya Roslan | Josephine Wright | Greg Goodall

Gene Regulation Laboratory

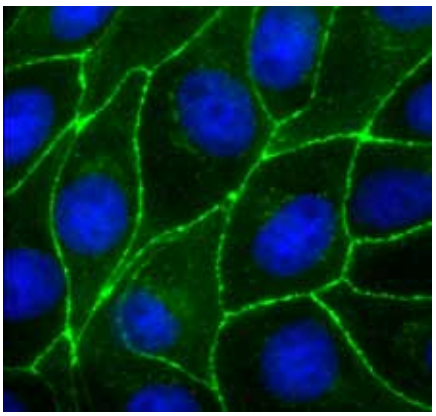
Professor Greg Goodall PhD

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

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

EMT is driven by coordinated changes in the expression of hundreds of structural and regulatory proteins. These changes are determined by integrated gene expression networks that themselves involve numerous components. We have identified microRNAs that play a central role in controlling and coordinating the regulatory networks that underlie EMT in cancer cells. Our current work focuses on developing our understanding how microRNAs control EMT and examining their consequences for cancer progression. The project areas include:

- investigating the mechanisms that regulate expression of microRNAs in EMT
- identifying authentic targets of microRNAs involved in EMT
- identifying coordinated effects of microRNAs on EMT pathways, in particular, control of the actin cytoskeleton and cell motility by miR-200 and coregulated microRNAs
- discovering other EMT pathways controlled by microRNAs
- identifying microRNAs controlling the maintenance and properties of cancer stem cells



Stably transfected mesenchymal MDCK cells that lack ZO-1 expression were treated with a chemical inhibitor of the TGF-β signaling pathway, which causes a mesenchymal-to-epithelial transition of the cells and re-expression of ZO-1 (green) on the plasma membrane. The cell nuclei are stained blue.

Eddie Yat Yuen Lim | Victoria Arnet | Rosemary Sladic | Daniel Thomson | Corine Ting | Matthew Anderson | Narrelle Mancini | Anna Tsykin | Kimi Honma

Key discoveries 2011

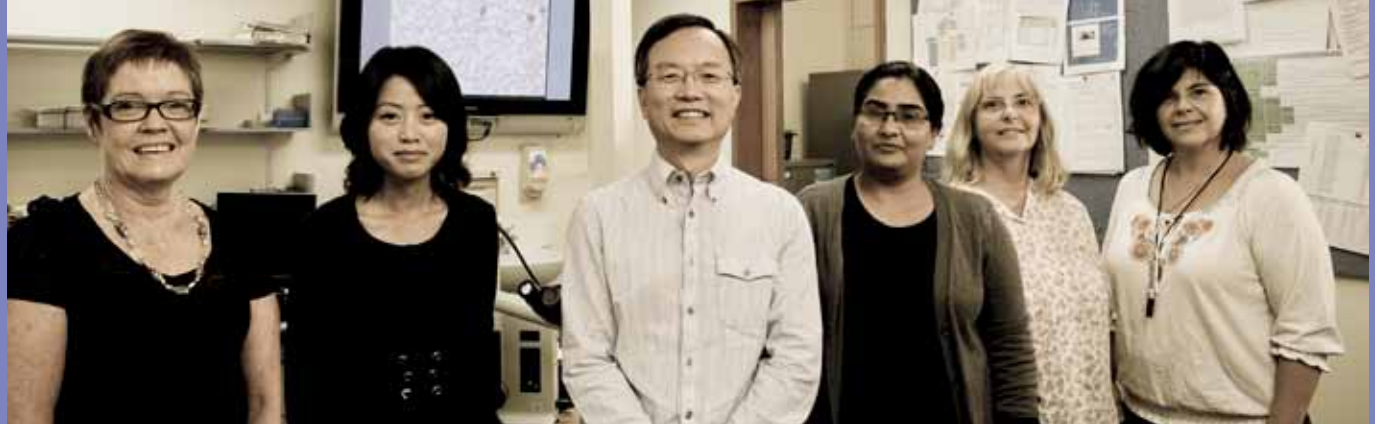
The Notch ligand Jagged2 promotes lung adenocarcinoma metastasis through a miR-200–dependent pathway in mice. EMT can be promoted through cell-cell contacts mediated by families of transmembrane receptors and ligands expressed on adjacent cells. A notable example of this is the Notch pathway intiated by interactions between the Notch receptors on the responding cell and cell surface ligands, such as Jagged1 and Jagged2, on adjacent cells. Jagged1-induced Notch activation promotes EMT of breast epithelial cells through Snail2, but the mechanism by which Notch increases Snail2 expression has not been elucidated. In collaboration with Don Anson and Jonathan Kurie at the MD Anderson Cancer Center, using a mouse model in which human lung adenocarcinoma calls are engrafted into mice, we have found that tumour cell EMT and metastasis are dependent upon Jagged2, which promotes EMT by decreasing miR-200 expression. Jagged2 promotes metastasis by increasing the expression of GATA-binding factors, which suppress expression of the miRNA-200 family of microRNAs that target the transcriptional repressors that drive EMT and thereby induced EMT. Reciprocally, miR-200 inhibited expression of Gata3, which reversed EMT and abrogated metastasis, suggesting that Gata3 and miR-200 are mutually inhibitory and have opposing effects on EMT and metastasis. (*J Clin Invest* 121: 1373-1385, 2011)

Genome-wide identification of targets of the miR-200 family. In vertebrates, the interaction between microRNAs and their targets usually involves only a limited extent of base pairing, typically just 6-8 nucleotides at the 5' end of the miRNA, which may be augmented by some base pairing of a few additional nucleotides elsewhere in the microRNA. This allows each miRNA to target many (hundreds of) different mRNAs and makes microRNAs ideally suited to function in complex regulatory networks, but predicting the targets of the microRNAs on the basis of sequence complementarity is highly unreliable. MicroRNAs are now relatively easy to discover, and to measure once they have been identified, and there are now efficient methods to both artificially introduce microRNAs into cells and to individually inhibit their functions. However, reliably identifying the targets of miRNAs has been a difficult and laborious process and the bottleneck in the pathway of discovering the biological functions of miRNAs is in identifying their molecular targets, the majority of which remain unknown. We have implemented a high-throughput method for function-based identification of authentic microRNA targets and applied it to miR-200 in breast cancer cells. This has revealled many individual targets and whole networks that are targetted, that control crucial processes in metastasis. This is the first time such an investigation has been undertaken with any of the EMT and cancer-related microRNAs.

Responses of Estrogen Receptor-positive Breast Carcinoma Cells to retinoid involves induction of the miR-21 "oncomiR". All-trans-retinoic acid (ATRA) and its derivatives (the retinoids) are promising agents for the prevention or treatment of some breast cancers. Together with our collaborators at the Mario Negri Institute for Pharmalogical Research in Milan, Italy, we examined whether microRNAs may be involved in the responses of breast cancer cells to retinoids. We found that the effects of all-trans-retinoic acid (ATRA), which suppresses the proliferation of estrogen receptor-positive (ER+) breast carcinoma cells, such as MCF-7, but not estrogen receptor-negative cells, such as MDA-MB-231, involves the pro-oncogenic microRNA, miR-21. This microRNA was selectively induced by ATRA in ER+ cells and counteracts the anti-proliferative action of ATRA, but has the potentially beneficial effect of reducing cell motility. We were able to identify three novel direct mRNA targets miR-21: the pro-inflammatory cytokine IL1B, the adhesion molecule ICAM-1, and PLAT, the tissue-type plasminogen activator. The role of miR-21 and the three novel targets has implications for the therapeutic use of these agents (*J Biol Chem* 286: 4027-42, 2011).

Outcomes for the Community

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



Pam Dyson | Mengjun Zhu | Bik To | Smita Hiwase | Susan Rogers | Samantha Parletta

Haematology Clinical Research Unit

Professor Luen Bik To MBBS MD MRCP FRCPA FRACP

Associate Professor Ian Lewis MBBS PhD FRCPA FRACP

The Haematology Clinical Research Unit has a core focus of improving the treatment of patients with malignant and non-malignant diseases of the blood.

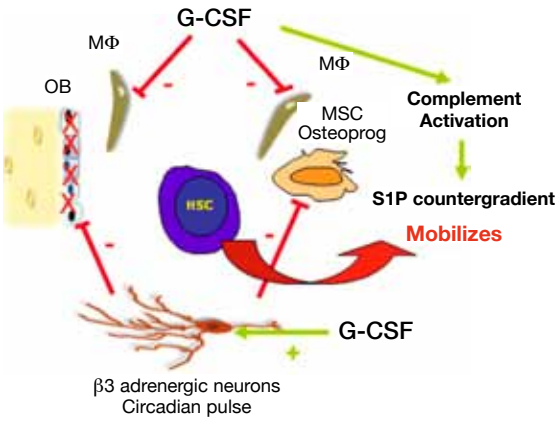
The Clinical Research Unit focuses on disease and treatment directed research. It encompasses several research teams in the Royal Adelaide Hospital Department of Haematology, including the Therapeutic Product Facility, Haemostasis Laboratory and the Clinical Trials Unit.

Research endeavours focus on clinical trial participation which allows patients access to novel treatments, as well as provision of infrastructure to facilitate fundamental research and clinical trial activity. 2011 has seen a lot of progress in the area of stem cell mobilization, acute myeloid leukaemia, lymphoma and bleeding disorders, some a result of international collaborations.

Two particularly important grant funding successes will enable the establishment of the South Australian Blood Cancer Tumour Bank and a negative pressure clean room facility. Both are vital for building research infrastructure to enable further development of campus strength in leukaemia and myeloma research.

The objectives of the South Australian Blood Cancer Tumour Bank are to:

- create a Statewide Blood Cancer Tissue Bank
- establish a unified collection and consistent process across multiple sites
- maintain a centralised database
- provide a central standardised processing facility.



Schematic representation of interactions in response to G-CSF β-adrenergic neuron activation by G-CSF inhibits SDF-1 production by MSCs, osteoprogenitors, and osteoblasts and inhibits bone formation by osteoblasts (solid red bars). Stimulation of osteomacs and CD169+ macrophages by G-CSF (solid red bars) suppresses their supportive function for MSCs and osteoblasts. Consequently, expression of SDF-1, Kit ligand, and VCAM-1 by osteoprogenitors and MSCs is down-regulated. Complement cascade is activated by G-CSF, resulting in S1P release into the blood.

Peter Harrison | Julia Hamilton | Bronwen Cox | Christine Hoare | Richard Bright | Elizabeth Duncan | Ian Lewis

Key discoveries 2011

1 Peripheral blood stem cell mobilisation, an important component in the treatment of patients with haematological malignancies, has always been hampered by the inability to collect stem cells in some patients ('poor mobilisers'). The addition of Plerixafor, a chemokine which targets the haemopoietic stem cell niche, to the therapeutic armamentarium, has led to a new approach in mobilisation in these patients (Herbert *et al, Int Med J* 2011, To *et al, Pathology* 2011, To *et al*, *Blood* 2011, Beligasawatte *et al* 2011).

2 Peripheral T cell lymphoma (PTCL), a subtype of Non- Hodgkins Lymphoma, is particularly resistant to conventional chemotherapy. Romidepsin is a histone deacetylase inhibitor, a novel class of anti-cancer agents being evaluated in this disease. Patients with PTCL from the Royal Adelaide Hospital participated in a trial of this agent and results demonstrate this agent has efficacy in this disease and may be a significant therapeutic advance (Piekarz *et al* 2011).

3 Understanding the molecular heterogeneity of acute myeloid leukaemia is leading to the identification of new targets for therapy in a disease where current treatments are unsatisfactory. The identification of hypermethylation of KLF5 in some patients may lead to the use of hypomethylating agents as treatment (Diakiw *et al, Leukemia Research*, e-pub Oct 2011). Mutation of the FLT3 gene, a well recognised adverse prognostic factor, is leading to the use of FLT3 inhibitors in clinical trials (Levis *et al* 2011).

Outcomes for the Community

The clinical research unit has a core focus of improving the treatment of patients with malignant and non-malignant diseases of the blood. This is achieved by a core interest in fundamental research, involvement in clinical trials utilising novel agents and provision of infrastructure to allow these activities to expand. Specific outcomes for 2011 include improvement in the understanding of treatment of poor mobilisers, plasma cell leukaemia, AML, T cell lymphoma and von Willebrand's disease. Research infrastructure has been expanded by the establishment of the SABCTB to benefit future research in blood cancers such as leukaemia, myeloma, myelodysplasia, as well as the establishment of the new clean room facility to facilitate development cell based therapy for diseases such as leukemia and melanoma.

Nicholas Eyre | Karla Helbig | Guillaume Fiches | Michael Beard

Hepatitis C Virus Research Laboratory

Associate Professor Michael R Beard PhD

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

Current therapies do not work in all individuals and there is no vaccine. HCV specifically infects liver cells (hepatocytes) and the main focus of our laboratory is to define the host response to infection with HCV using both laboratory based models and clinical samples. We also have a focus on developing models to study the HCV-host interaction in living cells. Through this approach we hope to add to our understanding of how HCV causes disease and identify novel therapeutic targets.

Infection of hepatocytes with HCV results in activation of the early non-specific innate immune response that attempts to limit viral replication and spread. However, viruses and HCV is no exception, have developed mechanisms to counteract this early response. Central to activation of this anti-viral innate response is the production of interferon (IFN), a cytokine that induces the expression of hundreds of genes (termed interferon stimulated genes: ISGs) many of which have antiviral properties although the function of many of these genes remain unknown. Using microarray studies of HCV infected liver biopsy material and cultured cells stimulated with IFN we have identified hundreds of ISGs, many of which may have unidentified antiviral and immunomodulatory activity. Our initial work has focused on the ISGs Viperin and the IFITM family. We have shown that viperin and IFITM1 have novel anti-HCV activity through their interaction with both HCV encoded proteins and host proteins to block HCV replication and HCV entry respectively. Through collaborations with Professor Tony Cunningham, Westmead Millennium Institute, and Professor Tony Kelleher, Kirby Institute, Sydney, we have also shown that these ISGs have anti-viral activity against the human immunodeficiency virus (HIV). The benefits of this research include the potential for novel therapeutic strategies to help combat chronic viral infections and a better understanding of the host response to viral infection.

An important focus of our work is understanding the dynamics of viral replication at the cellular level and to this end we have developed a live cell imaging approach to study HCV replication in real time. Our collaborative work continues with Dr Stuart Turville at the Kirby Institute and we are now at the point of being able to visualise HCV replication in living cells. This is achieved by using a small (6-12 amino acid) genetically encoded tetracysteine peptide sequence that can be introduced into viral proteins and labelled by fluorescent dyes.

Furthermore, we can also visualise HCV RNA and are now in a unique position to investigate the interaction between HCV proteins, HCV RNA and host factors in living cells. Until now visualisation of host viral interactions has been limited to static images that provides information at a defined point in time. Trafficking viral replication in living cells has revealed that HCV replication is a very dynamic process and far more complex than what is revealed in static fixed images of virally infected cells. This work has the ability to change the way we think about virus replication and its interaction with host cell proteins.

A spin off from our microarray work has been the observation that the transcription factor STAT-3 is significantly upregulated in HCV infected cells. STAT3 is activated by a wide variety of cytokines and exerts a diverse range of biological responses. It is significantly activated in many cancers including hepatocellular carcinoma (HCC). We have established that STAT3 is activated (tyrosine 705) in the presence of replicating HCV. Blocking STAT3 activation with the specific STAT3 inhibitors AG490 and STA-21 decreased HCV replication while siRNA knockdown of STAT3 also reduced HCV replication by approximately 50%. This suggests that HCV induces activation of STAT3 to benefit viral replication through an as yet unknown mechanism. However the constitutative activation of this transcription factor that is know to play a role in the development of cancer may have implications for the development of liver cancer that sometimes develops in persons chronically infected with HCV. Pharmacological intervention of STAT-3 action may show promise in the fight against HCV related liver cancer.

Amanda Aloia | Erin McCartney | Sumudu Narayana | Kate Muller | Kylie Van der Hoek | Edmund Tse

Key discoveries 2011

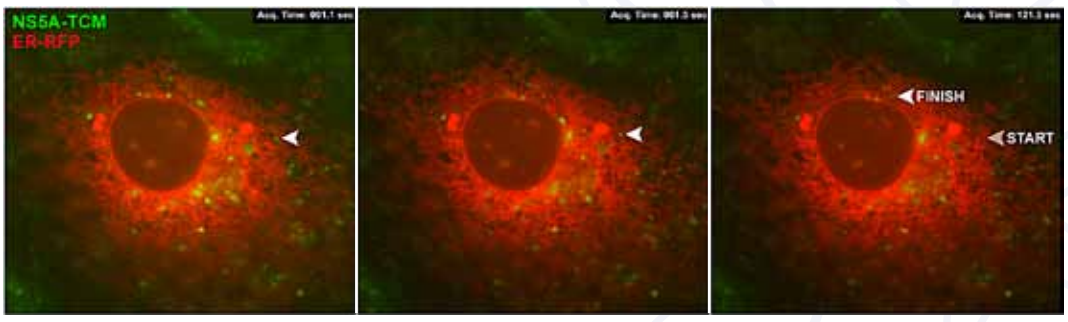
Dynamic imaging of the HCV life cycle

In collaboration with Dr Stuart Turville from the Kirby Institute, Sydney, we have developed a HCV genome that contains a small tetracysteine motif (TCM) within the NS5A protein that allows us to track the NS5A protein in living cells. The HCV NS5A protein is a critical regulator of both viral genome replication and viral particle assembly although its role at the molecular level is not well understood. We have shown that NS5A exists as two distinct populations, (1) stationary structures and (2) fast moving motile structures that are dependent on the microtubule network for traffic. Using host cell factors and organelles that have been tagged with the fluorescent protein GFP we have shown that these fast moving structures complex with known HCV pro-host factors and organelles such as the ER (Figure 1). The challenge will now be to determine the relative roles of these NS5A structures in the HCV life-cycle. Interestingly, these fast moving NS5A structures have a dynamic interaction with lipid droplets, suggesting that they may be important in the delivery of newly synthesised RNA to sites of virion assembly at the lipid droplet interface. Through the use of pharmacological inhibitors of cellular pathways and viral protein function we are now in a position to dissect the HCV life-cycle in real-time.

The ISG viperin interacts with viral and host factors to limit HCV replication

Building on our identification that the ISG viperin is antiviral against HCV we have shown that viperin exerts its antiviral effect through a direct interaction with the HCV NS5A protein and the pro-viral host factor VAP-A. HCV replication takes place within rearranged host cell membranes termed the membranous web that contain all the necessary machinery for replication including NS5A and VAP-A. We have demonstrated that viperin physically interacts with NS5A and VAP-A and we hypothesise that viperin acts to destabilise the HCV replication complex leading to abrogation of HCV replication. This represents a novel mechanism whereby a host protein acts to limit viral replication and adds to our understanding of the viral host relationship.

Traffic of the NS5A-TCM protein (FlAsH-labelled; green) with respect to the ER (red) in Jc1/5A-TCM infected Huh-7 cells. Arrows indicate the movement of the NS5A protein over a period of 2 min. These NS5A structures move throughout the cell at speeds of 1 µm/s in a microtubule-dependent manner.



Outcomes for the Community

Chronic hepatitis C often results in serious liver disease including the development of liver cancer and places a significant burden on our health system. Our work investigating the host response to infection with HCV has significant implications in that a greater understanding of how the liver combats HCV infection is essential for the development and implementation of new therapeutic strategies. Pinpointing the anti-HCV mechanisms of novel host interferon stimulated genes will uncover novel therapeutic targets for the development of new therapies for chronic hepatitis C.

Junia Melo | Debora Casolari | Duncan Hewett

Leukaemia Biology Group

Professor Junia V. Melo MD PhD FRCPath

Chronic myeloid leukaemia (CML) is a paradigm of cancer of the bone marrow, where leukocytes, which would normally be produced only when needed, proliferate uncontrollably and accumulate deleterious DNA mutations which lead to a malignant process.

CML was the first human disease to be associated with a consistent molecular abnormality, the Bcr-Abl fusion protein, a constitutively activated tyrosine kinase that is produced as a of a reciprocal t(9;22) chromosomal translocation.

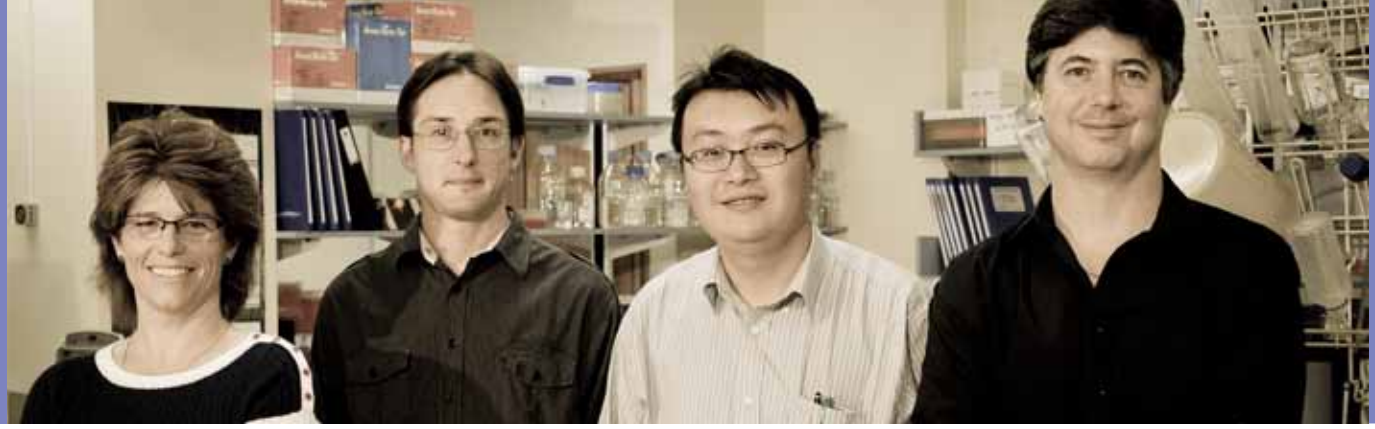
The main area of interest of the Leukaemia Biology Group, established three years ago, is the molecular biology and cell kinetics of chronic myeloid leukaemia (CML), related myeloproliferative disorders (MPDs) and myelodysplastic syndrome (MDS), aiming at identifying new molecular targets for the treatment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

With the introduction of targeted tyrosine kinase inhibitors (TKI), CML has been transformed from a disease with median survival of five years to one compatible with normal life expectancy if patients comply with daily oral medication for life. This is a first in cancer therapy and has brought entirely new problems of management. Although a relatively rare malignancy, effective therapy has dramatically changed its prevalence. In fact, for an increasingly large population of patients, CML has become a chronic illness, like diabetes, hypertension or AIDS.

CML affects all age groups with a median age of onset in the mid-50s. It is not unreasonable to assume that the average life span of these patients after diagnosis is now 30 years. With estimated TKI costs of AUD 30,000–50,000 per annum per patient, each successive year adds at least AUD 900 million in projected drug spend, a figure that does not include hospital care, regular monitoring and management of non-responders by stem cell transplant, let alone the indirect costs of failure to return to work. Because TKIs are so effective, we have seen a remarkable change in the impact of diagnosis from a fatal disease to a chronic condition that simply requires a daily tablet. It is timely to consider a change of mindset in patients, carers and healthcare workers to allow patients to return to a normal place in society. This brings a new focus on 'Living with CML' and on finding the best therapeutic and support approach for patients with this chronic condition.

Unfortunately, despite the impressive success of TKIs for CML, a significant proportion of patients do not achieve optimal response, and many more relapse under this form of treatment. The reasons for this are still largely unknown. It is vital therefore to devise a treatment strategy which allows complete eradication of the leukaemic clone, leading ultimately to total cessation of treatment. This can only be achieved through extensive investigations on the molecular mechanisms of leukaemogenesis, as we are undertaking in our laboratory. If successful in CML, the discoveries could have a far ranging applicability in other chronic illnesses.

The main focus of our research is to understand how the oncogenic BCR-ABL gene is regulated, so that we can then devise a tool to switch it off. Such regulation is bound to be exerted at the level of DNA to RNA transcription and also of RNA to protein translation. This is a relatively new area of biological research in human cells, and very little was know on the structure and possible 'functional switches' in the BCR-ABL gene before we started our research three years ago. Therefore, we are presently looking broadly at large regions of the gene, mapping candidate DNA sequences which have the potential to include the regulatory elements, before narrowing down to specific parts where we hope to identify a mechanism that can be manipulated for curative therapeutic purposes.



Vicki Wilczek | Bradley Chereda | Stanley Cheung | Brett Johnson

Current Specific Questions 2011

What comes 'before' the BCR-ABL fusion gene: are there genetic lesions preceding CML, and can we unravel them by studying identical twins?

What regulates BCR-ABL: how is the BCR-ABL gene expression controlled at the transcriptional and translational levels?

What is regulated by Bcr-Abl: which are the downstream genes (proteins) that are essential for the leukaemic (chronic phase) phenotype?

What adds to/replaces Bcr-Abl signalling to result in disease progression: what are the molecular mechanisms of blastic transformation, a progressive stage of the disease which is nearly invariably fatal, even with the current TKIs?

What determines the difference in disease progression rate and response to treatment: can we identify, at diagonis, those patients whose disease has an intrinsically indolent versus an aggressive nature, through the establishment of prognostic and predictive gene (expression) signatures?

What determines CML stem cell quiescence and possibilities to reverse it: which genes are differentially expressed (in comparison with normal stem cells) that can be therapeutically targeted?

How is the BCR-ABL gene regulated?

Transcription:
BCR promoter

Post-transcription:
microRNAs on the 3'ABL

Rationale and general strategy for one of the research areas in the LBG
Unlike the strategy behind the tyrosine kinase inhibitor (TKI) drugs, which function by de-activating the ready-made cancer protein, our investigations aim at finding a way to intervene even earlier in the biological process of leukaemogenesis — to prevent the BCR-ABL gene from transmitting the genetic code for the production of the oncoprotein. For this, we need to identify and block the controlling elements on the 'head' (BCR- promoter) and the 'tail' (3' ABL) of the fusion gene.

Outcomes for the Community

The unravelling of the mechanisms that regulate expression of the BCR-ABL oncogene will allow us to design a specific way to 'shut it down', thus providing an alternative target for therapy of CML. This will bring significant translational gains to the community:
1 it will provide the principle by which similar research in other types of leukaemias and cancer can progress (ie, using CML as a model, the same or similar mechanisms may be uncovered in various malignant disorders);
2 discovery/identification of a new molecular target will naturally lend itself to patents and the derived commercialisation;
3 it will provide the fundamental data for a drug (small chemical compound, specific antibodies etc) to be designed for elimination of the leukaemia stem cell (which is largely refractory to TKIs), and thus pave the way to a cure in CML, rather than merely a long drug (TKI)-dependent survivorship;
4 achievement of the latter will result in substantial savings in terms of public health expenditure, as discussed above.

Haley Altamura | Jodi Prime | Alex Yeoman | Chani Field | Sue Branford

Leukaemia Unit, Genetics and Molecular Pathology

Associate Professor Susan Branford PhD MHGSA FFSc (RCPA)

Mutation within the gene that causes chronic myeloid leukaemia (CML) leads to drug resistance and disease relapse. Characterising these mutations is essential to guide appropriate therapy to restore response and avoid progression to a fatal acute leukaemia.

This laboratory investigates the molecular response to therapy by an examination of the *BCR-ABL1* gene. This abnormal gene is caused by a chromosomal rearrangement and all patients with CML have the genetic abnormality, which leads to constant activation, marked cell proliferation and genetic instability. Specific therapy targets the leukaemic cells and inhibits the abnormal activation. Long term survival for most patients is now achievable and is evident by a rapid reduction of the *BCR-ABL1* levels. We monitor these levels and failure to achieve certain reductions at specific time-points predicts suboptimal response or treatment failure. The aim is to achieve rapid *BCR-ABL1* reduction within the first 6 to 12 months to achieve an optimal response and long term survival. Failure to achieve these responses leads to a change of therapy to improve the chances of survival.

Our laboratory is a reference laboratory involved in an international effort to standardize molecular methods for consistency of reporting *BCR-ABL1* levels. This is essential to ensure the reliable interpretation of therapy response and appropriate therapy changes for suboptimal responders.

Most patients respond well to inhibitor therapy, however, approximately 20% of patients have drug resistance. The inhibitor drugs bind to the *BCR-ABL1* protein and inhibit its activity. The most common mechanism of acquired drug resistance is mutation within the region of the *BCR-ABL1* gene involved in drug binding. There are many locations where these mutations occur and they have varying effects on drug binding. Some occur at sites that lead to complete reactivation of leukaemia, whereas others may only slightly impair drug binding. More than 100 mutations have been identified but most patients only have one mutation detectable at the time of resistance. The type of mutation can affect the patient outcome. Some mutations are associated with a poor outcome and progression to an acute leukaemia. These mutations are among the most common. Other mutations have a mild impact and response may be restored with an increased drug dose. Our laboratory sequences the *BCR-ABL1* gene in patients with a suboptimal response or pending loss of response.

The problem of resistance and mutations has led to the development of more potent drugs that are now approved for resistant patients. Most of the resistant mutations are responsive to the more potent inhibitors, however, one mutation is resistant to all currently approved drugs and a small number of other mutations are resistant to some of the drugs. Therefore, the type of mutation can determine the appropriate therapy after resistance. We have been investigating the impact on response of low-level mutations using mass spectrometry. These mutations are not detectable using standard techniques at the time of commencing rescue therapy. Some of these low-level mutations are associated with a poor response to subsequent therapy and we have demonstrated the clinical utility of including sensitive mutation analysis into monitoring strategies.

A major problem for clinicians treating patients with CML is non-adherence to the prescribed drug dose. Most patients may require life long, daily drug intake for an optimal response. Studies have suggested that only 15% of patients are completely compliant with taking their daily drug. Failure to take the drug can lead to a suboptimal response or loss of response. The detection of a mutation in a patient with loss of response is an indication of true, clinical resistance. But without any evidence of clinical resistance it is difficult for clinicians to know whether loss of response is due to mutation-independent drug resistance or non-adherence. Therapeutic intervention will differ depending on the cause of loss of response. We are investigating whether loss of response due to non-adherence can be distinguished from drug resistance by an examination of the kinetics of molecular loss of response.

Linda Fletcher | Sunil Abraham | Wendy Parker | Brad Sullivan | Emma Channon | Zoe Donaldson

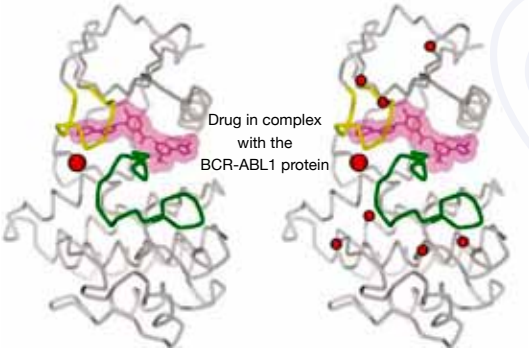
Key discoveries 2011

The presence of multiple sub-clonal *BCR-ABL1* mutations impacts drug response

Using sensitive mutation analysis we had previously demonstrated that low-level *BCR-ABL1* mutations not detectable by standard techniques, can lead to treatment resistance to more potent kinase inhibitors. This was when the low-level mutation was one of the few mutations known to confer resistance to the more potent drug. These resistant mutations are rapidly selected and become a predominant clone. Usually, patients only have one predominant mutation at the time of drug resistance, although a minority of patients have more than one. Very rarely, patients have up to four predominant mutations. Using our sensitive mutation technique we detected many mutations in some patients after failure of their initial drug therapy. Up to 10 low-level mutations were detected. We investigated the impact of multiple mutations on the subsequent response to more potent drug therapy. Patients where all of their mutations were known to be sensitive to the more potent inhibitor were investigated. These patients were not considered to be at risk of treatment failure on the basis of their mutation status. However, we found that patients with multiple low-level mutations had a significantly poorer outcome compared with patients with only one or no mutations (*Blood*, 2012. In Press). Therefore, we identified a substantial subgroup of patients who may benefit from alternative therapy. The low level mutants may represent a pool of sub-clonal mutations that each contribute to resistance and may be a marker of a more genetically unstable disease.

The kinetics of a *BCR-ABL1* rise may distinguish drug resistance from non-adherence

A rise in *BCR-ABL1* is the molecular marker for potential loss of response. We and others previously demonstrated that the rate of *BCR-ABL1* increase determines the disease phase at relapse. A rapid rise is characteristic of relapse into an advanced disease, whereas a slow rise indicates relapse into chronic phase. We aimed to determine if dose interruption leads to characteristic kinetics that may distinguish non-adherence from drug resistance. Kinetics were examined by calculating the number of days over which *BCR-ABL1* doubled (doubling-time) in various clinical situations: documented dose interruption or discontinuation, the acquisition of a *BCR-ABL1* mutation, and relapse into an acute leukaemia (blast crisis). Unexpectedly, the kinetics of relapse when dose was interrupted or discontinued was as rapid as that of patients who relapsed directly into blast crisis. In the absence of blast crisis, a short *BCR-ABL1* doubling-time is strong evidence of non-adherence. In contrast, patients with a mutation who maintained chronic phase had significantly longer doubling-times, indicating slow leukaemic cell expansion. Long doubling-times observed with mutations in chronic phase are reassuring for clinicians as it may allow time to consider therapeutic options. The difference in kinetics in various clinical situations was not evident from the magnitude of the rise. Current patient monitoring guidelines mandate an assessment of the magnitude of the rise to determine when to test for resistance.
We suggest the BCR-ABL1 doubling-time calculation is a more appropriate assessment to examine the kinetics of response and provides evidence for non-adherence.



Patient 1:
1 predominant mutation

Patient 2:
1 predominant mutation
7 sub-clonal mutations

Outcomes for the Community

Our research has benefited patients by providing guidance for clinicians when determining the most appropriate therapy after drug resistance. This will avoid costly and time consuming trials of inappropriate kinase inhibitor drugs. It is important that the *BCR-ABL1* mutation status is known since some mutations may cause subsequent resistance to certain more potent inhibitors. Sensitive mutation analysis is necessary to detect low-level resistant mutations or patients with multiple low-level mutations, since these may impact response.

Natasha Harvey | Kelly Betterman

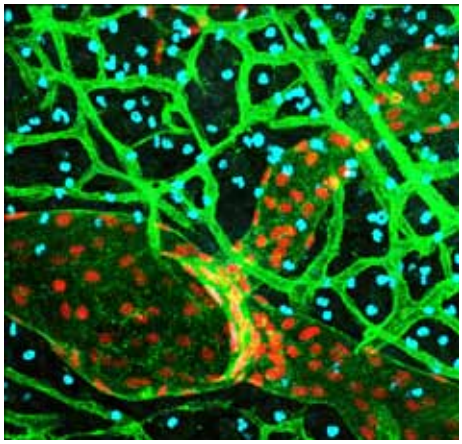
Lymphatic Development Laboratory

Dr Natasha Harvey PhD

Lymphatic vessels are crucial for returning interstitial fluid and protein to the bloodstream, trafficking cells of the immune system and absorbing lipids from the digestive tract.

The cardiovascular system, comprised of the heart, blood vessels and lymphatic vessels, is the first organ network to develop in the vertebrate embryo. While blood vessels are essential for the delivery of oxygen and nutrients to the tissues, lymphatic vessels are crucial for returning interstitial fluid and protein to the bloodstream, trafficking cells of the immune system and absorbing lipids from the digestive tract. The aberrant growth and development of lymphatic vessels (lymphangiogenesis) is associated with a growing catalogue of human disorders; insufficient or abnormal growth, development or function of lymphatic vessels manifests in conditions including lymphoedema and vascular malformations, while excessive lymphangiogenesis exacerbates inflammatory diseases and cancer. The major goal of research in the Lymphatic Development Laboratory is to identify and characterise signals important for the construction, maturation and function of lymphatic vessels, with the aim that they may prove to be targets for the generation of novel therapeutics designed to stimulate, or ablate lymphangiogenesis. Pro-lymphangiogenic agents should prove valuable for repairing hypoplastic or damaged lymphatic vessels and thereby treating lymphoedema, while anti-lymphangiogenic agents are likely to provide novel therapeutics for the prevention of tumour metastasis and treatment of inflammatory diseases.

Despite the importance of the lymphatic vessels in development and disease, little is understood about the signals that control their growth and maturation. Our current research utilises a combination of genetic, cellular and molecular approaches to identify and characterise signals that direct the construction of lymphatic vessels in the mouse embryo.



Lymphatic vessels (red), blood vessels (green) and cells of the immune system (cyan) in embryonic mouse skin.

Genevieve Seker | Jan Kazenwadel

Key discoveries 2011

Identification of mutations in the transcription factor GATA2 that result in human lymphoedema and MDS/AML

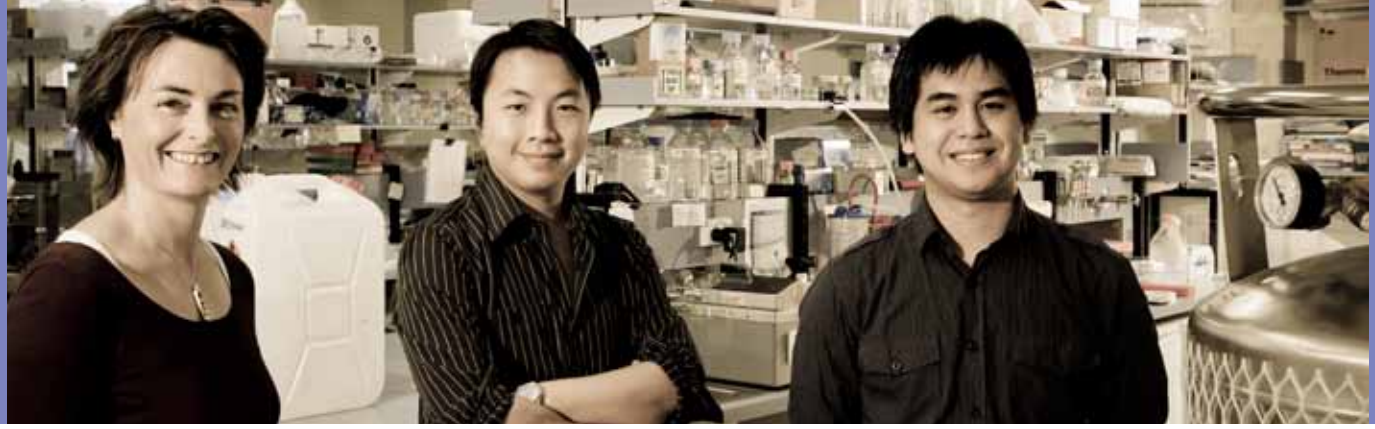
GATA2 is a zinc finger transcription factor that plays key roles in hematopoiesis as well as neural and urogenital development. Together with Professor Hamish Scott's team at the Centre for Cancer Biology, we recently made the landmark discovery that heritable mutations in GATA2 predispose carriers to lymphoedema and myelodysplasia syndrome (MDS)-acute myeloid leukaemia (AML) (Kazenwadel *et al*, *Blood* 2011). This discovery revealed a key role for GATA2 in controlling lymphatic vascular development and/or function. Our recent work has revealed that GATA2 is present at high levels in lymphatic vessel valves from the onset of valve formation and that GATA2 regulates the expression of genes required for valve development. As lymphatic vessel valves are crucial for unidirectional lymph flow, we predict that valve development, maintenance and/or function is likely to be disrupted by GATA2 mutation, resulting in lymphoedema. Current work aims to define how GATA2 regulates the growth, development and maturation of the lymphatic vasculature, to understand how GATA2 mutations result in lymphoedema and MDS/AML and to identify new therapeutic targets for the treatment of lymphoedema.

High resolution imaging of the cellular events that initiate development of the lymphatic vasculature in the mouse embryo

During lymphatic vascular development in the mammalian embryo, a subset of endothelial cells in the cardinal veins is reprogrammed to adopt a lymphatic endothelial fate once they 'switch on' the transcription factor Prox1. However, very little is known about how these cells exit the veins to form the lymphatic vasculature. In collaboration with Dr Mat Francois and Professor Peter Koopman at IMB, Brisbane, we used advanced, high resolution imaging techniques to uncover three key stages of lymphatic vascular morphogenesis in the mouse embryo (Francois *et al* 2011). First, we defined discrete territories or 'pre-lymphatic clusters' of Prox1-positive lymphatic endothelial progenitor cells along the antero-posterior axis of the cardinal veins. Second, we revealed that pre-lymphatic clusters undergo progressive extrusion, or 'ballooning', to generate primitive lymph sacs. Third, we identified a sub-population of lymphatic endothelial progenitor cells with a distinct set of cell surface markers, that generate lymphatic vessels by sprouting from the cardinal veins and lymph sacs. Our data support a new model for lymphatic vascular patterning and morphogenesis, and lay a foundation for the identification of molecular cues governing these processes.

Outcomes for the Community

Lymphatic vessels are of major importance to cancer patients. Cancer cells exploit lymphatic vessels as a route of metastasis and can either enter pre-existing lymphatic vessels, or promote the growth of new lymphatic vessels in order to access the lymphatic vascular network. Lymphatic vascular damage following lymph node resection can result in secondary lymphoedema, a major problem for many cancer patients and for which an effective treatment is lacking. By understanding the signals that control the growth and development of lymphatic vessels, we hope to design new therapeutics that either block, or promote the growth of lymphatic vessels. Such agents should prove invaluable for the inhibition of tumour metastasis, or for the repair of lymphatic vessel damage and treatment of secondary lymphoedema.



Michele Grimbaldeston | David Yip | Houng Taing

Mast Cell Laboratory

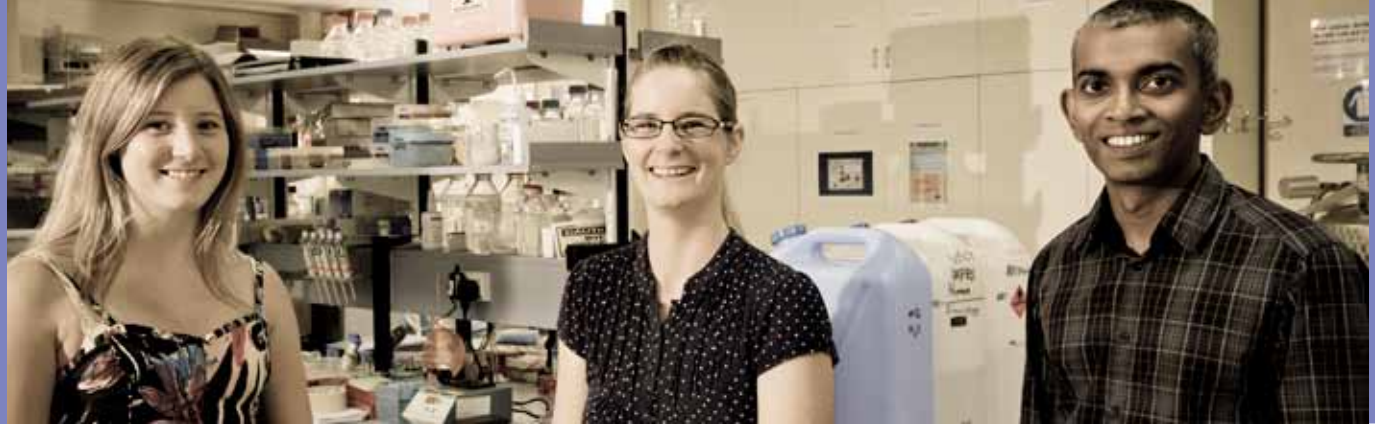
Dr Michele Grimbaldeston PhD

Mast cells are unique immunocytes that normally reside in tissues, particularly those that are exposed to the external environment such as the skin, gut and lung. Historically, they are depicted as major effector cells of asthma and other IgE-associated allergic disorders and immune responses to parasites.

However, in addition to their ability to initiate and amplify inflammation, mast cells can also regulate such responses to protect against pathological effects of excessive inflammation and aide the processes of restoring tissue homeostasis.

Research being undertaken by the Mast Cell Laboratory focuses on the novel regulatory abilities of mast cells, with an emphasis on how this dynamic cell contributes to the regulation of inflammation associated with allergy and skin cancer development. In a recent paper (*J Exp Med* 207: 455-63, 2010), we identified the molecular basis for the protective effects of mast cell-dependent limitation of chronic ultraviolet B (UVB) irradiation-induced skin damage. Key to the beneficial capabilities of mast cells in this setting, is their ability to produce the anti-inflammatory cytokine, IL-10, in response to vitamin D_3. For over eighty years vitamin D_3 has been recognised as the 'sunshine' vitamin. Although it can be sourced from dietary intake, the skin also plays a crucial role in its synthesis; a process initiated by and dependent on exposure of the skin to UVB radiation, a component of sunlight. The findings from this study provided the first *in vivo* evidence of a regulatory axis between vitamin D_3 and mast cells.

In collaboration with Dr Michael Samuel, we are investigating the important question of whether mast cell function at the peri-lesional interface provides a permissive tumourigenic environment or guards against rapid neoplastic progression during skin carcinogenesis. Dr Samuel was recruited to the Centre of Cancer Biology in 2011 from the Beatson Institute for Cancer Research (BICR), UK, where he made the novel discovery that ROCK activation in the epidermis promotes tumourigenesis by a mechanism involving reciprocal cell tension and tissue rheology changes which activate β-catenin to induce cell proliferation (*Cancer Cell* 19: 776-91, 2011).

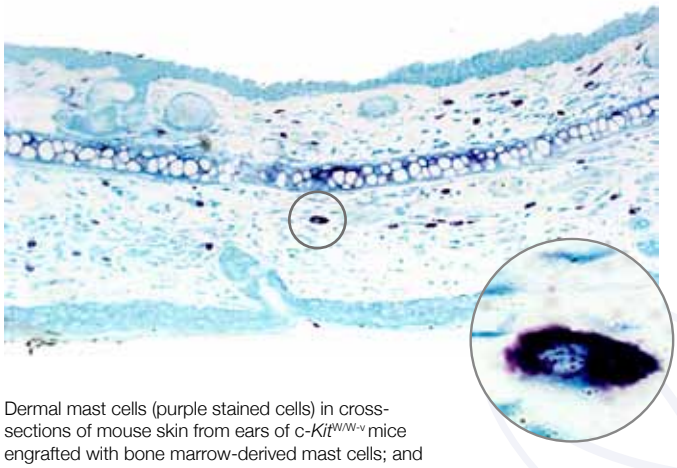


Katlin Scheer | Natasha Pyne | Michael Samuel

Key discoveries 2011

Vitamin D_3 suppresses IgE-mediated mast cell activation

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



Dermal mast cells (purple stained cells) in cross-sections of mouse skin from ears of c-$Kit^{W/W\text{-}v}$ mice engrafted with bone marrow-derived mast cells; and May-Grunwald Giemsa stained mast cells (purple)

Outcomes for the Community

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

Laura Eadie | Dale Watkins | Deborah White | Phuong Dang | Oi-Lin Lee | Stephanie Arbon | Tamara Leclercq | Devendra Hiwase | Chung Kok | Amity Frede

Melissa White Laboratory

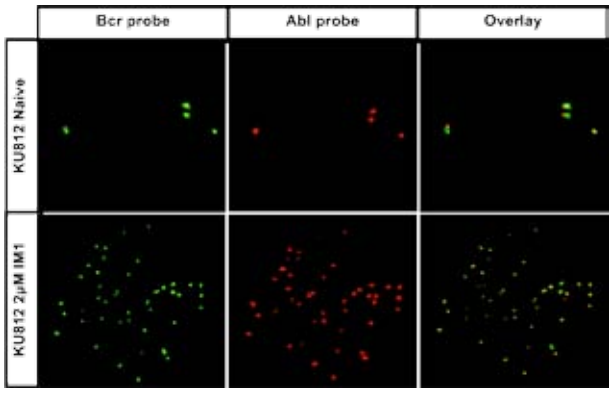
Clinical Laboratory: Professor Timothy Hughes MD FRACP FRCPA MBBS

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

The Melissa White Laboratory is dedicated to improving outcomes for patients diagnosed with Chronic Myeloid Leukaemia (CML). CML is a fatal myeloid proliferative disorder with about 300 new cases diagnosed in Australia each year.

The disease is caused by BCR-ABL, a constitutively active protein that causes white blood cells to multiply more than normal, leading to an accumulation of immature cells in the blood and bone marrow. If left untreated, the disease progresses from a chronic phase (lasting 3–5 years) before entering an accelerated phase (12 months) and finally blast crisis (3-6 months). However, the introduction of tyrosine kinase inhibitors (TKIs), such as imatinib, have revolutionised treatment for CML, with progression free survival in more than 90% of patients after 8 years of treatment.

Despite excellent overall responses, there remains a proportion of patients who display suboptimal response to imatinib, or develop resistance to the therapy after some time of treatment. In order to identify patients who will do poorly on imatinib, we have developed assays to measure a patient's sensitivity to the drug (IC50 assay) and to measure the activity of the organic cation transporter 1 (OCT-1) protein. OCT-1 is responsible for active influx of imatinib into cells where it can then bind and inhibit BCR-ABL.



Double minutes carrying BCR-ABL are present in an imatinib-resistant cell line
Shown above is a single, representative KU812 Naïve cell (top panel) and a single imatinib-resistant KU812 2μM IM1 cell (bottom panel). BCR-ABL amplification in the KU812 2μM IM1 cell line is evident due to numerous co-localising Bcr (green) and Abl (red) signals, seen in the 'Overlay' panel. This indicates that the double minutes (identified by karyotyping) carry BCR-ABL.

We have shown that OCT-1 activity, as measured by our assay, is predictive of long term outcome in chronic phase CML patients taking imatinib (*J Clin Oncol* 2010).

OCT-1 activity in patients can be divided into quartiles, with the lowest quadrant (Q1, where OCT-1 activity is less than 4ng/200000 cells) being at greatest risk of suboptimal response to imatinib. A particular interest of ours is to discover a genetic fingerprint for these patients using a MicroArray technique. Through collaboration with Associate Professor Richard D'Andrea (Acute Leukaemia Laboratory) we hope that identification of specific Biomarkers will allow us, and other laboratories around the world, to easily identify Q1 patients prior to therapy, and tailor TKI treatment accordingly. Recent work has also focussed on non-steroidal anti-inflammatory drugs which are frequently used by CML patients to manage musculoskeletal complaints. Ibuprofen significantly reduced OCT-1 activity and reduced imatinib effectiveness in vitro, while diclofenac was found to increase OCT-1 activity and improve imatinib potency in leukaemic cells. Although the search continues for other effective enhancers of OCT-1 activity, low OCT-1 activity in patients may be overcome by increasing imatinib dosage, or by using a second generation TKI such as nilotinib or dasatinib.

Nilotinib and dasatinib are studied in our laboratory to investigate differences in cellular transport and efficacy compared to imatinib. We have shown that nilotinib and dasatinib are not transported by OCT-1, and that cellular efflux of nilotinib is different to imatinib. Patients may also become resistant to TKI therapy due to mutations in the BCR-ABL protein which prevent these drugs binding. We have also been able to recapitulate TKI-resistance development, and the emergence of such mutations, using cell lines in our laboratory. The T315I mutation is of particular interest, as this BCR-ABL mutation causes resistance to the three currently available TKIs (imatinib, nilotinib and dasatinib). However, we have also been working with a recently developed drug called ponatinib which may offer hope to patients carrying the T315I mutation.

Carine Tang | Liu Lu | Lisa Schafraneck | Ljiljana Vidovic | Timothy Hughes | David Yeung | Eva Nievergall | Jenny McLean | Verity Saunders | Jarrad Goyne

Key discoveries 2011

Mutations in the kinase domain of BCR-ABL prevent binding of TKIs and therefore cause drug resistance in CML patients.

In order to understand what causes mutations to develop, we recapitulated TKI-resistance development *in vitro* in several human CML cell lines. A key finding of these studies was that BCR-ABL overexpression uniformly precedes the emergence of BCR-ABL mutations. This knowledge may enable early identification of patients at risk of developing mutations when BCR-ABL levels begin to rise. It was also observed that TKI-resistant cell lines showed some level of cross-resistance to the three TKIs tested (imatinib, nilotinib and dasatinib), suggesting that currently available drugs share the same susceptibilities to drug resistance (*Leukaemia & Lymphoma*, 2011). It is therefore imperative that we continue studies into TKIs and alternative or combination therapies in order to combat resistance emergence.

Ponatinib is a third generation TKI which was developed in response to the T315I mutation

The T315I mutation is a BCR-ABL mutation unlike others as it prevents all previous TKIs from binding BCR-ABL. The new drug ponatinib has been used in our laboratory to confirm its efficacy in cells carrying both mutated and unmutated BCR-ABL. We have also demonstrated that cellular efflux transporters that interact with imatinib, nilotinib and dasatinib do not impact the efficacy or mediate resistance to ponatinib (ASH abstract 2745, 2011). Thus, ponatinib may provide a treatment alternative for patients who have developed resistance to first and second generation TKIs.

OCT-1 activity in mononuclear cells is highly variable between patients and significantly correlates with a patient's molecular response to imatinib treatment and overall survival

Our group examined whether cell lineage and BCR-ABL expression influenced OCT-1 activity. It was found that OCT-1 activity in patient mononuclear cells is strongly related to cell lineage, particularly the presence of neutrophils in the peripheral blood.
Furthermore, BCR-ABL expression does not directly influence OCT-1 activity but may have an indirect role by enhancing granulocyte differentiation which in turn results in an increase in OCT-1 activity (*Haematologica*, 2011).

Outcomes for the Community

Understanding the molecular mechanism at the root of CML has enabled the development of targeted therapies which have been highly successful. However, not all patients respond well to currently available TKIs due to resistance or intolerance. Research in our laboratory has given new insights into underlying disease biology to explain why some patients respond poorly and how we can improve the outcome for these patients.

Peter Brautigan | Alicia Byrne | Hamish Scott | Chris Hahn | Milena Babic

Molecular Pathology Research Laboratory

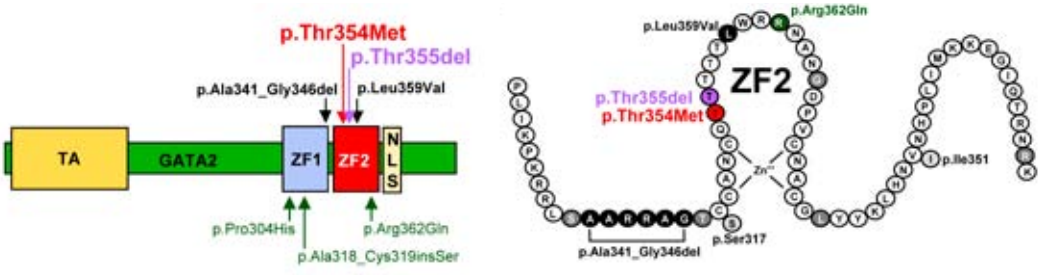
Professor Hamish S Scott PhD FFSc (RCPA)

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

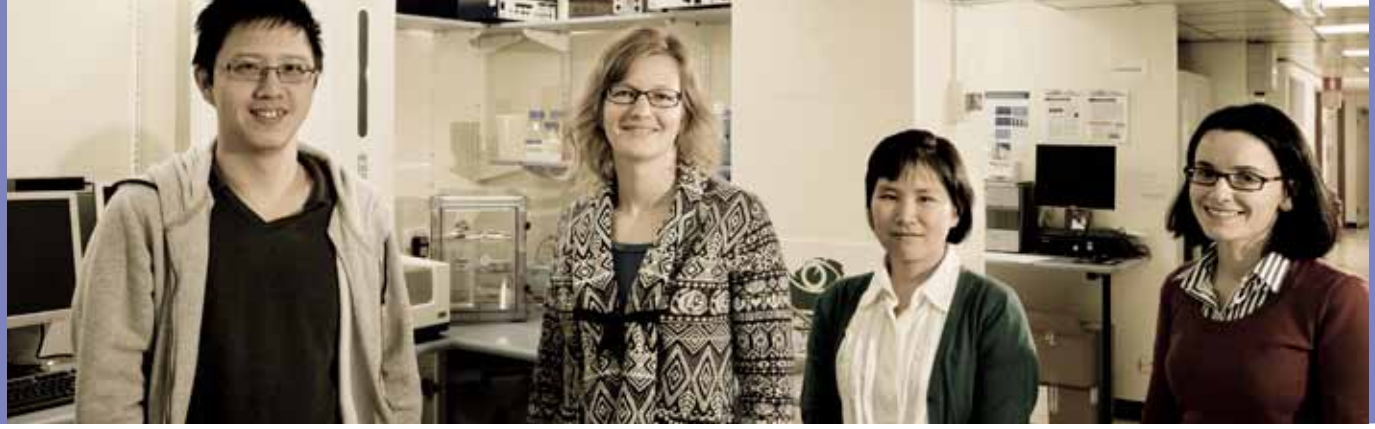
Our research program spans basic to applied genetic research. It takes advantage of existing and emerging technologies, and resources unique to our research team and collaborators, such as patient collections and mouse models. We are interested in how and why genetic mutations occur, how these changes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

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

Rare cases of predisposition to leukaemias and lymphomas, infection and autoimmunity, families with inherited predispositions to leukaemia's and lymphomas can provide insights into the initiation and progression of these diseases. With international and national collaborators as well as the South Australian Familial Cancer Service, we collect samples from rare families with predispositions to haematological malignancies (HMs) from across the country, and attempt to determine which genes are mutated to cause these disease predispositions. These studies are increasingly using the revolutionary 'next generation sequencing' technologies that have reduced the price of whole genome sequencing (sequencing a persons entire DNA composition or genome) to only a few thousand dollars. While in the past, much of the technology and analyses have been performed in collaboration with other academics and service providers, we are making huge strides in introducing these technologies and skills locally to South Australia. These studies have immediate and direct implications for affected families and individuals and are beneficial for counselling, family planning and, ultimately, choices of therapy. The genes responsible for familial HMs are also likely to be of considerable importance in sporadic HMs.



Identification of novel germline p.Thr354Met and p.Thr355del variants in the highly conserved zinc finger 2 domain of GATA2 that is associated with MDS-AML.



Chan Eng Chong | Brita Ardesjo Lunogren | Young Kyung Lee | Lucia Gagliardi

Key discoveries 2011

The Autoimmune regulator gene (*AIRE*) does more than induce the ectopic expression of self-antigens

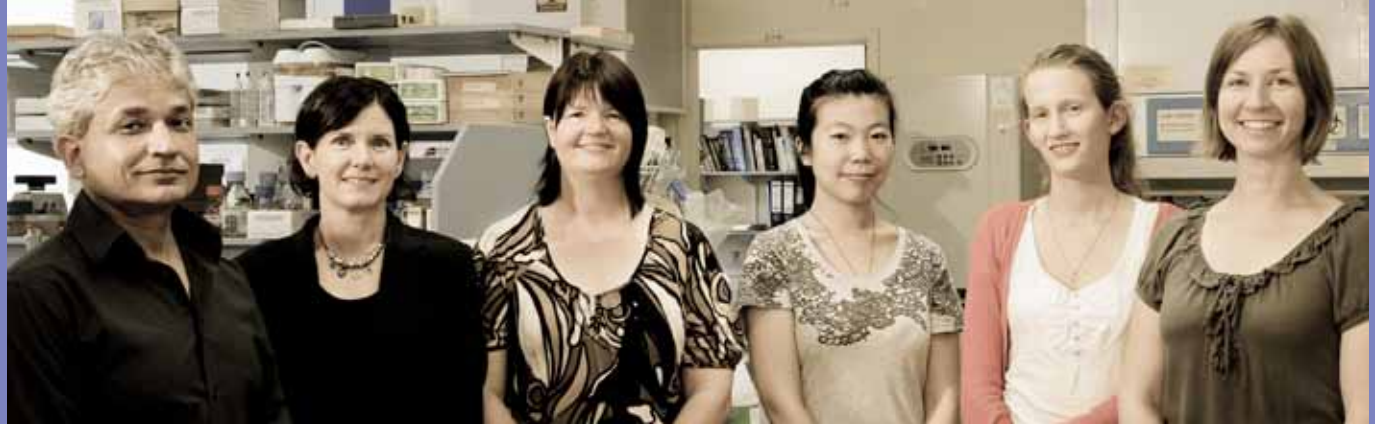
We have shown that AIRE also regulates the expression of chemokines and cytokines in mTECs. This causes bone marrow derived dendritic cells (DCs) to be co-localised in the thymus with AIRE expressing mTECs. As a result, when AIRE expressing mTECs apoptose and die, autoantigens not regulated by AIRE can be absorbed by DCs and again used in the negative selection process (*Blood* 118: 2462-2472, 2012). Despite the process of negative selection largely controlled by AIRE in the thymus, self-reactive T cells inevitably escape into the body. Here however, they are normally kept under control (so as not to cause disease) by a diverse group of poorly understood and rare cells called regulatory T-cells. Many regulatory T-cells are thought to also develop in the thymus. We have shown that CD8+CD28 low regulatory T lymphocytes from AIRE-deficient mice, while apparently transcriptionally and phenotypically normal completely fail to prevent experimental colitis in mice compared to the same cell population from wildtype mice. This demonstrates that AIRE plays an important role in the *in vivo* function of a naturally occurring regulatory T-cell population. (*Proc Natl Acad Sci USA* 108:12437-12442, 2011)

New Predisposition Gene to Leukaemias

We lead international collaborations which have identified that germline *GATA2* mutations cause familial myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML, Nat Genet 44:9-10, 2011), and Emberger syndrome (primary lymphoedema with MDS/AML, *Blood* 119:1283-1291, 2012). Others then also identified germline GATA2 mutations in Emberger syndrome, MonoMAC syndrome (also called DCML deficiency, an immunodeficiency with MDS/AML), revealing a diversity of clinical presentations. While the role of the GATA2 transcription factor in differentiation, proliferation and survival of haematopoietic stem cells and progenitor cells was well known, its role in lymphatic vascular development as suggested by the patients with primary lymphoedema is less well described. In familial MDS/AML, the mutations reside within the second zinc finger of GATA2 which mediates DNA-binding and protein-protein interactions. In contrast, the germline mutations in Emberger syndrome are often *de novo,* and complete loss of function mutations, and thus spread throughout the gene. We showed differential effects of the mutants on transactivation of target genes, cellular differentiation, apoptosis and global gene expression. Identification of such predisposing genes to familial forms of MDS and AML is critical for more effective diagnosis and prognosis, counselling, selection of related bone marrow transplant donors, and development of therapies.

Outcomes for the Community

We have had concrete clinical outcomes for the South Australian, Australian and international community this year. Our discovery that germline *GATA2* mutations predispose to MDS and AML was spearheaded in a South Australian family with 13 affected members. Even before these results were published in a scientific journal we were able to transfer our research results to the diagnostic laboratory and offer diagnostic testing and genetic counselling. This was a world first and diagnostic samples have been received from all over the world. This has help guide selection of donors and protocols for therapy by bone marrow transplantation. To date, at least 17 families carrying germline *GATA2* mutations have been identified with a total of 134 predisposed or affected individuals identified, including additional South Australians.



Sharad Kumar | Donna Denton | Natasha Boase | Wenying Zhu | Shannon Nicolson | Kathryn Mills

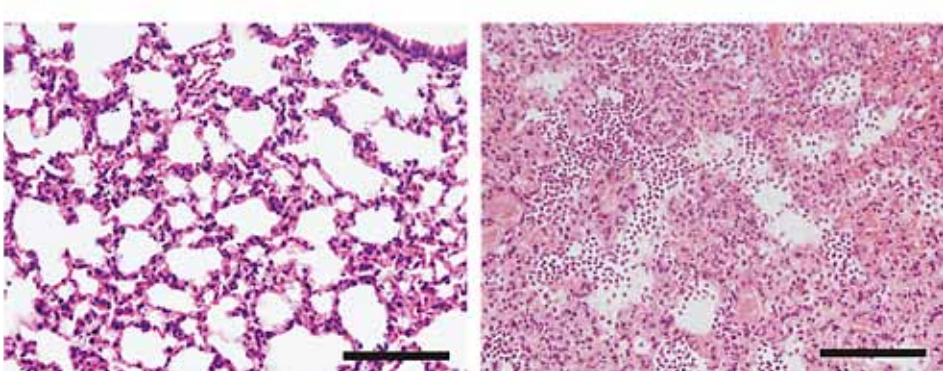
Molecular Regulation Laboratory

Professor Sharad Kumar MSc PhD

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

Millions of cells in the human body die every minute as part of normal homeostasis by a special process termed apoptosis. Apoptotic cell death plays a fundamental role in cell and tissue homeostasis and too little or too much of it can lead to many human diseases including cancer. Given the essential role of cell death in normal functioning of the human body, deciphering the mechanisms of apoptosis is essential for understanding disease processes and to design effective treatment strategies for diseases which arise due to inappropriate apoptosis. We study the mechanisms and regulation of cell death in normal homeostasis and during animal development, with a particular emphasis on the roles of the cell death and survival machinery in cancer.

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



Nedd4-2$^{+/+}$ Nedd4-2$^{-/-}$

Surviving *Nedd4-2* $^{-/-}$ mice develop lethal lung inflammation
The small percentage of *Nedd4-2*$^{-/-}$ mice that overcome perinatal lethality then die around 3 weeks of age due to inflammation of the lung, seen here in haematoxylin and eosin-stained P21 lung sections. Scale bars 50 µm

May Aung-Htut | Loretta Dorstyn | Claire Wilson | Jantina Manning | Natalie Foot | Joey Puccini | Sonia Shalini

Key discoveries 2011

The ubiquitin ligase Nedd4-2 is essential for regulating the epithelial sodium channel and animal survival

The epithelial sodium channel (ENaC) is essential for sodium homeostasis in the body. ENaC activity is required for maintenance of blood volume and blood pressure in adults and for lung fluid clearance in newborn animals. In a paper published in *Nature Communications* (2: 287), we reported that knockout of Nedd4-2 in mice leads to increased ENaC expression and activity in embryonic lung. This increased activity is the likely reason for premature foetal lung fluid clearance in Nedd4-2-deficient animals, resulting in a failure to inflate lungs and lethality at birth due to respiratory distress. A small number of Nedd4-2-deficent animals survive birth and live for up to 22 days. These animals also show increased ENaC expression and develop lethal inflammation of the lung. Our work provides critical *in vivo* evidence that Nedd4-2 is essential for regulating ENaC expression, lung function, and animal survival.

A novel mechanism of iron homeostasis and its implications in inflammation and anaemia

We recently described a novel mechanism of regulation of iron homeostasis in the body. We found that the primary non-heme iron transporter DMT1 is down-regulated by members of the Nedd4 family of ubiquitin ligases and requires the adaptors Ndfip1 and Ndfip2, previously identified by us as Nedd4 WW domain interacting proteins. Consistent with these observations *Ndfip1*-deficient mice fed a normal diet showed increased accumulation of iron stores in the liver and spleen. In further studies we found that in *Ndfip1*-deficient mice fed a low iron diet, DMT1 expression and activity were significantly elevated compared to the wild-type mice. However, despite the increased iron uptake, *Ndfip1*-deficient mice developed severe anaemia due to a combined effect of iron deficiency and inflammatory disease in these animals. *Ndfip1*-deficient animals are known to develop severe inflammatory disease, and our new observations suggest that iron deficiency may accentuate this phenotype (*Blood* 117: 638-646). Our work thus provides evidence that Ndfip1 is a critical regulator of DMT1 and iron homeostasis, especially under iron-limiting conditions.

Ndfip is a novel regulator of Notch signalling

Notch signalling is critical for many cell fate decisions, including cell differentiation and cell death, and its misregulation is linked to cancer and developmental disorders. In a recent paper (*Cell Death Differ* 18: 1150-1160), using *Drosophila* as a model system we found that Ndfip is an important regulator of Notch. We showed that the *Drosophila* homologue of Ndfip (dNdfip) interacts with the *Drosophila* Nedd4-like ubiquitin ligases and its expression dramatically enhances dNedd4 and Su(dx)-mediated wing phenotypes via disruption of Notch signalling in a ligand independent manner. dNdfip expression in the wing leads to ectopic Notch signalling. The opposing effects of dNdfip expression on Notch signalling and its late endosomal localization support a model whereby dNdfip promotes localization of Notch to the limiting membrane of late endosomes allowing for activation.

Outcomes for the Community

The main anticipated outcomes from our research are a better understanding of disease mechanisms and the functioning of the human body; discovery of new disease markers and discovery of potentially novel therapeutic targets.

Jason Powell | Huashena Chan | Aneta Zysk | Stuart Pitson | Julia Dobbins | Heidi Neubauer | Paul Moretti

Molecular Signalling Laboratory

Associate Professor Stuart Pitson PhD

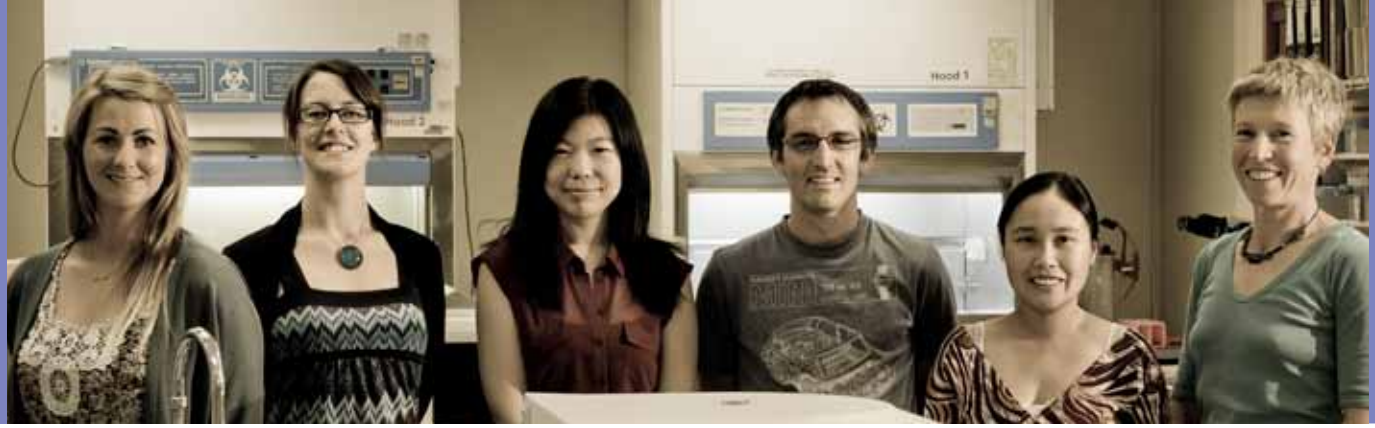
Understanding the factors that control the growth and survival of cells has important implications for cancer therapy as defects in these pathways often drive transformation of normal human cells into highly malignant derivatives. The sphingolipids have emerged as key regulators of these processes and present attractive targets for cancer therapy.

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

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

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

Recent work in the Molecular Signalling Laboratory has concentrated on understanding the biochemistry of sphingosine kinase, identifying the mechanisms regulating the activity and subcellular localisation of this enzyme, and on the (patho-) physiological functions of signal transduction pathways it controls. Understanding these factors may allow for the development of novel therapeutics. In particular we have made several major breakthroughs in understanding how this enzyme in activated, relocalised to the plasma membrane, and deactivated, which have provided novel therapeutic targets to control cancer. We have also identified that the substrate of sphingosine kinase, sphingosine, is a key regulator of the pro-survival 14-3-3 proteins. Indeed, our work suggests that inactivation of 14-3-3 by sphingosine is a key control mechanism that if dysregulated can enhance tumorigenesis. Thus, this pathway also represents novel therapeutic target that may be exploited to control cancer.



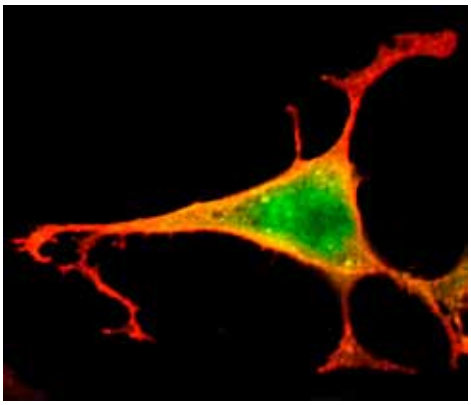
Kristy Alexander | Melissa Pitman | Wenying Zhu | Carl Coolen | Duyen Pham | Joanna Woodcock

Key discoveries 2011

Sphingosine kinase mediates oncogenic signalling by EF1A

We have recently identified that regulation of sphingosine kinase can be achieved through another protein called EF1A. Notably, EF1A has been implicated in inducing the formation of some solid tumours, but the mechanism was unknown. Our findings show that the oncogenic effects of EF1A are mediated by sphingosine kinase, and thus indicates that targeting this enzyme is a therapeutic option for these EF1A-induced cancers

Leclercq TM, Moretti PAB and Pitson SM (2011) Guanine nucleotides regulate sphingosine kinase 1 activation by eEF1A and provide a mechanism for eEF1A-associated oncogenesis. *Oncogene* 30, 372-378.



Normal sphingosine kinase (green) is mainly localised to the cell cytoplasm, while highly oncogenic forms of sphingosine kinase (red) are present at the plasma membrane.

Distinct protein phosphatase 2A complexes control oncogenic signalling by sphingosine kinase

We have revealed a crucial mechanism by which sphingosine kinase is regulated via its dephosphorylation by protein phosphatase 2A. We found that sphingosine kinase is inactivated by this dephosphorylation, catalysed specifically by protein phosphatase 2A complexes containing the B'α regulatory subunit. Since defects in B'α function are widely implicated in these findings provide us with the unique opportunity to develop potential anti-cancer therapies to specifically target this pathway.

Pitman MR, Barr RK, Gliddon BL, Magarey AM, Moretti PAB and Pitson SM (2011) A critical role for the B'α regulatory subunit of protein phosphatase 2A in dephosphorylation of sphingosine kinase 1. *Int J Biochem Cell Biol* 43: 342-347.

Outcomes for the Community

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

Andrew Zannettino | Duncan Hewett | Kate Vandyke | Sharon Paton | Annie Chow | Sharon Williams

Myeloma Research Laboratory

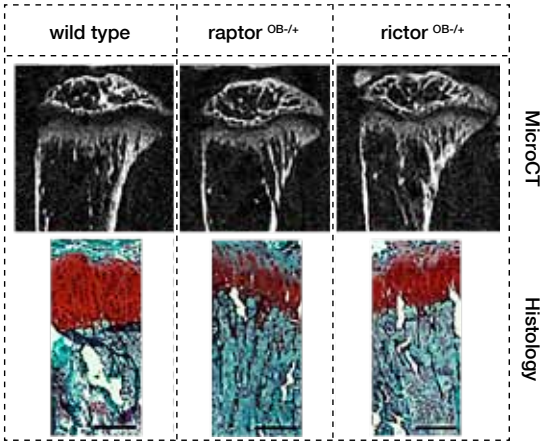
Professor Andrew Zannettino PhD

Multiple myeloma (MM) is an incurable haematological malignancy characterised by the clonal proliferation of malignant plasma cells (PC) within the bone marrow (BM). MM is the second most common haematological malignancy after non-Hodgkin's Lymphoma, with approximately 1,400 newly-diagnosed patients each year in Australia.

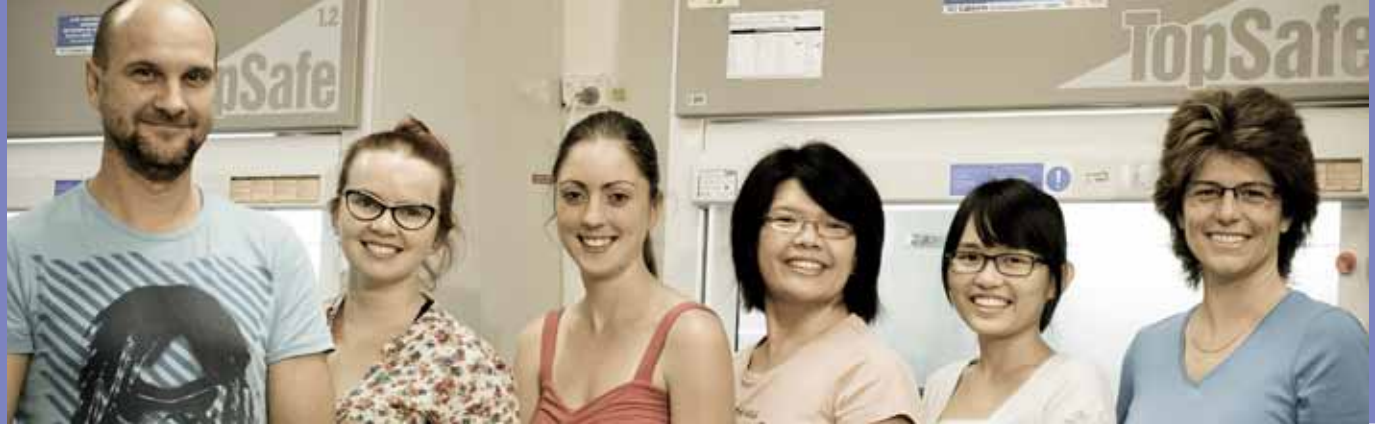
Despite recent advances in treatment, MM remains almost universally fatal with a 10 year survival rate of approximately 17%. The main clinical manifestations of MM are the development of osteolytic bone lesions, bone pain, hypercalcaemia, renal insufficiency, suppressed immunoglobulin production and increased BM angiogenesis. It is now widely accepted that most, if not all, MM is preceded by a premalignant MGUS (monoclonal gammopathy of uncertain significance) stage. However, the genetic factors which trigger the progression from asymptomatic MGUS to overt malignant MM remain to be determined.

Current projects are focused on identifying:

- key genetic changes that 'drive' the progression from asymptomatic MGUS to overt malignant MM
- novel BM microenvironmental factors which contribute to MM disease progression and
- novel signalling pathways with roles in mesenchymal stem cell differentiation which may be manipulated to increase bone formation in MM patients.



mTOR complexes are important in skeletal development
Osteoblast specific deletion of raptor or rictor results in a 11% reduction in animal height which is associated with a significant reduction in tibial growth plate thickness as measured by micro-computed tomography (microCT). Histological assessment of the tibial growth plate architecture shows a reduction in cartilagenous tissue (red stain). Bar=100μm



Steve Fitter | Mary Matthews | Jacqueline Noll | Catherine Gan | Chee Man Cheong | Vicki Wilczek

Key discoveries 2011

The Myeloma Research Laboratory has discovered:

Longitudinal examination of the global gene expression profile in PC derived from individual patients when first diagnosed with MGUS and subsequently with MM has identified key genes which drive MM disease progression.

Loss of function of the putative tumour suppressor gene *SAMSN1* contributes to the progression of MGUS to MM and is an indicator of poor prognosis in MM. Restoration of *SAMSN1* function inhibits disease progression in a mouse model of MM.

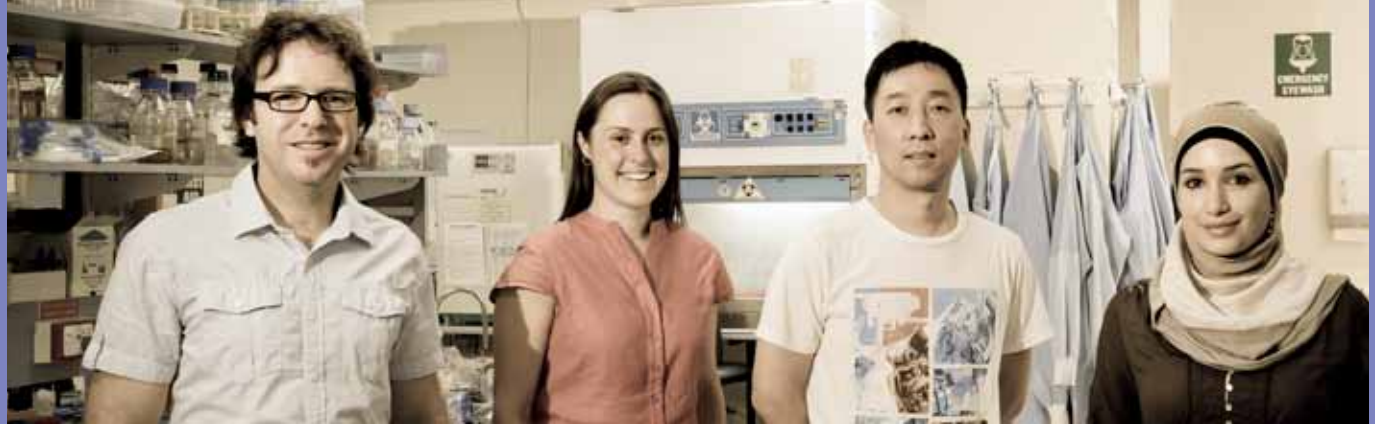
MM PC modify the BM microenvironment by inhibiting osteoblast differentiation and stimulating mesenchymal stem cell (MSC) proliferation to form an 'MSC-rich' niche which supports myeloma PC growth.

The mTORC1 and mTORC2 signalling pathways are critical regulators of MSC fate. Osteoblast-specific knockout of *raptor* (mTORC1) or *rictor* (mTORC2) leads to changes in embryonic and postnatal skeletal development.

Elevated N-cadherin expression in MM PC is associated with poor prognosis and can be used as a novel prognostic marker of high risk myeloma patients. Using a mouse model of MM, we show that therapeutic targeting of N-cadherin inhibits the homing to and growth of MM PC in the BM microenvironment.

Outcomes for the Community

In view of the diverse treatment options for multiple myeloma, the Medical and Scientific Advisory Group of the Australian Myeloma Foundation prepared *Clinical Practice Guidelines for Myeloma*, coordinated by Dr Hang Quach and Prof Miles Prince. These guidelines provide direction to specialist haematology and oncology physicians as to the most effective treatment strategies for MM. These guidelines are freely accessible on the Myeloma Foundation of Australia website: myeloma.org.au



Quenten Schwarz | Michaela Scherer | Xiangjun Xu | Samuela Kabbara

Neurovascular Research Laboratory

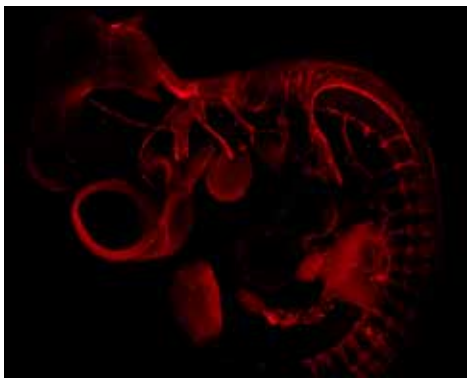
Dr Quenten Schwarz PhD

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

Recent advances, including our own, conclusively show that similar molecules are recruited by both systems to coordinate development.

Our laboratory is particularly interested in understanding the signaling pathways controlling neural stem cell development with the aim of idenitifying molecular defects underlying neurodevelopmental disorders including tumours, neurocristopathies and neuropsychiatric illness. Together, these disorders affect over 3% of the population and arise from aberrant neuronal development.

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



These images depict the emergence (left) and differentiation (below) of neural crest cells in the peripheral nervous system.

Left: Wnt1 is expressed in the dorsal ridge between the neural and non-neural epithelia to mark the region of neural crest cell formation at E9.5.

Below: neurofilament staining identifies differentiated neurons at E10.5

Rachael Lumb | Sophie Wiszniak | Eiman Saleh

Key discoveries 2011

Distinct stem cell precursors of sympathetic and sensory neurons

Neuroblastoma is the most prevalent extracranial solid tumour in childhood and is widely believed to arise from aberrant differentiation of sympathoadrenal neural crest stem cell precursors of sympathetic neurons and adrenal chromaffin cells. Our work has recently identified a cell surface marker of the sympathoadrenal neural crest cell precursors. By creating unique animal models to specifically mark these cells we are now using this knowledge to provide insight to the developmental programs of these cells during normal development.

Signalling molecules coordinating neural crest stem cell migration with differentiation

During development neural crest stem cells migrate extensively throughout the embryo to give rise to an immense variety of derivatives. Their choice of migration path is intimately linked to their developmental potential. A fundamental question in the neurodevelopment field has been the identity of the molecules that direct neural crest cells along spatially distinct pathways to coordinate migration with cell differentiation. Our work has shown that the cell surface receptors, Nrp1 and Nrp2, are expressed by different populations of neural crest cells to control their choice of migration path.

A key signalling molecule in neurodevelopment and schizophrenia

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

Outcomes for the Community

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

Lachlan Moldenhauer | Claudine Bonder | Lisa Ebert | Nikhil Thyagarajan | Katie Tooley

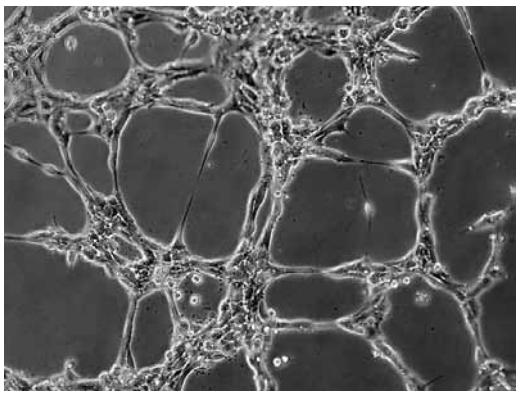
Vascular Biology and Cell Trafficking Laboratory

Dr Claudine Bonder PhD

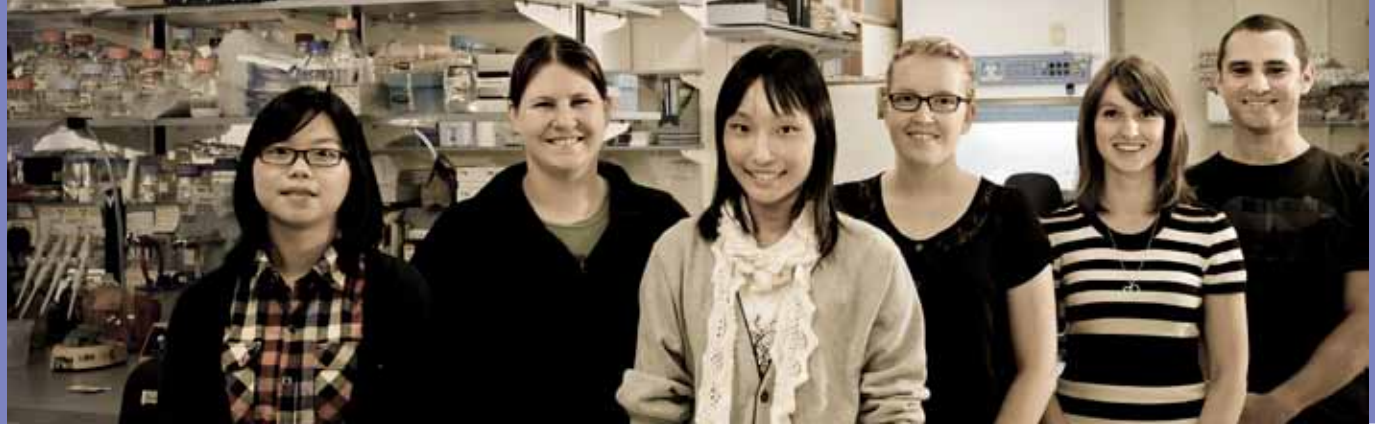
Blood vessels contribute to life threatening diseases but are also essential for tissue regeneration and organ transplantation. Our work may provide new opportunities to augment blood vessel development in patients with cardiovascular disease, and ablate blood vessel development in cancer patients.

Blood vessels contribute to life threatening diseases but are also essential for tissue regeneration and organ transplantation. Endothelial progenitor cells (EPCs) directly contribute to blood vessel formation (vasculogenesis) in physiological 'repair' processes of wound healing and foetal development as well as the pathological settings of cardiovascular disease, cancer, diabetes, arthritis and ischemia/reperfusion injury. More specifically, on the one hand, coronary artery disease and stroke patients have ~40% less circulating EPCs when compared to age-matched healthy controls; and on the other hand, recruitment of EPCs may be a mechanism by which cancer progresses, as reduced EPC mobilization was associated with impaired tumour vasculogenesis, reduced tumour formation and increased cancer patient survival. Because of this worldwide recognition that EPCs are key determinants of many life threatening and fatal diseases, there are currently over 180 clinical trials involving EPCs registered. However, initial results have not been promising with their lack of success likely due to the lack of distinct EPC markers for identification as well as insufficient EPC differentiation, survival and retention.

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



Blood vessel formation by endothelial cells
The use of a 3-dimensional matrix both *in vitro* and ***in vivo*** helps elucidate the vascular potential of cells and allows us to determine key pathways involved.



Lih Tan | Michaelia Cockshell | Wai Sun | Kate Parham | Emma Thompson | David Dimasi

Key discoveries 2011

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 that mainstay of treatment for symptomatic relief, their effectiveness is varied; thus, a better understanding of acute allergic reactions is required. In collaboration with Associate Professor Stuart Pitson, we have undertaken to examine the role of sphingosine kinase (SK) mediated P-selectin expression on ECs for the rapid recruitment of neutrophils. SK is a highly conserved lipid kinase that catalyses the phosphorylation of sphingosine to form sphingosine-1-phosphate. SK is ubiquitously expressed but stored at varying levels in different cell types. We have identified that i) histamine induced P-selectin expression on human umbilical vein ECs requires SK activity and (ii) that histamine-induced neutrophil rolling along the vasculature *in vitro* and *in vivo* is SK dependent. Administration of FTY720 (approved pro-drug for the treatment of multiple sclerosis) attenuates histamine-induced neutrophil recruitment (*Am J Pathol*, 2011 in press). Our contention that SK may be a target for developing new treatments to attenuate allergic inflammation was recognised by a three year NHMRC project grant to Dr Bonder.

Blood vessels are critical for pancreatic islet function:

Pancreatic islet transplantation is an emerging cure for Type 1 Diabetes but success is limited by death of insulin producing beta cells post-transplantation. Vasculogenic endothelial progenitor cells (EPCs) have the potential to improve islet engraftment, and may also improve islet graft function. In collaboration with Dr Claire Jessup and Assoc Professor Toby Coates we have combined EPC and islets into functional mosaic clusters *in vitro* and assessed the interactions between islets and EPC *in vitro* and *in vivo* in a diabetic mouse model of islet transplantation. To date we have shown that mosaic islet clusters can form successfully, using both rat and mouse cells and using confocal microscopy we have demonstrated distribution of EPC throughout rat mosaic islet clusters and glucose stimulation index function was superior to clusters comprised of islet cells only (*Penko Islets* 3: 1, 2011). This work has been recognized by a three year Medvet grant to Dr Jessup.

Defining a new EPC signature

To overcome the problems that preclude the clinical investigation of EPCs, we recently developed a protocol for human and rodent EPC isolation, culture and expansion and have made key discoveries in EPC differentiation where we observed that the enzyme sphingosine kinase (SK) 1 regulates the rate and direction of EPC differentiation without effect on the haematopoietic compartment (*Blood* 113: 2108-17, 2009).

In 2011 we extended this work to human cells. Briefly, primary human endothelial cells were altered to overexpress SK-1 and the ability of SK-1 to de-differentiate these cells was investigated. We observed that increasing SK-1, significantly increased the expression of progenitor cell markers as well as a key progenitor transcription factor NANOG and that ECs overexpressing SK-1 were similar to naturally occurring EPCs (*Microcirculation* 18:583, 2011). We recently executed the first gene expression analysis between naturally occurring human EPCs and their donor matched mature blood vessel endothelial cells. This study has identified new surface proteins on EPCs and together with the CRC for Biomarker Translation these proteins are being investigated for diagnostic and therapeutic potential. This work has been recognised by the funding of a three year NHMRC project grant to Dr Bonder. Our vision of identifying what controls EPC differentiation, survival and recruitment will ultimately target vasculogenesis and as such come closer to long lasting therapies and perhaps a cure.

Outcomes for the Community

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

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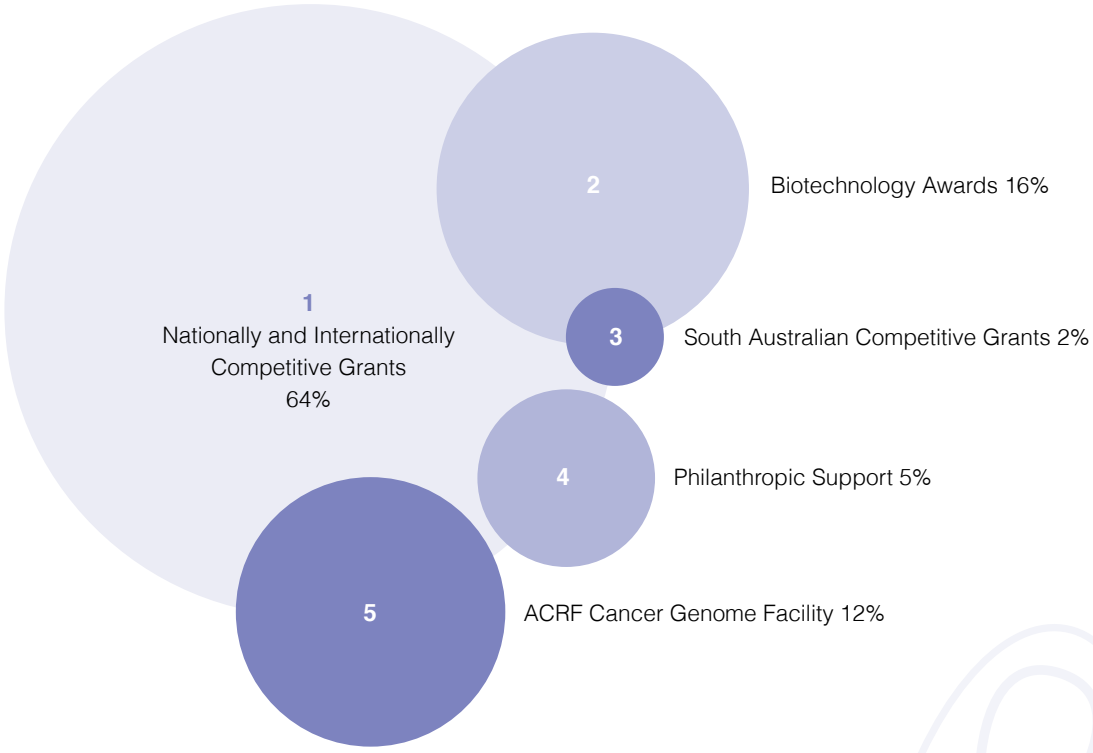
Financial Highlights

Research Income 2011

1	Nationally and Internationally Competitive Grants		8,973,646
2	Biotechnology Awards		2,320,809
3	South Australian Competitive Grants		238,454
4	Philanthropic Support		745,080
5	ACRF Cancer Genome Facility		1,725,500
	Total	AUD	14,003,489

All amounts shown are in Australian currency



New Grants and Fellowships Awarded in 2011

Investigator	Title	Granting Body
Anderson R, Gregory P, Goodall G, Johnstone C, Khew-Goodall Y, Phillips K	Regulation of breast cancer metastasis by miR-193b and miR-342-3p	National Health and Medical Research Council
Beard M, Eyre N, Turville S	Imaging the hepatitis C virus life cycle in living cells	National Health and Medical Research Council
Beard M, Carr J, Locarnini S	Analysis of Boceprevir drug susceptibility and resistance in HCV genotype 6	Merck Investigator Studies Program
Bonder C, Pitson S	A new target for allergic inflammation: the sphingolipid pathway	National Health and Medical Research Council
Bonder C, Shackleton M	A new biomarker for vascular progenitor cells	National Health and Medical Research Council
Bracken C, Goodall G	Uncovering global patterns of miRNA-mediated gene regulation in epithelial-mesenchymal transition	Association for International Cancer Research
Branford S, Hughes T, Scott H, Adelson D	Assessment of markers of genomic instability for the prediction of treatment response in chronic myeloid leukaemia	National Health and Medical Research Council
D'Andrea R, Wei A, Lewis I, To LB	GADD45A promoter methylation and poor prognosis in AML: mechanism and clinical significance	National Health and Medical Research Council
Dorstyn L	SACRC Senior Research Fellowship	South Australian Cancer Research Collaborative
Ebert L	Florey Fellowship	Royal Adelaide Hospital
Ekert P, Lopez A	A new survival pathway in haematopoietic cells	National Health and Medical Research Council
Gagliardi L, Torpy D, H Scott, C Hahn	Genetic studies of familial Cushing's syndrome due to ACTH-independent macronodular adrenal hyperplasia	The Gum Bequest for Endocrine Research, Royal Adelaide Hospital
Goodall G, Bracken C	Targets of epithelial microRNAs	National Health and Medical Research Council
Gronthos S, Zannettino A	Mesenchymal Stem Cell maintenance and recruitment during skeletal repair are dependent on EphB-ephrinB signalling	National Health and Medical Research Council
Harvey N	National Heart Foundation Career Development Fellowship	National Heart Foundation
Harvey N	Characterising signals important for lymphangiogenesis in development and disease	National Health and Medical Research Council
Harvey N	Defining the role of the ubiquitin protein ligase Nedd4 in vascular development	National Health and Medical Research Council
Hughes T, White D, Rasko J	Rational development of a bioassay-based treatment algorithm for kinase inhibitor therapy in CML	National Health and Medical Research Council
Khew-Goodall Y	A novel regulator of insulin-regulated glucose uptake	Diabetes Australia Research Trust
Khew-Goodall Y, Goodall G	Inhibiting cancer-associated fibroblasts activation in breast cancer by miR-29	South Australian Health & Medical Research Institute
Kumar S	Understanding the role of caspase-2 in cellular stress response and aging	National Health and Medical Research Council
Kumar S	Physiological function of Nedd4-2 in regulating ENaC and CFTR	National Health and Medical Research Council
Lewis I	Developing immunotherapy for cancer	Education Investment Fund, Super Science Initiative
Lewis ID, D'Andrea RJ	Identification of candidate acute myeloid leukaemia genes using a genetic screen in mice	RAH Contributing Haematologists' Committee
Lopez A, Kumar S, Scott, H	Translating Health Discovery into Clinical Applications	Dept of Industry, Innovation, Science, and Research

Investigator	Title	Granting Body
McCartney E	The role of Stat3 in the life cycle of hepatitis C virus and hepatocellular carcinoma development	Royal Adelaide Hospital
Melo J, Whitelaw M, Johnson B	Transcriptional and post-transcriptional regulation of the BCR-ABL gene in chronic myeloid leukaemia	Cancer Council of South Australia
Melo J, Hughes T, Johnson B	Transcriptional regulation of the BCR-ABL oncogene	RAH Contributing Haematologists' Committee
Pitson SM	Fay Fuller Foundation Fellowship	Fay Fuller Foundation
Pitson SM, Powell JA, Pitman MR, D'Andrea RJ	Targeting sphingosine kinase as a therapy for childhood leukemia	Channel 7 Children's Research Foundation
Samuel M	Understanding how cancers progress from benign to malignant forms	National Health and Medical Research Council
Samuel M	Elucidating the outcomes of ROCK activation, a potential preventative and therapeutic target	Royal Adelaide Hospital
Schwarz Q	How does VEGF control heart development?	National Heart Foundation
Scott H	NHMRC Principal Research Fellowship with Clinical Support Enhancement Option	National Health and Medical Research Council
Scott H, Hahn C, Fuller S, Horwitz M, Adelson D	Identification of genes responsible for familial predispositions to haematological malignancies	National Health and Medical Research Council
To LB, Hughes T, Lopez A, Zannettino A, Scott H, D'Andrea R, Kuss B, Lewis I, Cambareri T, White D	South Australian Blood Cancer Tumour Bank	SA Cancer Research Collaborative, MedVet Science, and Community donor
White D, Hughes T, D'Andrea R	Characterisation of a new poor-risk sub-category of chronic phase chronic myeloid leukaemia	National Health and Medical Research Council
Zannettino A, Purton L, To LB	Does modifying the bone marrow stromal microenvironment alter the disease course of multiple myeloma?	Cancer Council South Australia / SAHMRI
Zannettino A, Gronthos S, Fitter S	The role of raptor and rictor signalling pathways in osteogenesis and mesenchymal stem cell fate determination	National Health and Medical Research Council
Zannettino A, To LB	Is elevated N-cadherin expression a poor prognostic indicator in multiple myeloma patients?	Cancer Australia and Leukaemia Foundation of Australia

Seminar Program

Prof Nick Nicola
Joint Division Head, Cancer and Haematology Laboratory, Walter & Eliza Hall Institute, Melbourne
Molecular mechanism of action of Suppressor of Cytokine Signalling 3 (SOCS3) 24/02/11

Prof James Whisstock
ARC Federation Fellow, Honorary NHMRC Principal Research Fellow, Monash University, Melbourne
A common fold mediates immune defence and bacterial attack: Structural studies on perforin and perforin-like proteins 10/03/11

Prof René St-Arnaud
Professor of Medicine, Surgery and Human Genetics McGill University, Montreal, Canada
Post-translational modifications regulating the activity of the alphaNAC transcriptional regulator in bone 17/03/11

Prof John Hamilton
NHMRC Senior Principal Research Fellow University of Melbourne
Colony stimulating factors, macrophage populations and inflammatory/autoimmune disease 24/03/11

Prof Jozef Gecz
Head, Neurogenetics, Genetics and Molecular Pathology, University of Adelaide
Capitalising on genomics to understand the biology of neurological disorders 31/03/11

Prof Ashley Dunn
Honorary Professorial Fellow, University of Melbourne
Charles Darwin: Back to the Future 7/04/11

Prof David Adelson
Head, School of Molecular and Biomedical Science, University of Adelaide
Retrotransposon Defined Ancestral Territories in Mammalian Genomes 14/04/11

Prof Andras Nagy
Mount Sinai Hospital, Samuel Lunenfeld Research Institute, Toronto, Canada
VEG-A: the double-edged sword in cancer 21/04/11

Prof Tony Burgess
Ludwig Institute for Cancer Research, Melbourne
Colon cancer cell biology: Interactions between wnt signalling and LGR5 28/04/11

Dr Michael Piper
NHMRC Research Fellow, School of Biomedical Science, and Queensland Brain Institute
Transcriptional control of gliogenesis in development and disease 5/05/11

Assistant Prof Sudha Rao
Faculty of Applied Science, University of Canberra
The Duplicity of Protein Kinase C theta: A novel role in modulating gene expression programs and microRNAs 12/05/11

Dr James Godwin
Senior Research Fellow, Australian Regenerative Medicine Institute (ARMI), Monash University, Melbourne
Investigating the requirements for scar-free wound healing and regeneration in the salamander 19/05/11

Prof Christophe Marcelle
Professor, Australian Regenerative Medicine Institute (ARMI) Monash University, Melbourne
Morphogenesis and Growth of Skeletal Muscles in Vertebrate Embryos 26/05/11

Dr Simon Phipps
Senior Lecturer, School of Biomedical Sciences, University of Qld, Brisbane
Defective innate anti-viral pathways underlie the inception and progression of asthma 2/06/11

Dr Peter Farlie
Group Leader, Craniofacial Research, Murdoch Children's Research Institute, Melbourne
Identifying the molecular regulators of skeletal morphogenesis and development 9/06/11

Prof Julio Licinio
Director, John Curtin School of Medical Research, Canberra
Pharmacogenomic approaches to obesity and depression 23/06/11

Dr Bryan Haines
Lecturer, Discipline of Biochemistry, School of Molecular and Biomedical Science, University of Adelaide
Leucine rich repeat transmembrane proteins: Novel regulators of cell signalling during mouse development 30/06/11

Assoc Prof Maarten van den Buuse
NHMRC Senior Research Fellow; Head, Behavioural Neuroscience Lab, Mental Health Research Institute, Melbourne
Neurodevelopmental animal models of schizophrenia 7/07/11

Dr Heather Young
NHMRC Senior Research Fellow, Anatomy & Cell Biology, University of Melbourne
Getting to the guts of neural crest cell migration 14/07/11

Dr Michael Samuel
Group Leader, Cancer Models and Tissue Biology, Centre for Cancer Biology, Adelaide
The Rho/ROCK signalling axis: Regulating tissue rheology and tumour progression 21/07/11

Dr Ben Croker
Laboratory Head, Inflammation Laboratory Walter & Eliza Hall Institute, Melbourne
Regulation of inflammation by a death receptor 28/07/11

Dr Mark Hutchinson
ARC Research Fellow, Neuroimmunopharmacology Laboratory Leader, University of Adelaide
Exploring the neuroimmunopharmacology of opioids: Implications for pain, drug abuse liability and beyond 4/08/11

Dr James Murphy
Researcher, Molecular Medicine
Walter & Eliza Hall Institute, Melbourne
A novel molecular mechanism by which the key hematopoietic protein kinase, Jak2, is negatively regulated 11/08/11

Dr Edwina McGlinn
EMBL Australia Partner Group Leader, Australian Regenerative Medicine Institute, Monash University, Melbourne
A role for miR-196 in patterning the early vertebrate embryo 18/08/11

Dr Benjamin Kile
Laboratory Head, Cancer and Haematology,
Walter & Eliza Hall Institute, Melbourne
Apoptotic processes in megakaryocyte and platelet function 25/08/11

Dr Steven Lane
Team Hesad, Translational Leukaemia Research,
Queensland Institute of Medical Research (QIMR), Brisbane
Characterizing the disease initiating cell population in a murine model of Jak2V617F-positive myeloproliferative neoplasm 1/09/11

Dr Scott Mueller
ARC QEII Fellow, Department of Microbiology and Immunology
University of Melbourne
Intravital imaging reveals distinct memory CD4+ and CD8+ T cell migration patterns in the skin 8/09/11

Prof David Jans
NHMRC Senior Principal Research Fellow
Monash University, Melbourne
Nucleocytoplasmic Trafficking of Gene Products from RNA Viruses: Targets for Anti-virals 15/09/11

Assoc Prof Stuart Pitson
NHMRC Senior Research Fellow; Head, Molecular Signalling Lab,
Centre for Cancer Biology
Sphingosine kinase signalling in cancer 22/09/11

Assoc Prof Jean-Pierre Levesque
Senior Research Fellow, Haematopoietic Stem Cell Laboratory
Mater Medical Research Institute, Brisbane
Can a bone keep haematopoietic stem cells happy in their niche? 6/10/11

Dr Nicolas Plachta
EMBL Australia Group Leader, Australian Regenerative Medicine Institute (ARMI), Monash University, Melbourne
Imaging gene regulatory molecules in living mouse embryos 13/10/11

Assoc Prof Grant McArthur
Consultant Medical Oncologist; Head, Translational Research Group; Head, Molecular Oncology Laboratory, Peter MacCallum Cancer Centre, Melbourne
Targeting Oncogenes for the Treatment of Cancer: Successes and Opportunities 20/10/11

Dr Christian Engwerda
Group Leader, Immunology and Infection Laboratory,
Queensland Institute of Medical Research, Brisbane
Immune regulation during parasitic diseases 3/11/11

Dr Alex Swarbrick
Group Leader, Tumour Progression Group, Cancer Program,
Garvan Institute of Medical Research, Sydney
Arrested Development: Developmental pathways controlling cancer phenotype 10/11/11

Dr Marnie Blewitt
Laboratory Head, Molecular Medicine,
Walter & Eliza Hall Institute, Melbourne
Epigenetic control in haematopoietic stem cells 17/11/11

Prof Jérôme Galon
Research Director, Integrative Cancer Immunology Laboratory,
Cordeliers Research Center, Paris, France
Immune contexture: A novel paradigm for cancer 29/11/2011

Prof Heddy Zola, Ms Tracie Dawber, Mr Quinton Swanepoel
Research Director; Business Performance and Continuity Manager;
Director Commercial Contracts & Proposal Managment
SA Pathology Staff Presentation 1/12/11

Dr Aleksandra Filipovska
Head, Mitochondrial Medicine & Biology, WAIMR, Perth
The human mitochondrial transcriptome and its regulation by nuclear encoded proteins 8/12/11

Invited Presentations

Acute Leukaemia Laboratory

Assoc Professor Richard D'Andrea

Invited Speaker and/or Session Chair:

Haematology Society of Australia & New Zealand (HSANZ), SA Annual Scientific Meeting. Adelaide, September

Human Genetics Society of Australia, SA Branch Annual Symposium. Adelaide, September

Grand Round: The Queen Elizabeth Hospital. Adelaide, July

Australasian Society of Cytogeneticists (ASoC) and Molecular Genetics Society of Australasia (MGSA) Combined Scientific Meeting. Adelaide, March

Cell Signalling Laboratory

Dr Yeesim Khew-Goodall

Invited Speaker and/or Session Chair:

5th Barossa Meeting: Cell Signalling and Molecular Medicine. Barossa Valley, South Australia, November

The International EMT Conference. Singapore, October

ComBio 2011. Cairns, Australia. September

Cytokine Receptor Laboratory

Prof Angel Lopez

Invited Speaker and/or Session Chair:

41st Australasian Society for Immunology Conference. Adelaide, December

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

Peter Mac for the VCCC Joint Seminar Series. Melbourne, October

ANZAC Research Institute's 10th Annual Symposium. Sydney, August

ESH Conference. Mandelieu, France. May

Colloquium at University of Buenos Aires, Argentina. February

Conference Convenor:

5th Barossa Meeting: Cell Signalling and Molecular Medicine. Barossa Valley, South Australia, November

Gene Regulation Laboratory

Professor Gregory Goodall

Invited Speaker and/or Session Chair:

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

AMATA 2011. Canberra, October

ComBio 2011. Cairns, Australia. September

Australian and New Zealand Society of Nephrology Annual Scientific Meeting. Adelaide, September

Plenary Lecturer, Endocrine Society of Australia and APEG Combined Meeting. Perth, August

RCPA Short Course on Medical Genetics and Genetic Pathology. Melbourne, August

Prof John Wallace Festschrift Symposium. Adelaide, July

Keystone Symposium: Epithelial Plasticity and Epithelial to Mesenchymal Transition. Vancouver, Canada. February

Conference Convenor:

5th Barossa Meeting: Cell Signalling and Molecular Medicine. Barossa Valley, South Australia. November

Dr Cameron Bracken

5th Barossa Meeting: Cell Signalling and Molecular Medicine. Barossa Valley, South Australia. November

ComBio 2011. Cairns, Australia. September

Dr Philip Gregory

12th Australasian Prostate Cancer Conference. Melbourne, August

Haematology Clinical Research Unit

Professor L Bik To

Keynote Speaker:

5th Asia Pacific Transplantation Forum. Shanghai, China. May

Invited Speaker and/or Session Chair:

RAAF Base presentation, Edinburgh, South Australia. September

HAA 2011: HSANZ Masterclass Number 2. Sydney, October

Hong Kong Society of Haematology. Hong Kong, May

Associate Professor Ian Lewis

Invited Speaker and/or Session Chair:

Haematology Society of Australia & New Zealand Annual Scientific Meeting. Sydney, October

Plenary Speaker: Australian Institute of Medical Scientists and New Zealand Institute of Medical Laboratory Science: South Pacific Congress. Gold Coast, Qld. August

Asia Pacific Transplant and Hematology Forum. Shanghai, China. May

Hepatitis C Virus Research Laboratory

Assoc Professor Michael Beard

Invited Speaker and/or Session Chair:

18th International meeting on HCV and Related Viruses. Seattle, USA. September

Australian Society of Microbiology Symposium. Hobart, July

4th Sino-Australian Meeting on Infectious Diseases. Melbourne, July

Australian Institute for Infectious Diseases (AID), University of Queensland. Brisbane, June

Leukaemia Unit, Genetics and Molecular Pathology

Assoc Professor Susan Branford

Invited Speaker and/or Session Chair:

Brazilian Hematology Congress Satellite Symposium and Meet the Expert session. São Paulo, Brazil. November

Ariad Pharmaceuticals: Workshop Meeting. Boston, USA. November

Fifth National Histotechnology Meeting. Sydney, November

Satellite Symposium at the Haematology Society of Australia and New Zealand Annual Meeting. Sydney, October

European School of Hematology 13th International Conference on CML: Biology and Therapy. Estoril, Portugal. September

Journal Club meetings in Sydney: Westmead Hospital, Concord Hospital and St George Hospital. Sydney, August

Novartis Oncology Asia Pacific Summit 2011. Singapore, July

Nilotinib Molecular Steering Committee Meeting. Prague, Czech Republic. June

Sansom Weekly Seminar series, University of South Australia. Adelaide, June

Satellite Symposium at the 2011 Highlights of ASH in Latin America meeting. Punte Del Este, Uruguay. April

Preceptorship Latin American Meeting, Fundaleu Hospital, Buenos Aires. April

Singapore Society of Haematology annual meeting Symposium. Singapore, April

Novartis Mexico VI Post-ASH Meeting. Dallas, USA. February

Nilotinib Molecular Steering Committee Meeting. Mannheim, Germany. January

Leukaemia Biology Group

Professor Junia V. Melo

Keynote Speaker:

New Frontiers in Myeloid Malignancies Meeting of the European Leukemia Net (ELN). Berlin, Germany. October

Invited Speaker and/or Session Chair:

Educational Session on Chronic Myeloid Leukemia at the 53rd Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December

Year 2011 Working Conference on Cancer Stem Cells. Vienna, Austria. September

16th Congress of the European Hematology Association (EHA-16). London, UK. June

Novartis Oncology 9th LEAD (Leading Experts Advising on Development) Summit. Prague, Czech Republic. June

20th Porto Cancer Meeting. Porto, Portugal. April

Lymphatic Development Laboratory

Dr Natasha Harvey

Invited Speaker and/or Session Chair:

5th Barossa Meeting: Cell Signalling and Molecular Medicine, Barossa Valley, South Australia. November

ComBio 2011. Cairns, Australia. September

19th Annual Australian Vascular Biology Society Meeting, Bowral, Australia. September

Flinders University, Adelaide, March

Mast Cell Laboratory

Dr Michele Grimbaldeston

Invited Speaker and/or Session Chair:

41st Australasian Society for Immunology Annual Meeting. Adelaide, December

Molecular and Experimental Pathology Society of Australasia Annual Meeting. Brisbane, December

5th Barossa Meeting: Cell Signalling and Molecular Medicine. Barossa Valley, South Australia. November

Queensland Institute of Medical Research. Brisbane, October

Adelaide Immunology Retreat-7. Warrawong Wildlife Sanctuary, Adelaide. September

Melbourne University, Immunology Seminar Series. Melbourne, March

Invited Presentations continued

Mast Cell Laboratory continued

Dr Michael Samuel

Invited Speaker and/or Session Chair:

5th Barossa Meeting: Cell Signalling and Molecular Medicine. Barossa Valley, South Australia. November

ComBio 2011. Cairns, Australia. September

Department Seminar Series, School of Molecular and Biomedical Science, University of Adelaide. Adelaide, August

Diamantina Institute Seminar Series. Brisbane, June

Garvan Institute Seminar Series. Sydney, June

Ludwig Institute Seminar Series. Melbourne, June

RNA Interest Group. Adelaide, June

Melissa White Memorial Laboratory

Professor Timothy Hughes

Invited Speaker and/or Session Chair:

HAA, Sydney. October/November

13th European School of Haematology/International CML Foundation Conference. Estoril, Portugal. September

16th Congress of European Haematology Association, Satellite Symposium. London, UK. June

BTG (Bridge the Gap) International Hematology Conference, Singapore. March

Global Opinion Leader Summit on Chronic Myeloid Leukaemia. Basel, Switzerland. March

Middle East Oncology Summit. Dubai, UAE. February

Conference Convenor:

13th European School of Haematology: International Chronic Myeloid Leukaemia Foundation. Estoril, Portugal. September

Assoc Professor Deborah White

Invited Speaker and/or Session Chair:

American Society of Haematology ASM: CML Therapy. San Diego, December.

Leukaemia and Lymphoma Society (USA) Translational Science Meeting. New York, November

CML Preceptorship (COLT) Program. Adelaide, October

Novartis ENESTxtnd Clinical Trial Launch. Melbourne, March; Brisbane, May; Sydney, October

CML: Biological Basis of Therapy. Estoril, Portugal. September

Flinders University Medical Research Forum Lecture Series. Adelaide, June

Pharmacology Lecture Series. University of Adelaide. Adelaide, June

Molecular Pathology Research Laboratory

Professor Hamish Scott

Invited Speaker and/or Session Chair:

Nepean Hospital Scientific Day. Sydney, November

12th International Congress of Human Genetics and the 61st Annual Meeting of the American Society of Human Genetics. Montreal, Canada. October

Australian Genome Research Facility (AGRF), next generation sequencing special interest group. Adelaide, May

South Australian Government, Department of Health, Health and Wellbeing tour. Adelaide, May

Australasian Society of Cytogeneticists (ASoC) and Molecular Genetics Society of Australasia (MGSA) Combined Scientific Meeting. Adelaide, March

Molecular Regulation Laboratory

Professor Sharad Kumar

Invited Speaker and/or Session Chair:

Project Grants Workshop, University of Technology. Sydney, December

ANZSCDB Adelaide Cell and Developmental Biology Symposium. Adelaide, November

5th Barossa Meeting, Cell Signalling and Molecular Medicine. Barossa Valley, South Australia. November

University of Rome Tor Vergata. Rome, Italy. October

School of Medical Sciences, RMIT. Bundoora, Victoria. October

International Symposium on Intracellular Proteolysis and Cancer. Valencia, Spain. October

1st Australian Workshop on Cell Death. Lindeman Island, Queensland. August

Peter McCallum Cancer Institute. Melbourne, May

Biochemistry Seminar, Monash University. Clayton, Victoria. May

36th Lorne Conference on Protein Structure and Function. Lorne, Victoria. February

Ubiquitin and ubiquitin-like protein: Satellite Meeting. Melbourne, Victoria. February

Dr Loretta Dorstyn

1st Australian Workshop on Cell Death. Lindeman Island, Queensland. August

Dr Donna Denton

1st Australian Workshop on Cell Death. Lindeman Island, Queensland. August

Mr Joey Puccini

1st Australian Workshop on Cell Death. Lindeman Island, Queensland. August

Molecular Signalling Laboratory

Assoc Professor Stuart Pitson

Invited Speaker and/or Session Chair:

ComBio2011. Cairns, Australia. September

FASEB Summer Research Conference on Lysophospholipid Mediators in Health and Disease. Ciocco, Barga, Italy. August

Conference Convenor:

5th Barossa Meeting: Cell Signalling and Molecular Medicine, Barossa Valley, South Australia. November

Myeloma Research Laboratory

Professor Andrew Zannettino

Invited Speaker and/or Session Chair:

Myeloma Foundation of Australia, Medical and Scientific Advisory Committee Meeting. Sydney, October

School of AMME/Faculty of Engineering and IT and Bosch Institute, University of Sydney. Sydney, October

Combined Probus Club of West Beach Inc. Adelaide, September

2nd Asia Pacific Osteoporosis and Bone Meeting, IOF/ANZBMS. Gold Coast, Queensland, September

Neurovascular Research Laboratory

Dr Quenten Schwarz

Invited Speaker and/or Session Chair:

5th Barossa Meeting, Cell Signalling and Molecular Medicine. Barossa Valley, South Australia. November

ANZSCDB Adelaide Cell and Developmental Biology Symposium. Adelaide, November

ComBio2011. Cairns, Australia. September

Early career research network, RIAUS

Vascular Biology and Cell Trafficking Laboratory

Dr Claudine Bonder

Invited Speaker and/or Session Chair:

41st Australasian Society for Immunology Annual Meeting. Adelaide, December

The 5th Barossa Meeting: Cell Signalling and Molecular Medicine. Barossa Valley, South Australia. November

Australian Society for Medical Research, SA Meeting. Adelaide, June

Queen Elizabeth Hospital seminar series. Adelaide, May

Conference Convenor:

41st Australasian Society for Immunology Annual Meeting. Adelaide, December

Awards

Gene Regulation Laboratory

Greg Goodall
NHMRC Senior Research Fellowship

Philip Gregory
Australian Institute of Policy and Science 2011 Tall Poppy Award

Philip Gregory
South Australian Cancer Research Collaborative Senior Research Fellowship

Emily Paterson
PhD Thesis Research Excellence Award
2011 Centre for Cancer Biology Prize
(Sponsor: ASI)

Hepatitis C Virus Research Laboratory

Erin McCartney
PhD with Special Commendation

Sumudu Narayana
APA Scholarship

Leukaemia Biology Group

Junia V. Melo
2011 NHMRC '10 of the Best' Research Projects of the past ten years for the 2007 project grant (Timothy Hughes & Junia V. Melo)

Lymphatic Development Laboratory

Kelly Betterman
PhD with Commendation

Kelly Betterman
Best Postdoctoral Oral Presentation, ANZSCDB
Adelaide Cell and Development Biology Symposium

Kelly Betterman
Winner, Annual Images of the ANZSCDB Competition

Natasha Harvey
National Heart Foundation Career Development Fellowship

Melissa White Memorial Laboratory

Jane Engler
Best CCB Student Publication
2011 Centre for Cancer Biology Prize
(Sponsor: Miltenyi)

Devendra Hiwase
PhD Thesis Research Excellence Award
2011 Centre for Cancer Biology Prize
(Sponsor: BD)

Timothy Hughes, Deborah White and Colleagues
2011 National Health and Medical Research Council
10 of the Best Research Projects

Deborah White and Colleagues
Best Publication from a CCB Researcher
2011 Centre for Cancer Biology Prize
(Sponsor: Miltenyi)

Molecular Pathology Research Laboratory

Hamish Scott
NHMRC Principal Research Fellowship
with Clinical Support Enhancement Option

Lucia Gagliardi
Eli Lilly Bryan Hudson Clinical Endocrinology Award

Lucia Gagliardi
Endocrine Society of Australia Travel Grant

Molecular Regulation Laboratory

Loretta Dorstyn
Inaugural South Australian Cancer Research Collaborative
Senior Research Fellowship

Donna Denton and Shannon Nicolson
Best Overall Poster Award
ANZSCDB Adelaide Cell and Developmental Biology Symposium

Donna Denton
Affiliate of the University of Adelaide

Jantina Manning
CCB Early Career Researcher Award
2011 Centre for Cancer Biology Prize
(Sponsor: Qiagen)

Joey Puccini
Best Student Poster Award at the ANZSCDB
Adelaide Cell and Developmental Biology Symposium

Molecular Signalling Laboratory

Kate Jarman
PhD Thesis Research Excellence Award
2011 Centre for Cancer Biology Prize
(Sponsor: ASBMB)

Melissa Pitman
Travel Fellowship and Collins Bursary
Australian Society for Biochemistry and Molecular Biology

Stuart Pitson
2011 Merck Millipore Research Medal
Australian Society for Biochemistry and Molecular Biology

Myeloma Research Laboratory

Kate Vandyke
University of Adelaide Doctoral Research Medal
for Medical Science

Neurovascular Research Laboratory

Dr Quenten Schwarz
BioSA 2011 SA Young Achiever Award

Vascular Biology and Cell Trafficking Laboratory

Lisa Ebert, Tall Poppy Finalist

Lisa Ebert, Florey Fellowship

Victoria Montandon
Heart Foundation Summer Scholarship, 2011–12

Kate Parham, PhD student
Australaisian Society for Immunology Poster Award

Wai Yan Sun, PhD student
Australasian Society for Immunology Poster Award

Wai Yan Sun, PhD student
Adelaide Research and Innovation Pty Ltd
Best Commercialisation Potential

Devendra Hiwase was presented with a PhD Thesis Research Excellence Award, sponsored by BD, at the inaugural CCB annual general meeting by the Hon John Hill MP, Professor Joseph Trapani and Professor John Wallace.

Jantina Manning pictured with Qiagen representative Cath Moore, the Hon John Hill MP and Professor Joseph Trapani received the 2009/10 CCB Early Career Researcher Award.

Associate Professor Deborah White pictured with Miltenyi Biotech representative Astrid Lefringhausen, the Hon John Hill MP and Prof Joseph Trapani received the Award for the 2009/10 Best Publication from a CCB Researcher.

Research Staff and Students

Acute Leukaemia Laboratory

Richard D'Andrea
Ian Lewis
Sarah Bray
Anna Brown
Carolyn Butcher
Sonya Diakiw
Grant Engler
Chung Kok
Michelle Perugini
Diana Salerno
Amilia Wee

Students

Nick Li (Hons)
Nisha Rao (PhD)
Teresa Sadras (PhD)
Nur Hezrin Shahrin (PhD)

Cell Growth and Differentiation Laboratory

Mark Guthridge
Emma Barry
Jason Powell

Students

Yang Kong (PhD)
Daniel Thomas (PhD)
Nhan Truong (PhD)

Cell Signalling Laboratory

Yeesim Khew-Goodall
Leila Belle (nee Wyatt)
Lesley Crocker
Samuel Dyer
Freya Gehling
Xiaochun Li
Ana Lonic

Students who completed their degrees in 2011

Leila Belle (nee Wyatt) (PhD)
James Paltridge (Hons)

Cytokine Receptor Laboratory

Angel Lopez
Mara Dottore
Sue Heatley
Tim Hercus
Rebecca Krake
Barbara McClure
Melanie Pudney
Natasha Pyne
Hayley Ramshaw
Anna Sapa
Frank Stomski

Students

Nicole Christie (PhD)
Phillip Nguyen (B Med Sci Hons)
Daniel Thomas (PhD)
Karthik Venkataraman (B Med Sci Hons)

Students who completed their degrees in 2011

Jarrod Sandow (PhD)

Gene Regulation Laboratory

Greg Goodall
Matthew Anderson
Joanne Attema
Andrew Bert
Cameron Bracken
Philip Gregory
Kimi Honma
Narelle Mancini
Emily Paterson
Suraya Roslan
Rosemary Sladic
Anna Tsykin
Josephine Wright

Students

Natasha Kolesnikoff (PhD)
Yat Yuen Lim (PhD)
Daniel Thomson (PhD)
Victoria Arnet (Hons)

Haematology Clinical Research Laboratory

L Bik To
Ian Lewis
Peter Bardy
Pratyush Giri
Noemi Horvath
Cindy Lee
Simon McRae
Marion Roberts

Clinical Trial Coordinators

Lisa Carne
Kylie Chapman
Chris Hoare
Tania Lewis
Bronwen Ortlepp
Che To
Mengjun Zhu

Data Managers

Venus Au
Brian Gue
Andrew Vanlint

Scientific Staff

Malgorzata Badowicz
Richard Bright
Tony Cambareri
Elizabeth Duncan
Pam Dyson
Peter Harrison
Smita Hiwase
Monica Kutyna
Kerry Munro
Thanh Nguyen
Trevor Rawling
Susan Rodgers
Judy Stevens
Michael Vo

Hepatitis C Virus Research Laboratory

Michael Beard
Amanda Aloia
Nicholas Eyre
Karla Helbig
Kylie Van der Hoek
Erin McCartney
Gemma Sharp

Students

Guillaume Fiches (PhD)
Jason Gummow (Hons)
Kate Muller (PhD)
Sumudu Narayana (PhD)
Eddie Tse (PhD)

Students who completed their degrees in 2011

Erin McCartney (PhD)

Leukaemia Unit, Genetics and Molecular Pathology

Susan Branford
Emma Channon
Chani Field
Linda Fletcher
Jasmina Georgievski
Bronte Jamison
Wendy Parker
Stuart Phillis
Haley Prime
Jodi Prime
Eve Raets
Brad Sullivan
Alex Yeoman
Goldy Yong

Students

Zoe Donaldson (Hons)

Leukaemia Biology Group

Junia V Melo
Debora Casolari
Duncan Hewett
Brett Johnson
Vicki Wilczek

Students

Stanley (Ka Chun) Cheung (PhD)
Bradley Chereda (PhD)
Fong Chan Choy (Hons)
Gink Nanxing Yang (Hons)

Lymphatic Development Laboratory

Natasha Harvey
Jan Kazenwadel
Genevieve Secker

Students who completed their degrees in 2011

Kelly Betterman (PhD)

Mast Cell Laboratory

Michele Grimbaldeston
Michael Samuel
Lisa Biggs
Boris Fedoric
Emma Gordon
Houng Taing
Kwok Ho Yip

Students

Joanne Giermanski (B Med Sci Hons)
Kaitlin Scheer (Undergrad)
Anastasia Yu (PhD)

Students who completed their degrees in 2011

Renee Gilbey (Hons)

Melissa White Laboratory

Timothy Hughes
Deborah White
Stephanie Arbon
Bronwyn Cambareri
Phuong Dang
Amity Frede
Jarrad Goyne
Devendra Hiwase
Chung Hoow Kok
Tamara Leclercq
Jenny McLean
Eva Nievergall
Kelvin Groot Obbink
Verity Saunders
Carine Tang
Ljiljana Vidovic
David Yeung

Students

Laura Eadie (PhD)
Oi-Lin Lee (PhD)
Lisa Schafranek (PhD)
Dale Watkins (PhD)
Jackie Wong (PhD)

Students who completed their degrees in 2011

Devendra Hiwase (PhD)
Liu Lu (Hons)
Carine Tang (PhD)

Molecular Pathology Research Laboratory

Hamish Scott
Christopher Hahn
Milena Babic
Peter Brautigan
Alicia Byrne
Lucia Gagliardi
Young Lee
Brita Ardesjö Lundgren
Wendy Parker
Lih Tan

Students

Chan Eng Chong (PhD)
Zoe Donaldson (Hons)
Scott Warming (Hons)

Molecular Regulation Laboratory

Sharad Kumar
May Aung-Htut
Natasha Boase
Hazel Dalton
Donna Denton
Loretta Dorstyn
Natalie Foot
Jantina Manning
Kathryn Mills
Shannon Nicolson
Sonia Shalini
Claire Wilson
Wenying Zhu

Students

Joey Puccini (PhD)

Molecular Signalling Laboratory

Stuart Pitson
Kristy Alexander
Carl Coolen
Lorena Davies
Julia Dobbins
Briony Gliddon
Tamara Leclercq
Paul Moretti
Duyen Pham
Melissa Pitman
Joanna Woodcock

Students

Huasheng Chan (PhD)

Students who completed their degrees in 2011

Heidi Neubauer (Hons)

Myeloma Research Laboratory

Andrew Zannettino
Jenny Drew
Stephen Fitter
Duncan Hewett
Manami Ito
Sally Martin
Jacqueline Noll
Sharon Paton
Vicki Wilczek
Sharon Williams
Hongsheng Wang

Students

Chee Man Cheong
Lachlan Cooper
Catherine Gan
Carmen Macsai
Natalia Martin
Mary Matthews
Shriram Nath
James Richardson

Students who completed their degrees in 2011

Kate Vandyke (PhD)

Neurovascular Research Laboratory

Quenten Schwarz
Esamuela Kabbara
Michaela Scherer
Sophie Wiszniak
Xiangjun Xu

Students

Rachael Lumb (Hons)
Eiman Saleh (PhD)

Vascular Biology and Cell Trafficking Laboratory

Claudine Bonder
Lisa Ebert
Michaelia Cockshell
David Dimasi
Lachlan Moldenauer
Emma Thompson
Katie Tooley

Students

Kate Parham (PhD)
Wai Yan Sun (PhD)

Students who completed their degrees in 2011

Emma Thompson (Hons)
Daniella Penko (Hons)

Organisational Chart

Supporting Our World Class Research

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

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These can be from 1–5 years and can be named after a family, a family member, or a company.

Contact

For all support enquiries or donations, please contact us on
+61 8 8222 3422, email Anna.Nitschke@health.sa.gov.au
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or

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Our Supporters

The Centre for Cancer Biology wishes to thank all of our supporters and sponsors for their significant financial or in-kind assistance, members of the public who donate to support our work, and the RAH Research Fund team.

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Mr Michael and Mrs Andrea White and extended family
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The Cancer Council South Australia
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National Breast Cancer Foundation
The University of Adelaide
Royal Adelaide Hospital Research Fund
BioSA
Government of South Australia
Research Australia
Australian Government, Australian Research Council
Leukaemia Foundation, Vision to Cure, Mission to Care
Leukemia & Lymphoma Society, fighting blood cancers

Thank you to South Australian viticulturists Shaw + Smith, Hentley Farm, Penfolds, Clarendon Hills, Seppeltsfield, Torbreck, and Cascabel who generously supported the 5th Barossa Meeting

Mark Goldsmith and his team at the RAH Research Fund work to raise funds for the Centre for Cancer Biology

Publication Coordination

Anna Nitschke
Centre for Cancer Biology

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Catherine Buddle
Buddle Design

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Mark Fitz-Gerald
SA Pathology Photo & Imaging