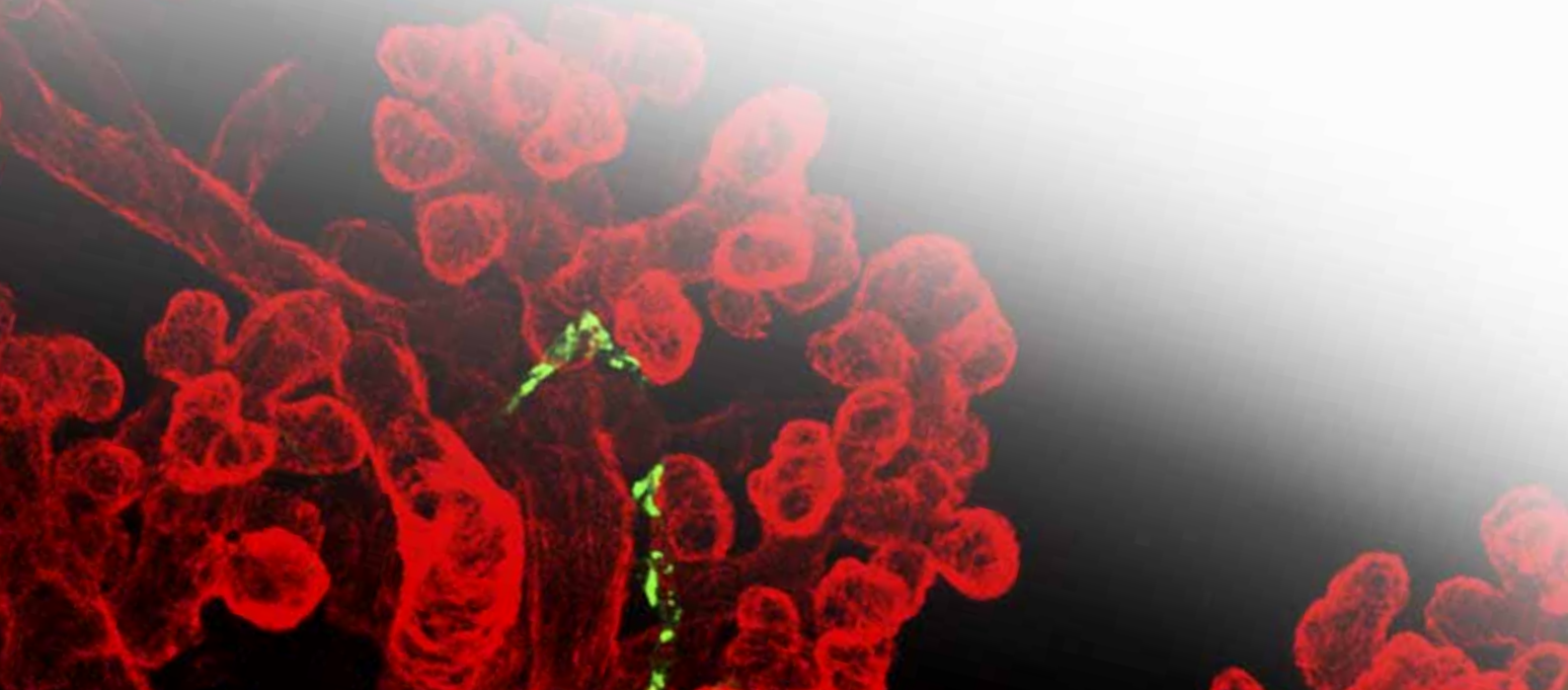
Annual Report 2010

Centre for Cancer Biology



Coordinating Editor
Kirsty Brunsden

Design and production
Sue Dyer Design

Photos and figures
Centre staff and Mark Fitz-Gerald

We gratefully acknowledge the support
and valuable contribution to this publication
of Heddy Zola, Anna Nitschke, Mark Goldsmith
and Frank Stomski

Contents

SA PATHOLOGY
Executive Director's Report

Professor Ruth Salom
Executive Director SA Pathology

CANCER is a leading cause of death and it is estimated that one in every two Australians will be diagnosed with cancer by the age of 85. Encouragingly however, new research is leading to more effective diagnostics, procedures and treatments, which have seen the survival rate for many common cancers increase by 30 per cent in the past two decades.

THESE ARE genuinely exciting times, as we move away from conventional methods and towards more targeted, personalised and effective treatments. But amidst all of this progress and the tangible improvements that increasingly benefit cancer patients, we need to remind ourselves that there is a long road ahead. For breakthroughs to occur, we need to galvanise the significant commitment of our cancer researchers in an environment that nurtures their capacity and their interactions. We have been very conscious of the power of this formula since establishing the Centre for Cancer Biology two years ago.

The Centre for Cancer Biology performs its research within SA Pathology (which trades as IMVS Pathology), alongside professional colleagues that provide quality clinical diagnostic pathology services. This dual activity of SA Pathology is highly conducive to excellence in both areas. On the one hand, researchers benefit from easy access to well studied and documented patient samples through our highly regarded tissue bank collection and pathology expertise. On the other hand, the very cutting edge cancer research that is conducted next door provides our pathologists with new insights into cancer progression and therapies well before they reach the medical press.

This is of great benefit to our South Australian patients and we know that they appreciate this unique mix. This vital interface must be continually strengthened as we move forward and I'm delighted that the Centre for Cancer Biology has kept this very much in mind when conducting its training program to prepare our scientific and medical colleagues of the future.

I congratulate our co-Directors Professor Angel Lopez and Professor Sharad Kumar for their work in leading the Centre, and for both receiving significant recognition for their valuable contributions to research.

Professor Angel Lopez shared the highly-coveted *2010 South Australian Scientist of the Year* title in the annual South Australian Science Excellence Awards, and received a *2010 South Australian of the Year* award in the Science category.

For almost 25 years, Professor Lopez's research has focused on cytokines that regulate blood cell production and function. The *South Australian Scientist of the Year* award recognised many seminal discoveries of Professor Lopez that have led to the better understanding of the functioning of cytokines and cytokine receptor networks in normal physiology and in diseases such as leukaemia and asthma.

Opening of the Centre for Cancer Biology on April 16th 2009 by Professor Ian Frazer, inventor of the cervical cancer vaccine, and SA Health Minister John Hill

Professor Angel Lopez accepting the $3.5 million grant from the ACRF to establish the South Australian Cancer Genome Facility

Professor Sharad Kumar won the prestigious *Ranbaxy Research Award 2009* in Medical Sciences for his seminal contributions to the understanding of programmed cell death and the regulation of the protein function by ubiquitination. His group also made key contributions to the fundamental understanding of developmental cell death, caspase function and cancer biology. The work from his laboratory on the Nedd4 family of ubiquitin ligases and apoptosis has led to many seminal discoveries impacting on the understanding of human diseases.

During 2010, Professor Kumar was also awarded the highest level of National Health and Medical Research Council (NHMRC) Research Fellowship. These highly sought after fellowships provide the opportunity for outstanding biomedical and health researchers with proven track records that place them in the top 5-10% of their fields, to perform full-time research of major importance in the medical and health arena.

As a non-profit organisation, all of the work of the Centre for Cancer Biology is funded through internal support from SA Pathology (trading as IMVS Pathology) as well as grants and donations. SA Pathology, the South Australian Government's pathology service, has shown its long term commitment to cancer research by substantial financial support through surpluses generated from private pathology patient fees. The Centre for Cancer Biology also had a strong year in funding, winning many personal fellowships and attracting significant funding from the NHMRC.

As is detailed in the Co-Directors' Report, in conjunction with researchers from the University of Adelaide, the Centre for Cancer Biology successfully won a bid to establish the South Australian Cancer Genomics Facility, and was awarded $3.5 million by the Australian Cancer Research Foundation, $1.05 million from the South Australian Government and $525,000 from Cancer Council SA.

This is the first time South Australia will have a facility of this capacity, with equipment that can perform sophisticated analysis and a team of senior scientists to analyse and apply findings. It will facilitate discovery and innovation by our researchers and help their translational efforts in developing better diagnostics and more effective anti-cancer drugs.

It is our hope that the research outcomes from the Cancer Genomics Facility will contribute to the eventual reality of personalised medicine with fewer long-term side effects and better patient outcomes. The field of personalised medicine is certain to expand rapidly in the near future as we increasingly understand the way specific genes work with medicines. We are proud to be at the forefront of this genetic research into gastrointestinal, colon, prostate, breast, ovarian, neuronal and haematological malignancies.

"For breakthroughs to occur, we need to galvanise the significant commitment of our cancer researchers in an environment that nurtures their capacity and their interactions".

The success in winning financial support for the South Australian Cancer Genomics Facility gives me great pleasure for the added reason that whilst medical research is a very competitive activity, we have demonstrated our awareness of the need and benefits of meaningful collaborations. I am grateful to the University of Adelaide, Flinders University and the University of South Australia in supporting our bid, and to our Royal Adelaide Hospital colleagues for their enthusiastic participation. Their collegiality and belief in the greater good augur very well for the successful future utilisation of this Facility.

I extend my sincere thanks and appreciation to the heads of each laboratory and the dedicated staff striving for research excellence and better cancer patient care. Above all, the story of the Centre for Cancer Biology is one of endurance, expectation and hope for the cure of cancer. I, like the researchers of the Centre, remain fully committed to continue building on our achievements as one of Australia's leading cancer research organisations.

CENTRE FOR CANCER BIOLOGY
Co-Directors' Report

WHAT IS THE CENTRE FOR CANCER BIOLOGY ABOUT?

Professor Sharad Kumar
Co-Director
Centre for Cancer Biology

Professor Angel Lopez
Co-Director
Centre for Cancer Biology

IT HAS BEEN two years since the launch of the Centre for Cancer Biology. The vision to bring together some of the best South Australian cancer researchers under a single umbrella and governance, materialised into the formation of the Centre for Cancer Biology. In this, our inaugural Annual Report, we would like to pay tribute to Professor Ruth Salom, Executive Director of SA Pathology, Professor Heddy Zola, and Health Minister John Hill, for their enthusiastic support, and to Professor Ian Frazer, 2006 Australian of the Year, and a creator of the HPV vaccine against cancer, who officially opened the Centre on April 16th 2009. They share with us the dream and the promise of the Centre for Cancer Biology.

THE CENTRE studies basic mechanisms of cancer and carries out translational clinical research. Our six major fundamental research themes include stem cells, programmed cell death or apoptosis, metastasis, cancer immunology, tumour vascularisation, and cell signalling. These themes encompass critical processes that affect the vast majority of cancers irrespective of the organ of origin. On the translational front, our clinical research focusses largely on leukaemia, lymphoma and myeloma.

We are strong believers in innovation, and of the need for fundamental discoveries to fuel new ideas to alleviate human suffering. It is the understanding of basic and fundamental biological processes that plants the seeds of breakthroughs, with their translation ultimately leading to better cancer patient management. Secondly, we think that studying common denominators in cancer gives us a tremendous opportunity to impact on several cancers at once. For example, our studies on stem cells of endothelial, neuronal, lymphatic, mesenchymal, and hemopoietic origin are showing us the key requisites for normal stem cell behaviour and how this is subverted in cancer stem cells. This is critical information as we are targeting the cancer stem cell for long-lasting therapies.

Similarly, fundamental studies into metastases, a major cause of death in many cancers, by Associate Professor Gregory Goodall and Dr Yeesim Khew-Goodall (published in *Nature Cell Biology*), are revealing the molecular basis of the epithelial-mesenchymal transition. Thirdly, we aim to rapidly translate our fundamental discoveries into better clinical practice. Although this can take many years, recent advances by Professor Timothy Hughes and Associate Professor Deborah White are already improving the lives of patients with chronic myeloid leukaemia by understanding drug resistance and optimising their treatment options.

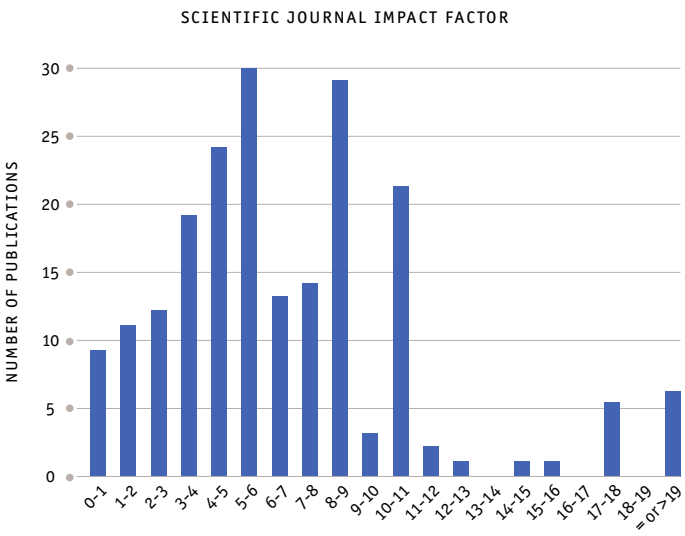
Left: Professor Angel Lopez being co-awarded *South Australian Scientist of the Year* in the 2010 South Australian Science Excellence Awards

Right: Professor Sharad Kumar receiving the *Ranbaxy Research Award 2009* in Medical Sciences

HOW CAN WE MONITOR HOW WELL THE CENTRE FOR CANCER BIOLOGY IS DOING?

SOME OF THE best key performance indicators are the number of scientific manuscripts we publish and where we publish. The prestige and breadth of readership of the international scientific journals is often measured as Impact Factor (IF). We are very pleased to say that the Centre for Cancer Biology has published approximately 200 manuscripts in the last two years and a great number have been in journals of high impact factor. For example, over 62% of our manuscripts were published in journals with an impact factor of >5, over 17% of articles were published in journals of impact factor of >10, and 2.5% in journals of impact factor of more than 22. This indicates that the Centre for Cancer Biology ranks among the top research organisations nationally.

In setting up the Centre for Cancer Biology, we recognised that a key ingredient that drives innovation is a critical mass of highly motivated researchers working closely together and aided by state-of-the-art infrastructure. We have been very fortunate in the last two years with successes in grant funding that allowed us to grow, but more so in recruiting highly talented and energetic young researchers. Dr Michele Grimbaldeston's arrival from Professor Steven Galli's Lab at Stanford University to set up her Mast Cell Laboratory invigorated the Centre for Cancer Biology, and her three National Health and Medical Research Council of Australia (NHMRC) grants and an NHMRC Career Development Fellowship attest to her calibre.



Similarly, Dr Quenten Schwarz recently arrived from University College, London, and his hard work has already been rewarded with several grants and also an NHMRC Career Development Fellowship. We recognise the support of Professor Salom in facilitating this recruitment. We look forward to the imminent arrival of Dr Michael Samuel from the Beatson Institute to energise our studies on signal transduction and skin cancer development. The ten Fellowships gained in 2009-2010, several operationally-funded scientists and the SA Pathology infrastructure are underpinning our research effort. This powerful mix has provided strong leverage for attracting grants and funding from the NHMRC, the biotechnology sector, and from several charitable foundations.

As with every professional biomedical research organisation, new technology and state-of-the-art infrastructure are required to make significant advances. We are very pleased to report that in the last two years the Centre for Cancer Biology has won major competitive infrastructure funds. Of note is the support of $3.5 million we received (in conjunction with the University of Adelaide researchers) from the Australian Cancer Research Foundation to set up the South Australian Cancer Genomic Facility, supplemented by generous grants from the SA Government, and the Cancer Council of SA. This will allow us for the first time to study genetic changes in patients that contribute to their cancer and their response to cancer drugs. We hope to not only understand how some cancers arise and progress but also bring closer to reality the concept of personalised medicine. We look forward to this new Facility to open and be fully operational by the end of this year.

One of the most pleasing recent developments in the Centre has been the strong influx of students. These are the next generation of scientists and medical doctors, and our future colleagues. We are very proud of our strong postgraduate program in association with the three South Australian universities, and are pleased with the number and level of scholarships obtained from many organisations.

We are confident that in its third year, the Centre for Cancer Biology will continue to produce exciting new discoveries through constant striving for scientific excellence, further promoting collaborative interactions among our scientists, and exploiting the opportunities that arise from new technological developments, such as our new Cancer Genomics Facility.

Acute Leukaemia Laboratory

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

ABERRANT cytokine receptor signalling occurs frequently in myeloproliferative neoplasms (MPN) and acute myeloid leukaemia (AML), and identification of key downstream events provides an approach for the development of targeted therapies with reduced toxicity (*Perugini et al, Leukemia 2009*).

MPN occurs as a result of changes acquired in the haemopoietic stem cell compartment, which induce aberrant growth factor responses and over-production of mature myeloid and erythroid cells.

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 leukaemia. We are using novel systems to dissect signalling pathways that control cytokine-induced cell survival, proliferation, differentiation and self-renewal (*Perugini et al, Blood 2010*).

We are also utilising molecular and proteomic approaches to identify factors that contribute to the therapeutic response and relapsed disease in AML (*Powell et al, Blood 2009 and Kok et al, Leukemia 2010*). Through molecular and genetic cohort studies of patients with MPN, we aim to understand the nature of the changes that are associated with disease initiation, long-term maintenance of disease, and disease progression in these patients (*see Butcher et al, BJH in press*).

Finally, we are investigating new approaches to monitor disease and classify AML patients using novel markers and bioassays (*Patil et al, Bone Marrow Transplant 2010 and Al Mawali et al, AM J Clin Pathol 2009*).

KEY DISCOVERIES IN 2009-2010

MODES OF GM-CSF RECEPTOR SIGNALLING

GM-CSF promotes growth, survival, differentiation and activation of normal myeloid cells, and plays an important role in myeloid leukaemias. The GM-CSF receptor (GMR) shares a signalling subunit, β_c, with IL-3 and IL-5 receptors, and has recently been shown to act via formation of a unique dodecameric receptor complex. We have used two activated β_c mutants that display distinct signalling capacity and have a differential requirement for the specific GM-CSF receptor α-subunit (GMRα), to dissect the signalling pathways associated with GM-CSF response.

In a recent paper (*Blood 115: 3346-3353, 2010*), we relate the non-overlapping nature of signalling by these two activated mutants to the structure of the unique GM-CSF receptor complex, and propose alternative modes of receptor activation, differentially dependent on JAK2 and SFK, and acting synergistically in the mature liganded receptor complex.

A NOVEL DETERMINANT OF RESPONSE IN AML

In 2009 (*Leukemia 23: 729-738, 2009*), we identified the stress-induced tumour suppressor gene *Growth Arrest and DNA Damage inducible 45*α (*GADD45A*) as a down-regulated gene in AML, and showed that silencing of *GADD45A* contributes to the growth, survival and blocked differentiation typical of AML cells. Recently, we discovered that *GADD45A* is associated with promoter hyper-methylation and silencing in a significant proportion of patient AML samples.

Analysis of clinical outcome data shows that hyper-methylation in the proximal promoter of *GADD45A* defines a sub-class of AML (>30% of patients) with a particularly poor outcome despite intensive chemotherapy. Importantly, we show that in

1 Ian Lewis
2 Diana Salerno
3 Sonya Diakiw
4 Richard D'Andrea
5 Anna Brown
6 Nick Li
7 Teresa Sadras
8 Michelle Perugini
9 Grant Engler

normal karyotype AML (NK-AML) this is predictive of outcome, independent of other key prognostic mutations such as those in *FLT3*. Our analysis of a small transplant cohort suggests that AML patients with this methylation mark respond poorly to haemopoietic stem cell transplantation (HSCT), therefore, we hypothesise that *GADD45A* hypermethylation confers chemo-resistance in LSC and is associated with high risk of relapse in AML patients.

TREATMENT OF AML WITH MLL TRANSLOCATIONS

MLL is an epigenetic modulator located on 11q23 that when fused to binding partners has the unique ability to confer stem cell renewal properties to committed progenitors. A recent body of work suggests there are intrinsic differences between MLL-leukaemic stem cells and normal haematopoietic stem cells that can be therapeutically exploited. To this end, using a novel *in silico* bioinformatic drug screening approach, we have discovered a small molecule that shows selective toxicity in MLL-leukaemia and kills leukaemia stem cells *in vitro* while sparing normal stem cells.

Whilst the precise mechanism of action in MLL-LSCs remains to be determined, our data suggests that targeting mitochondrial metabolic function and the amino acid deprivation response may be particularly effective in this AML subtype, which is associated with a poor prognosis on standard chemotherapy.

Outcomes for the community

Haemopoietic stem cell transplantation is an important salvage option for some leukaemic patients, however, it is associated with a few problems. Our new data on the *GADD45A* gene helps subclassify some leukaemias and define patients that may or may not benefit from transplantation. This work impacts on cancer classification and treatment and is important for leukaemic patients for whom selection of treatment options is critical.

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 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 growth factor receptors, such as the granulocyte macrophage colony stimulating factor (GM-CSF) receptor and fibroblast growth factor receptor. These site-specific serine phosphorylation events allow the activated receptors to couple to specific intracellular signalling pathways and control cell survival, proliferation and differentiation.

This work challenges the well-established paradigm that growth factor and cytokine receptors initiate and regulate intracellular signalling and cellular responses primarily via receptor tyrosine phosphorylation and shows that diverse growth factor receptors also utilise novel phosphoserine docking sites for the regulation of pleiotropic biological responses.

KEY DISCOVERIES IN 2009-2010

1

Using innovative proteomic approaches for the analysis of site-specific tyrosine phosphorylation sites, we have shown that in addition to their well known properties of binding phosphoserine/threonine motifs, the 14-3-3 proteins are also phosphorylated on Tyr179, allowing them to directly couple with phosphotyrosine signalling pathways. We have shown that 14-3-3ζ is tyrosine phosphorylated, and functions as an intermolecular bridge that simultaneously binds phosphoserine residues and the SH2 domain of Shc via Tyr179. We have shown for the first time that the dual ability of 14-3-3ζ to transduce signals via both phosphoserine/threonine and phosphotyrosine is essential for the assembly of a PI 3-kinase signalling complex and cell survival (*Barry et al, J Biol Chem 284: 12080-12090, 2009*).

2

We have also shown that novel phosphoserine docking sites in the cytoplasmic tails of growth factor and cytokine receptors can act as 'oncogenic scaffolds' to deregulate cell survival programs in cancer. In the case of the GM-CSF and IL-3 receptors, Ser585 acts as an oncogenic scaffold to recruit PI3K signalling complexes and promote deregulated cell survival in acute myeloid leukaemia (AML).

We have performed a global expression screen to identify gene targets of the Ser585 survival pathway, and have identified a unique transcriptional program enriched for PI3K targets. We showed that one Ser585-regulated gene, osteopontin (OPN), promotes the autonomous survival of AML stem and progenitor cells. Importantly, we have also shown that increased expression of OPN in patients at diagnosis is significantly associated with poor

1 Yang Kong
2 Nhan Truong
3 Mark Guthridge
4 Daniel Thomas
5 Hui Lim
6 Jason Powell
7 Emma Barry
8 Ana Lonic

prognosis and decreased overall patient survival. Thus, OPN represents both a potential therapeutic target and prognostic factor in AML (*Powell et al, Blood 114: 4859-4870, 2009*).

3

In collaboration with Professor Tim Hughes (**Melissa White Memorial Laboratory–Clinical**), we have also found that the Ser585 survival pathway is constitutively activated in >70% of primary human CML samples. In fact, we have shown that such cytokine receptor-mediated pathways may provide a mechanism by which CML cells can overcome inhibition of Bcr-Abl by the tyrosine kinase inhibitors, imatinib or dasatinib. Thus, our findings suggest that targeting oncogenic Bcr-Abl tyrosine kinase pathways with imatinib or dasatinib in combination with inhibitors of cytokine-mediated survival pathways may have therapeutic benefit, and overcome drug resistance in CML (*Hiwase et al, Leukemia 24: 771-778, 2010*).

4

In collaboration with Dr Nikki Verrills (**University of Newcastle**) we have shown that targeting serine-threonine phosphatases may have clinical benefits in the treatment of AML. In particular, we have been able to show that the novel activator of the PP2A phosphatase, FTY720, is able to induce apoptosis in primary human AML cells that are refractory to inhibition of tyrosine kinase inhibitors. These findings suggest that targeting PP2A, either in conjunction with conventional therapeutics or in combination with tyrosine kinase inhibitors, may provide improved clinical outcomes in AML (*Roberts et al, Cancer Research 70: 5438-5447, 2010*).

Outcomes for the community

Cancer remains one of the most difficult diseases to treat, with the human and economic cost of this disease increasing substantially over the last 3 decades. It is clear that continuous incremental improvements in conventional therapies is not the answer and that new approaches that target the molecular defects in cancer cells are required. We have identified several new potential therapeutic targets in cancer cells and our findings suggest that they may have clinical potential. We hope that our discoveries will provide new approaches and therapies for the diagnosis and treatment of cancer, thereby providing improved clinical outcomes in the future.

Cell Signalling Laboratory

Dr Yeesim Khew-Goodall PhD

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.

Of key interest to the Cell Signalling Laboratory are the interactions of the cancer cell with its microenvironment and to understand how signals that are normally generated to maintain homeostasis, give rise to disease when dysregulated. Our disease model is breast cancer metastasis and our long term focus is to understand what turns a local and treatable benign cancer cell 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.

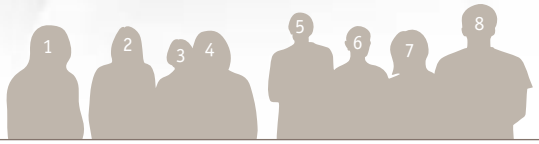
Recent studies have shown that the cancer 'secretome' can also prepare a metastatic niche in secondary organs to facilitate their ability to embed in those organs. To date however, little is known about the mechanism(s) by which the cellular secretome is regulated or how this regulation might be altered in cancer cells.

We have shown that the protein tyrosine phosphatase Pez, a protein that 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.

MicroRNAs are relatively newly-discovered small non-coding RNAs. Recognition of their roles in regulating cellular functions has increased enormously in the last few years. Using a cell culture model of epithelial-mesenchymal transition developed in our laboratory in collaboration with the **Cytokine Research Laboratory**, 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 **Cytokine Research Laboratory** and **Peter MacCallum Research Institute** in Melbourne, 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.



1 Ana Lonic
2 Freya Gehling
3 Lesley Crocker
4 Yeesim Khew-Goodall
5 Sam Dyer
6 Leila Belle
7 Xiaochun Li
8 James Paltridge

KEY DISCOVERIES IN 2009-2010

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, which 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

We have also discovered a novel signalling pathway for the recruitment of neutrophils into sites of inflammation (*Williams et al, J Immunol 185: 3057-3063, 2010*).

Outcomes for the community

Solid tumours make up the majority of human cancers, and 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.

Cytokine Receptor Laboratory

Professor Angel Lopez MBBS, PhD, FRCPA

CYTOKINE receptors present on the surface of hemopoietic cells are the conduit by which cells interact with the immediate microenvironment. Excessive stimulation of cytokine receptors, their abnormal expression or dysfunctional downstream signalling can lead to inflammatory diseases and cancer.

This laboratory seeks to understand the mechanism of cytokine receptor activation, in particular the GM-CSF, IL-3 and IL-5 receptors, in health and disease. This will reveal universal biological rules and allow the development of new drugs for unmet clinical needs such as leukaemia, asthma and arthritis.

Our research program incorporates structural biology approaches (in collaboration with Professor Michael Parker, **St Vincent's Institute of Medical Research**) to elucidate the structure and function of the GM-CSF, IL-3 and IL-5 receptors; and functional and proteomics approaches to elucidate the signalling mechanisms and functional consequences of cytokine receptor engagement.

Our initial solving of the structure of the human GM-CSF receptor complexed to GM-CSF (*Cell 134: 496-507, 2008*) has already revealed a new mode of cytokine receptor activation and new specific receptor sites. Based on this new proprietary information, approaches are under way to understand the functional significance of each site and develop new tools and potential drugs to interfere with receptor activation.

An important aspect of our work is to link the structural insights gained above to specific receptor activation functional outcomes. For example, we have previously reported that the pleiotropic activities of the GM-CSF receptor can be dissected to the point where activation of cell survival can be seen to be distinct from other functions such as proliferation ('cell survival-only' pathway). Our aim is now to molecularly define the distinct functional signosomes downstream of the GM-CSF and IL-3 receptors, and link their activation to the different forms of cytokine receptor assembly revealed by the crystal structures of the cytokine receptor complexes.

We are continuing our collaboration with Dr Mark Guthridge (**Cell Growth and Differentiation Laboratory**), Associate Professor Richard D'Andrea (**Acute Leukaemia Laboratory**), and Associate Professor Paul Ekert (**Walter and Eliza Hall Institute**) on the 'cell survival-only' pathway, and on the kinases that associate to the receptor complexes in normal and leukaemic stem cells. We believe that this may reveal the molecular basis of dysregulation in leukaemia. In particular, the 'survival-only' pathway may be critical for the patient's relapse seen in acute myeloid leukaemia and in chronic myeloid leukaemia, with the current collaboration with Professor Tim Hughes (**Melissa White Memorial Laboratory – Clinical**) already yielding important insights.

Interestingly, a central component of these receptor proximal signosomes, which control the balance of cell survival versus death, is the scaffold protein 14-3-3, and in collaboration with Dr Jo Woodcock and Associate Professor Stuart Pitson (**Molecular Signalling Laboratory**), we are studying its regulation by lipids and cytokines. Whilst these experiments have important implications in cancer, the fact that receptors such as IL-3 are key regulators of mast cells suggests a likely role in allergic inflammation, and experiments in collaboration with Dr Michele Grimbaldeston (**Mast Cell Laboratory**), are seeking to identify new signalling molecules uniquely associated with the mast cell IL-3 receptor.

As we obtain a detailed understanding of cytokine receptor structure and how they signal, we seek to use this new knowledge to develop potential new therapies for leukaemia and for chronic inflammatory conditions. In collaboration with Professor R Lock (**Lowy Institute, Sydney**), J Dick (**Canada Research Chair in Stem Cell Biology**, Toronto) and **CSL Ltd**, we are continuing to develop the IL-3 receptor α chain-specific MAb 7G3 towards use in clinical trials. In collaboration with Professor Michael Parker, we are also screening for small inhibitory molecules based on the 3-D structure of these cytokine receptors. Ultimately, we seek collaborations with clinical colleagues and the pharmaceutical industry to develop new drugs that can change clinical practice.

1 Bill Panagopoulos
2 Rebecca Krake
3 Hayley Ramshaw
4 Angel Lopez
5 Tim Hercus
6 Nicole Christie
7 Barbara McClure
8 Natasha Pyne
9 Anna Sapa
10 Frank Stomski

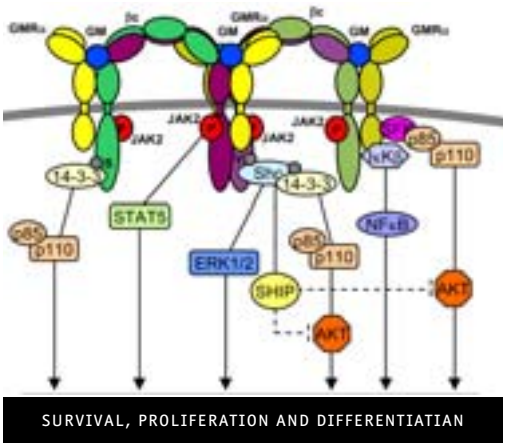
KEY DISCOVERIES IN 2009-2010

HIGH RESOLUTION SOLVING OF THE HUMAN GM-CSF RECEPTOR α CHAIN; GM-CSF COMPLEX

In collaboration with Professor Michael Parker, following our earlier determination of the human GM-CSF dodecameric complex, we have now solved the structure of the human GM-CSF receptor α chain in complex with GM-CSF to a resolution of 2.8Å that reveals for the first time intimate contact points between GM-CSF and its receptor α chain (Site 1). Interestingly, Site 1 is composed of domains 1 and 2 of the cytokine receptor module, and unexpectedly also by its N-terminal domain. Mutagenesis analyses and molecular modelling have revealed a unique arrangement for Site 1 likely to extend to other members of this cytokine receptor family, and a significant contribution of the N-terminal domain.

MONOCLONAL ANTIBODY-MEDIATED TARGETING OF CD123, IL-3 RECEPTOR α CHAIN, ELIMINATES HUMAN ACUTE MYELOID LEUKAEMIC STEM CELLS (LSC)

In collaboration with Professors Richard Lock, John Dick and CSL Ltd, we showed that the anti-interleukin-3 (IL-3) receptor α chain (CD123)-neutralising antibody (7G3) targeted AML-LSCs, impairing homing to bone marrow and activating innate immunity in a mouse model (*Cell Stem Cell 5: 31-42, 2009*). 7G3 treatment profoundly reduced AML-LSC engraftment and reduced AML burden in the bone marrow and periphery, and impaired secondary transplantation upon treatment, establishing that AML-LSCs were directly targeted. These results provide clear validation for therapeutic monoclonal antibody 7G3 targeting of AML-LSCs, and for translation of *in vivo* preclinical research findings toward a clinical application.



SURVIVAL, PROLIFERATION AND DIFFERENTIATIAN

Outcomes for the community

Cancer and inflammation affect the vast majority of our community at a significant human cost. There is also a growing economic burden in managing these health problems. Our effort to understand the basics of how cells behave in normal and disease circumstances is fundamental to devising new strategies to ameliorate disease. We are very encouraged by the ongoing translation of this newly-gained knowledge into drug candidates that may provide longer-lasting treatments with minimal side-effects.

Cytokine Research Laboratory

Associate 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 the transition of the cancer to an invasive form, a step that is now widely recognised to involve a recapitulation of the developmental process known as epithelial to mesenchymal transition (EMT).

This, along with the recent discoveries that cancer stem cells have EMT-like features and that EMT typically confers resistance to chemotherapy, places studies on the mechanisms that determine EMT at the nexus of investigations of the cause of cancer progression and 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 of 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 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
- investigating the role of microRNAs in cancer cell resistance to chemotherapy
- development of microRNA-derived diagnostic and therapeutic possibilities.

KEY DISCOVERIES IN 2009-2010

ENFORCED EXPRESSION OF MIR-200 CAN INHIBIT LUNG ADENOCARCINOMA METASTASIS

Our previous work identifying miR-200 as a controller of EMT raised the possibility that miR-200 may prevent EMT in cancer cells and thereby prevent the initial steps in tumour metastasis. 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 found that the enforced expression of miR-200 does indeed reduce metastasis. This provides encouragement for the long term prospect of using miR-200 in a therapeutic mode to inhibit cancer metastasis.

AN AUTOCRINE TGF-β/ZEB/MIR-200 SIGNALLING NETWORK REGULATES ESTABLISHMENT AND MAINTENANCE OF EPITHELIAL-MESENCHYMAL TRANSITION

Epithelial-mesenchymal transition (EMT) is a form of cellular plasticity that is critical for embryonic development and tumour metastasis. We previously discovered a double-negative feedback loop involving the miR-200 family and ZEB transcription factors, and postulated that this controls the balance between epithelial and mesenchymal states.

In collaboration with Dr Yeesim Khew-Goodall and the **Cell Signalling Laboratory** we have now demonstrated, using the epithelial MDCK cell line model, that although manipulation of the ZEB/miR-200 balance is able to repeatedly switch cells between epithelial and mesenchymal states, the induction and maintenance of a stable mesenchymal phenotype

1 Jo Attema
2 Cameron Bracken
3 Emily Paterson
4 Matthew Anderson
5 Jo Wright
6 Greg Goodall
7 Anna Tsykin
8 Daniel Thomson
9 Victoria Arnet
10 Suraya Roslan
11 Natasha Kolesnikoff
12 Andrew Bert

requires the establishment of autocrine TGF-β signalling to drive sustained ZEB expression. Furthermore, we found that prolonged autocrine TGF-β signalling induced reversible DNA methylation of the miR-200 loci with corresponding changes in miR-200 levels.

Collectively, these findings demonstrate the existence of an autocrine TGF-β/ZEB/miR-200 signalling network that regulates plasticity between epithelial and mesenchymal states. We found a strong correlation between ZEBs and TGF-β, and negative correlations between miR-200 versus TGF-β and between miR-200 versus ZEBs in invasive ductal carcinomas, consistent with an autocrine TGF-β/ZEB/miR-200 signalling network being active in breast cancers.

IDENTIFICATION OF WIDESPREAD miRNA-DEPENDENT AND miRNA-INDEPENDENT ENDONUCLEOLYTIC CLEAVAGE OF mRNAs IN MAMMALS

The mechanisms through which microRNAs control gene expression are of intense interest and incompletely resolved. It is well established in plants that miRNAs frequently target mRNAs for direct cleavage by the Argonaute subunit of the RISC complex. However, it has been an enigma that although mammals possess a functional Agonaute 2 and the capacity to directly cleave mRNA targets, as demonstrated by the effectiveness of siRNA-mediated knockdown in mammalian cells, there were almost no mRNAs identified as substrates for this form of targeting.

We performed a genome wide assessment of miRNA cleavage targets using bioinformatics to identify mRNAs that contain sequences with high complementarity to miRNAs, along with a deep sequencing approach designed to directly identify sites of cleavage. We identified numerous mRNAs that are targeted for cleavage by endogenous microRNAs, although at low level relative to the mRNA abundance, and identified N4BP1 mRNA as an efficient target of cleavage by miR-151-5p.

We also found numerous examples of non-miRNA-directed cleavage, including cleavage of a group of mRNAs within a CA-repeat consensus sequence. We also identified many examples of adenylated small non-coding RNAs, including microRNAs, tRNA processing intermediates and various other small RNAs, consistent with adenylation being part of a widespread proof-reading and/or degradation pathway for small RNAs.

Outcomes for the community

The majority of deaths from cancer are due to metastasis, the secondary tumours that arise from the progression of the primary tumour to an invasive stage. Our work has improved the understanding of the molecular mechanisms that determine how metastasis occurs. This will ultimately lead to identification of molecules that are useful for diagnosing and treating cancer metastasis. Our work is having an influence on cancer research internationally, with one of our 2008 papers listed as being among the 20 most cited papers on cancer published since 2008.

Haematology Clinical Research Unit

Professor L Bik To MBBS (HK), MD (Adel), MRCP (UK),PhD, FRACP, FRCPA
Dr Ian Lewis MBBS, PhD, FRACP, FRCPA

THE Haematology Clinical Research Unit manages an active clinical trial program, which is based in the Royal Adelaide Hospital and is also linked to clinical trial units in the South Australian public hospital system.

This brings new treatment modalities to South Australia, provides opportunities for collaborative research, and is a crucial factor for attraction and retention of staff.

Another important function of the Unit is to maintain the **Leukaemia Myeloma Tumour Bank**. Specimens are stored and the correlated clinical information allows major translational research studies to be carried out, with many significant publications having come out of this valuable resource. These include novel gene targets and leukaemic immuophenotypes in acute myeloid leukaemia, genetic studies and therapeutic trials in chronic myeloid leukaemia and bone changes in chronic myeloid leukaemia and multiple myeloma.

The Therapeutic Products Facility and the **Central Liquid Nitrogen Facility (CLNF)**, maintained by the **Haematology Directorate of SA Pathology**, are important components of the Clinical Research Unit. The Therapeutic Products Facility is the only TGA certified cell processing facility and is involved in mesenchymal cells and haemopoietic stem cell processing for therapeutic use.

The CLNF commenced operations in November 2006 to provide a centralised cryogenic facility service for the SA Pathology campus. This cryogenic facility provides medium to long-term storage solutions to a large variety of users.

A significant use of the facility is the storage of specimens for the **Haematology Biospecimen Bank**, involving several research groups within the Centre for Cancer Biology.

This bank has been building over many years and continues to grow. It is an invaluable resource to basic and clinical researchers alike, permitting retrospective studies of many disease states, and will ultimately lead to new discoveries and disease treatments.

The material stored in this facility is largely irreplaceable, and of immense value to current clinical practice and furthering scientific and clinical research endeavours for future generations. Currently, there are approximately 180,000 specimens in the collection, with a net increase of 13,300 samples in 2009, and an estimated 15,000 additional samples added in 2010. Collections previously held in the **Women's and Children's Hospital Haematology Department** have also been migrated into the collection.

During 2009 and 2010, the Haematology Clinical Research Unit conducted 32 clinical trials. Key trials are presented in the table, with a full list available on the Centre for Cancer Biology website.

1 Ian Lewis
2 Bik To
3 Lisa Carne
4 Bronwen Cox
5 Venus Au
6 Kylie Chaplin
7 Meng Jun Zhu
8 Peter Harrison
9 Kerry Munro
10 Monika Kutyna
11 Thanh Nguyen
12 Julia Hamilton
13 Andrew Vanlint
14 Noemi Horvath
15 Devendra Hiwase

KEY CLINICAL TRIALS

2009	PRINCIPAL INVESTIGATOR	DRUG COMPANY
A Phase 1/2 Study of Oral SB1518 in Subjects with Chronic Idiopathic Myelofibrosis	To, B	S*BIO Pty Ltd
A Safety and Efficacy Trial Evaluating the Use of Apixaban for the Extended Treatment of Deep Vein Thrombosis and Pulmonary Embolism	McRae, S	BMS/Pfizer
A Phase II Study of Dasatinib Combined with Induction Chemotherapy in Previously Untreated de novo Philadelphia Chromosome-Positive Acute Lymphoblastic Leukaemia	Hughes, T	

2010	PRINCIPAL INVESTIGATOR	DRUG COMPANY
A Randomised Controlled Trial of Prophylactic Vs No-Prophylactic Platelet Transfusions in Patients with Haematological Malignancies	Bardy, P	
A Randomised Multicentre Study Comparing G-CSF Mobilized Peripheral Blood and G-CSF Stimulated Bone Marrow in Patients Undergoing Matched Sibling Transplantation for Haematologic Malignancies	Lewis, I	
Response Post Tyrosine Kinase Inhibitor: Assessment of Sensitivity and Therapeutic Response to Next-Line Therapy in CML: The Australasian RESIST Study	Hughes, T	ALLG

Outcomes for the community

The active clinical trial program gives patients with haematological malignancies the opportunity to receive novel therapeutic agents which may not otherwise be available to them. The prospective storage of leukaemia and myeloma specimens is a valuable resource, which underpins a number of research projects that will have many benefits for the community.

Hepatitis C Virus Research Laboratory

Associate Professor Michael R Beard PhD

THERE ARE over 170 million persons worldwide infected with the hepatitis C virus (HCV), which results in significant liver disease (fibrosis/cirrhosis) and 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 live cells. Through this approach we hope to add to our understanding of how HCV causes disease, and identify novel therapeutics.

KEY DISCOVERIES IN 2009-2010

DYNAMIC IMAGING OF THE HCV LIFE-CYCLE

Using small (6-12 amino acid) genetically encoded tetracysteine peptide sequences that can be introduced into viral proteins and labeled by fluorescent dyes in living cells, we are investigating the traffic of HCV core protein (which forms the viral nucleocapsid) and HCV NS5A protein (which is a critical regulator of both viral genome replication and viral particle assembly) during HCV particle assembly, maturation and secretion.

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. The challenge will now be to determine the relative roles of these NS5A structures in the HCV life-cycle. Interestingly, we have noted that there is dynamic interaction between the motile NS5A structures with lipid droplets and Apo-E, suggesting that they may be important in virion assembly and viral secretion. 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.

CELLULAR FACTORS INVOLVED IN HCV ENTRY

HCV enters the host hepatocytes by clathrin-dependent endocytosis in a process that involves a number of plasma membrane proteins. Of these, CD81 (a tetraspanin), SR-B1 (a high-density lipoprotein receptor), claudin-1 (a tight-junction protein) and occludin (a tight-junction protein) are critical entry factors. Studies of SR-B1 function in mice have indicated that its interaction with a cytoplasmic adaptor molecule, PDZK1, is necessary for its stability and activity at the plasma membrane of hepatocytes.

We are investigating the importance of this interaction to the involvement of SR-BI in HCV entry. Beyond mapping domains of each protein involved in this interaction, we have shown that knockdown of PDZK1 expression and dominant-negative inhibition of SR-B1/PDZK1 interaction results in inhibition of HCV entry (*Plos Pathogens 7: 6-10, 2010*). This work may therefore reveal SR-BI/PDZK1 interaction as an attractive target of therapeutic interference with HCV entry.

HCV REPLICATION ACTIVATES STAT3

STAT3 is a transcription factor that 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 in microarray studies that STAT3 is upregulated in HCV infected hepatocytes, and demonstrated

1 Edmund Tse
2 Kate Muller
3 Sumudu Narayana
4 Karla Helbig
5 Erin McCartney
6 Guillaume Fiches
7 Michael Beard
8 Julie Calvert
9 Kylie Van der Hoek
10 Gemma Sharp
11 Jill Carr
12 Nicholas Eyer

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. This may have implications for the development of HCC, as STAT3 is often constitutively activated in HCC.

INTERFERON STIMULATED GENES THAT CONTROL HCV

Viral infection initiates a series of intracellular events that culminate in the generation of an antiviral state, directly within the infected cell and indirectly within the surrounding tissue, through the induction of interferon expression and associated interferon stimulated genes (ISGs). 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 (*J Virol 83: 836-846, 2009*).

We have identified the ISG Viperin and the IFITM family of ISGs to have anti-HCV activity. Viperin interacts with the HCV replication complex, specifically interacting with the core and NS5A proteins at the lipid droplet interface, while the IFITM family of proteins interact with the HCV cellular receptor CD81 to block HCV entry. The benefits of this research include the potential for novel therapeutic strategies to help combat chronic HCV infection.

INTERACTIONS BETWEEN HBV AND HCV *IN VITRO*

Infection with hepatitis B virus (HBV) and HCV is not uncommon as transmission routes are similar. In this scenario dual infection results in accelerated liver disease, increased propensity for HCC, and dominance of either one of the viruses. To investigate co-infection *in vitro*, we infected hepatocytes with both HBV and HCV and showed that there was very little effect of each virus on the other in regard to viral replication, with co-infected cells remaining viable.

This work indicated that HBV and HCV can replicate in the same hepatocyte without effect on viral replication and cell viability, and suggests that the effects noted in the co-infected liver are most likely a heightened immunological response in the co-infected liver (*J Hepatol 51: 446-457, 2009*).

Outcomes for the community

Our work investigating the host response to infection with HCV has significant implications, as a greater understanding of how the liver combats HCV infection is essential for the development and implementation of new therapeutic strategies.
As an example, 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.

Leukaemia Biology Group

Professor Junia V. Melo MD, PhD, FRCPath

CML is a paradigm of cancer of the haemopoietic system, in which cells that would normally develop into neutrophils, basophils, eosinophils, and monocytes become cancerous.

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

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

With the introduction of targeted tyrosine kinase inhibitors (TKIs), CML has been transformed from a disease with median survival of five years, to one compatible with normal life expectancy if patients comply with daily oral medication for life. This is a first in cancer therapy and has brought entirely new problems of management.

Although a relatively rare malignancy, effective therapy has dramatically changed its prevalence. In fact, for an increasingly large population of patients, CML has become a chronic illness, like hypertension, diabetes or AIDS.

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

The main focus of our research is to understand how the mutant gene Bcr-Abl is regulated, so that we can build a way to switch it off. In this early stage of the investigation, we are looking broadly at large regions of the gene, before focusing on specific components where we hope to fine tune a cure.

1 Duncan Hewett
2 Vicki Wilczek
3 Bradley Cheneda
4 Junia V. Melo
5 Deborah Cassolari
6 Fong Chan Choy
7 Brett Johnson
8 Ka Chung (Stanley) Cheung
9 Gink Nanxing Yang

SPECIFIC AREAS THAT ARE CURRENTLY BEING ADDRESSED

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

Outcomes for the community

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

Leukaemia Unit

Associate Professor Susan Branford PhD, FFSc(RCPA), AssocRCPA

PATIENTS with chronic myeloid leukaemia (CML) have a unique gene rearrangement that causes the disease; the Bcr-Abl1 gene. The gene is constantly active, which leads to marked cell proliferation, resistance to cell death and genetic instability.

The disease culminates in a rapidly fatal acute leukaemia within three to five years. However, the Bcr-Abl1 protein is extremely sensitive to inhibitor drugs. Most patients respond to therapy and have a significantly prolonged survival.

The Leukaemia Unit's area of research is the molecular investigation of patients with CML, focusing on molecular assessment to guide therapeutic decisions by (1) predicting the response of patients to kinase inhibitor drugs and (2) determining the mechanisms of drug resistance.

We evaluate the levels of Bcr-Abl1 messenger RNA to provide a precise assessment of drug response and standardise methods used internationally to an international reporting scale. We also study the levels of disease that predict patient outcome. Failure to achieve certain levels of reduction of Bcr-Abl1 within defined timelines indicates an increased risk of treatment failure and the need to change therapy. We aim to improve the limit of detection of residual disease to determine when it is safe for patients to cease inhibitor therapy without relapse.

Although most patients respond well to inhibitor drugs, some develop resistance and their disease returns. The most frequent mechanism is the acquisition of point mutations within the protein domain of Bcr-Abl1 where the inhibitor drugs bind. We study the molecular mechanisms of disease resistance and have detected more than 60 of these mutations and correlated different degrees of resistance according to the type of mutation. This provides information to the clinician for appropriate therapeutic intervention. We are investigating procedures to improve the limit of mutation detection using mass spectrometry and massively parallel deep sequencing. Other mechanisms of resistance are being investigated by a search for mutations in other genes that are associated with disease progression, using deep sequencing.

KEY DISCOVERIES IN 2009-2010

EVIDENCE FOR PERSISTENT LEUKAEMIA IN PATIENTS WHO SUCCESSFULLY CEASE INHIBITOR THERAPY

A minority of patients can successfully cease inhibitor therapy without relapse if they have had a prolonged period of sustained undetectable Bcr-Abl1 mRNA. It has not been known whether leukaemia was eradicated in these patients because RNA methods have a limited limit of Bcr-Abl1 detection. We developed a more sensitive method using genomic DNA to detect residual Bcr-Abl1. We found that DNA Bcr-Abl1 was detectable in patients who did not relapse after ceasing therapy. This indicates that it is not necessary to eradicate all leukaemic cells to maintain a complete remission after stopping therapy (*Leukaemia 24: 1719-1724, 2010*).

Further investigation is warranted to determine whether immunological reactivity against the leukaemic cells modifies the risk of early relapse when imatinib treatment is withdrawn.

SENSITIVE DETECTION OF RESISTANT MUTATIONS CAN LEAD TO THEIR RAPID CLONAL EXPANSION

Using highly sensitive mutation detection techniques, somatic mutations within Bcr-Abl1 have been detected in patients prior to commencing inhibitor therapy. However, their detection did not always lead to resistance and sensitive mutation detection was not considered of clinical benefit. Using mass spectrometry, we developed a sensitive multiplex method for the simultaneous detection of 31 common mutations. We investigated patients who had failed kinase inhibitor therapy and who were subsequently treated with more potent kinase inhibitor drugs. In samples collected prior to switching over to the potent inhibitor, we found a very strong correlation of the detection of certain subclonal mutations and their subsequent rapid expansion

1 Zoe Donaldson
2 Jasmina Georgievski
3 Wendy Parker
4 Bronte Jamison
5 Jodi Prime
6 Haley Prime
7 Linda Fletcher
8 Sue Branford
9 Emma Channon
10 Stuart Phillis
11 Chani Field
12 Brad Sullivan
13 Goldi Yong

and disease progression.
This study is the first to clearly demonstrate that subclonal Bcr-Abl1 mutations detected in patients after first-line inhibitor failure are clinically relevant. Our findings support the use of sensitive mutation testing in all patients to aid selection of the most appropriate therapy after inhibitor failure.

DETERMINED THAT BCR-ABL1 VALUES MEASURED EARLY IN THERAPY CAN PREDICT LONG TERM RESPONSE

Our laboratory has monitored the molecular response of patients in an international clinical trial since 2000 of the first kinase inhibitor drug, imatinib.
We determined that the response at eight years can be predicted by measuring Bcr-Abl 1 values as early as six months of therapy.

This has important implications for the international recommendations for monitoring CML patients that currently do not include molecular values for therapeutic decisions (*Blood 116: 3758-3765, 2010*).

Outcomes for the community

We have detected residual leukaemia in some patients below the level of detection of techniques that are currently used in clinical practice to monitor patients. This should help guide therapeutic decisions for clinicians and patients when considering a change of therapy. The detection of low levels of leukaemic cells in some patients that contain mutations with the potential to cause drug resistance upon a change of therapy will aid the categorisation of patients at high risk of treatment failure. This will avoid costly and time consuming trials of inappropriate kinase inhibitor drugs.

Lymphatic Development Laboratory

Dr Natasha Harvey PhD

LYMPHATIC vessels are a vital component of the cardiovascular system and play crucial roles during embryonic development and adult homeostasis. These specialised vessels return interstitial fluid and protein to the bloodstream, transport cells of the immune system and absorb lipids from the digestive tract.

The aberrant growth and development of lymphatic vessels (lymphangiogenesis) is associated with human disorders including lymphoedema, vascular malformations, inflammatory diseases and cancer.

The major focus of research in the Lymphatic Development Laboratory is to identify and characterise signals that direct the construction 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 development. 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.

KEY DISCOVERIES IN 2009-2010

IDENTIFICATION OF A MICRORNA, *miR-181a*, THAT REGULATES *Prox1*

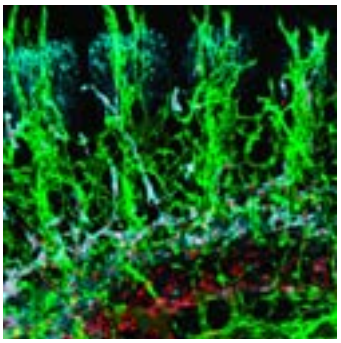
Prox1 is a key transcription factor required to turn on the program of lymphatic endothelial cell identity. To date, very little is known about the mechanisms that control *Prox1* expression and activity. Our recent work identified a microRNA, *miR-181a*, that binds to Prox1 mRNA and prevents it from being translated into protein (*Blood 116: 2395-2401, 2010*). We found that modulating *miR-181a* levels in endothelial cells resulted in the reprogramming of blood and lymphatic endothelial cell identity. Moreover, the levels of *miR-181a* were higher in embryonic blood endothelial cells than in lymphatic endothelial cells, suggesting that this microRNA might contribute to the silencing of *Prox1* in blood vessels. Our results have important implications for the control of *Prox1* and endothelial cell identity in development and disease.

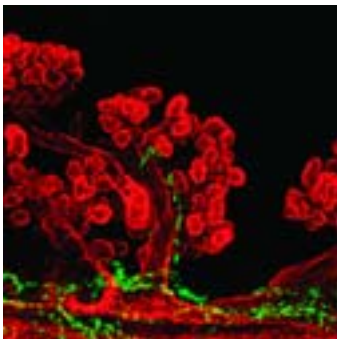
DEMONSTRATION OF A KEY ROLE FOR CELLS OF THE IMMUNE SYSTEM IN DEFINING THE SIZE OF LYMPHATIC VESSELS

Lymphatic vessels are an important route of transport for cells of the immune system during immune surveillance and infection. We have made the key discovery that certain cells of the immune system, macrophages, define the calibre of dermal lymphatic vessels in the mouse embryo by regulating lymphatic endothelial cell proliferation (*Development 137: 3899-3910, 2010*). In addition, we demonstrated that though macrophages are intimately associated with the developing lymphatic vasculature, they are not utilised as a source of lymphatic endothelial progenitor cells.

1 Genevieve Seker
2 Natasha Harvey
3 Kelly Betterman
4 Jan Kazenwadel

These data identify a novel role for macrophages during lymphatic vascular development and have important implications when considering the targeting of these cells as a strategy to treat lymphatic vascular disorders.





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.

Mast Cell Laboratory

Dr Michele Grimbaldeston BA BTh(Hons), PhD

THE MAST CELL is a fascinating cell with its densely packed granular cytoplasm; an appearance that provides insight into this cell's unique capabilities.

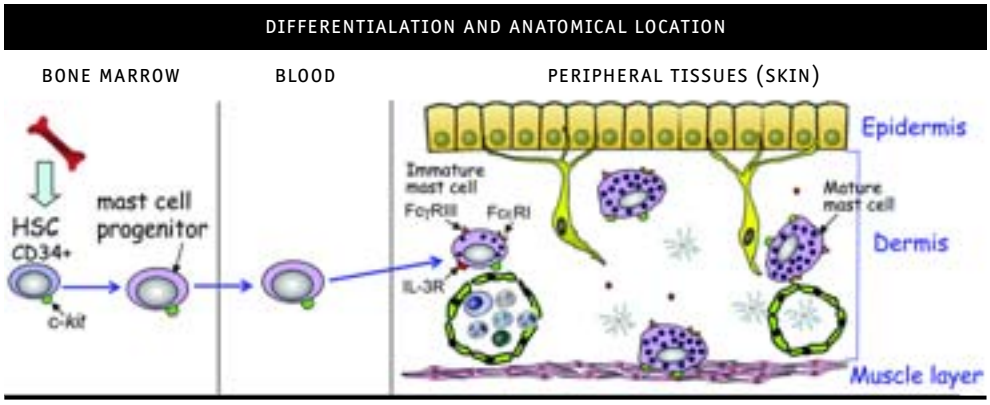
Until very recently, mast cells were historically depicted as primarily pro-inflammatory effector cells with a well-earned notoriety for unrestrained activation and exacerbation of immune responses in disease settings such as anaphylaxis and allergy.

However, there is now strong evidence that in addition to their ability to initiate and amplify inflammation, mast cells can also regulate such responses to protect against pathological effects of excessive inflammation and aid the processes of restoring tissue homeostasis. Identifying the possible settings in which this can occur has exploded into the international arena of mast cell biology and caught the attention of immunologists in general.

This is an exciting time to be investigating the role of mast cells in immune settings as this new role of mast cell-dependent immunoregulation is just emerging, and suggests that this function of mast cells might be of clinical importance.

The Mast Cell Laboratory was established in 2008 by Dr Grimbaldeston who was recruited from **Stanford University**, where she made the novel discovery that mast cell-derived interleukin-10 is immunomodulatory in certain settings of acquired and innate immunity (*Nat Immunol 8: 1095-1104, 2007*).

Research now being undertaken by the laboratory continues to focus on the novel negative 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. Our novel and surprising findings have led to a paradigm shift in the understanding of how this complex cell functions during immune responses.



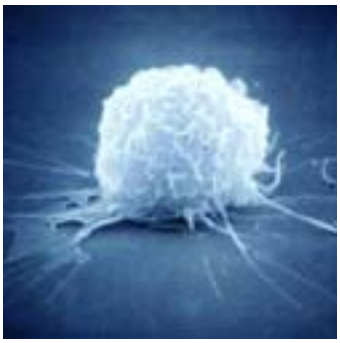
1 Anastasia Yu
2 Michele Grimbaldeston
3 Renee Gilbey
4 Lisa Biggs
5 Boris Fedoric

KEY DISCOVERIES IN 2009-2010

VITAMIN D3 PROMOTES MAST CELL-DEPENDENT REDUCTION OF CHRONIC UVB-INDUCED SKIN PATHOLOGY

Chronic exposure or high intensities of ultraviolet-B (UVB; wavelengths 280-320 nm) irradiation, a component of sunlight, can cause extensive skin damage, inflammation at the affected site and can lead to the development of skin cancer. While the detrimental effects of too much UVB exposure are well known to the Australian community, considerably less is appreciated about the beneficial effects of low dose UVB exposure to the skin. For over eighty years Vitamin D3 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.

In a recent paper (*J Exp Med 207: 455-463, 2010*), we identified the molecular basis for the protective effects of mast cell-dependent limitation of UV-induced skin damage. In response to UVB-induced biologically active vitamin D3, mast cells can produce anti-inflammatory cytokines, such as IL-10, to regulate inflammation *in vivo*. Utilising the powerful tool of mast cell-deficient *c-kit* mutant mice, which can be successfully repaired of their mast cell deficiency by selective engraftment of bone marrow-derived cultured mast cells, we provided evidence that to achieve optimal reduction of UV-induced inflammation and skin pathology, the resident mast cells in the skin had to express the vitamin D receptor. Our results provided the first *in vivo* evidence of a regulatory axis between vitamin D3 and mast cells.



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 D3-induced mast cell activation can initiate anti-inflammatory responses suggests that identifying potential druggable targets that engage the negative regulatory propensity of mast cells will enable new therapies to emerge. Such endeavours will be of paramount importance, for example, to people who suffer with allergic disease, a setting where mast cells can exacerbate the extent of the pathology.

Melissa White Memorial Laboratory

Clinical Laboratory – Professor Timothy Hughes MBBS, MD, FRACP, FRCPA

Research Laboratory – Associate Professor Deborah White PhD, FFSc(RCPA)

THE FOCUS of the Melissa White Laboratory is the cell and molecular biology of chronic myeloid leukaemia (CML), with specific emphasis on responses to the recently developed tyrosine kinase inhibitors (TKIs) including imatinib, nilotinib and dasatinib.

These TKIs specifically target and render inactive the Bcr-Abl protein known to cause CML. By furthering our understanding of CML cell responses to TKIs, we hope to gain insight into how therapy can be improved and individualised for each patient diagnosed with this type of leukaemia.

We have developed an assay (OCT-1 activity) in our laboratory that assesses the functional activity of the human organic cation transporter-1 (OCT-1) in patients at the time of CML diagnosis, prior to the start of any therapy. OCT-1 is the key active transporter protein responsible for the movement of imatinib into target leukaemic cells, enabling imatinib to inhibit the Bcr-Abl protein.

KEY DISCOVERIES IN 2009-2010

1

The OCT-1 activity assay is predictive of both short and long term response in CML patients treated with imatinib. We have demonstrated that patients with poor activity of this protein have significantly lower rates of both molecular response and disease-free survival, than patients with high OCT-1 activity (*J Clin Oncol 28: 2761-2767, 2010*). Furthermore, the effect of low OCT-1 activity can be partially overcome by increasing the dose of imatinib. Importantly, we have also demonstrated that nilotinib (*Blood 108: 697-704, 2006; Leukemia 24: 855-857, 2010*) and dasatinib (*Clin Cancer Res 14: 3881-3888, 2008*), in contrast to imatinib, are not transported by OCT-1. Hence, this assay enables the rationale choice of TKI, and in the case of imatinib the appropriate dose, to ensure maximum therapeutic benefit for the patient.

2

The harbouring of more primitive leukaemic haemopoietic (CD34+) cells has long been regarded as a likely cause of disease persistence and therapeutic failure. In a recent paper, we have demonstrated that the poor response observed in patients with low OCT-1 activity cannot be attributable to lower uptake of imatinib into CD34+ cells (*Leukemia 24: 765-770, 2010*). These findings suggest that a likely determinant of effective longer term response is early and rapid depletion of more mature leukaemic cells. Importantly, this validates a therapeutic approach that uses the most potent and effective therapy up front in patients with CML, and hence demonstrates the importance of rationale therapeutic selection based on assays performed on patient cells at the time of diagnosis.

1 Timothy Hughes
2 Jackie Wong
3 Lisa Schafranek
4 Jarrad Goyne
5 Kelvin Groot Obbink
6 Chung Hoow Kok
7 Dale Watkins
8 Amity Frede
9 Laura Eadie
10 Jane Engler
11 Verity Saunders
12 Stephanie Arbon
13 Carine Tang
14 Jenny Mclean
15 Eva Nievergall
16 Deborah White

Absent:
David Yeung
Devendra Hiwase
Sasha Wheeler
Phoung Dang (on maternity leave at time of photo)

3

The effect of combination therapeutic strategies on leukaemic cell eradication has also been a focus of our laboratory. We have demonstrated increased potency of dasatinib when it is combined with blockade of cytokine signalling. In the absence of blockade, cytokines may provide a pathway for leukaemic cells to escape TKI mediated cell death (*Leukemia 24: 771-778, 2010*). We have also demonstrated that the combination of nilotinib and dasatinib results in an increase in the intracellular concentration and hence efficacy of dasatinib, through blockade of proteins associated with drug efflux from leukaemic cells (*Leukemia 24: 658-660, 2010*). In addition, we have demonstrated that the combination of nilotinib and imatinib results in an increase in the intracellular concentration and effectiveness of nilotinib via the same efflux proteins (*Blood 109: 3609-3610, 2007*).

These important *in vitro* experiments and others ongoing in our laboratory, provide a strong rationale for future therapeutic approaches using drugs in combination to improve efficacy and hence survival in CML patients.

Outcomes for the community

The introduction of targeted therapy has heralded a significant step forward in the treatment of malignancies, specifically CML. The success of drugs such as imatinib will likely result in this approach being applied to other malignancies with identified key target proteins. However, surprisingly not all patients benefit from this targeted therapeutic approach. Understanding why some patients fail to respond is a critical step towards the era of personalised medicine, and is central to the research theme of our laboratory.

Molecular Pathology Research Laboratory

Professor Hamish Scott PhD, FFSc(RCPA)

RARE CASES of predisposition to leukaemias and lymphomas, including congenital diseases such as Down syndrome (DS) and families with inherited predispositions to leukaemias and lymphomas, can provide insights into the initiation and progression of these diseases.

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 ways of better treating and monitoring cancer. The 'model diseases' we are most interested in are blood cell diseases such as leukaemias, lymphomas and autoimmunity (e.g. arthritis). These diseases are mechanistically linked, being caused by excessive clonal expansion of a specific blood cell type, and may often occur together.

One of our diseases of interest is DS, which results from trisomy of chromosome 21, is the most common chromosomal disorder in humans with a frequency of approximately 1 in 800 live births. It is largely unknown why DS individuals are at risk of developing leukaemia.

With the **South Australian Familial Cancer Service**, we also collect samples from families with rare predispositions to haematological malignancies from across the country, and attempt to determine which genes are mutated. These studies have immediate and direct implications for affected families and are beneficial for counselling, family planning and, ultimately, choices of therapy. The genes responsible for familial haematological malignancies are also likely to be of considerable importance in sporadic haematological malignancies.

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. AIRE is expressed in thymic medullary epithelial cells (mTECs) where it regulates the expression of RNAs encoding proteins normally restricted to specific tissues or cell types. These tissue specific antigens (TSAs) can then be presented to autoreactive 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. In mouse mTECs, AIRE regulates the expression of the majority of genes encoding well known auto-Ags in human organ-specific autoimmune diseases (such as insulin-dependant diabetes). We are generating new mouse models for autoimmunity which will help us understand pathogenic mechanisms and develop new therapeutic strategies.

KEY DISCOVERIES IN 2009-2010

PREDISPOSITION TO LEUKAEMIAS

Down syndrome (DS) persons are born with various haematopoietic abnormalities, ranging from relatively benign, to a more severe premalignant transient myeloproliferative disorder (TMD) that may develop into acute megakaryocytic leukaemia (AMKL). We analysed the haematopoietic development of the Ts1Cje mouse model of DS. Our analyses identified defects in mature blood cells, including macrocytosis and anaemia similar to that seen in DS patients. While we also detected abnormalities in foetal liver, bone marrow stem and progenitor cell function, the Ts1Cje mice do not develop disease resembling either TMD or AMKL (*Blood 113: 1929-1937, 2009*).

In three families with predisposition to acute myeloid leukaemia (AML), direct sequencing detected CEBPA mutations in the largest family described to date, which is also Australian. This family had poor

1 Peter Brautigan
2 Brita Ardesjo Lungren
3 Milena Babic
4 Hamish Scott
5 Young Lee
6 Lih Yin Tan
7 Scott Warming
8 Chris Hahn

Absent:
King-Hwa (Michael) Ling
Lucia Gagliardi
Chang Eng Chong
Sarah Kinkel
Ming Lin

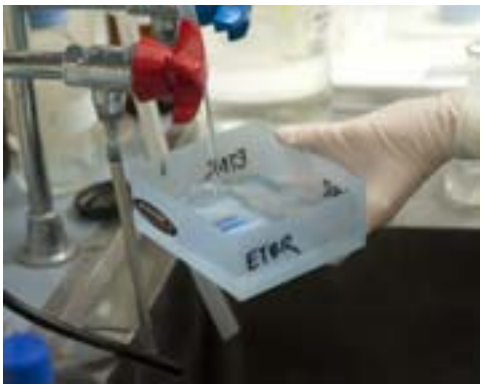
prognosis compared to other families and sporadic AML with CEPBA mutations, possibly due to downstream mutations affecting the *ATM, FLT3* and CDX2 genes that were detected using genomic arrays (*Br J Haematol 150: 382-385, 2010*).

While direct sequencing failed to detect mutations in either RUNX1 or CEBPA in the other two families, we identified intragenic RUNX1 deletions using genomic arrays. This included apparently unaffected children who on further inspection were shown to have thrombocytopenia. Genomic screening for whole or partial gene deletions and duplications should be included in the RUNX1 mutation analysis and considered in families with thrombocytopenia (*Leukemia 24: 242-246, 2010*).

GENERATION OF NEW MOUSE MODELS OF AUTOIMMUNITY

We have generated a mouse gene knockout model of APS1 with a mutation mimicking the common human 13-bp deletion mutation. Generated on an autoimmune resistant C57BL/6 isogenic genetic background, the AIRE-deficient mice present with only a mild autoimmune phenotype consisting of Sjögren's syndrome and autoimmune uveoretinitis (*J Immunol 182: 3902-3918, 2009*).

To date, we have induced organ-specific autoimmunity in AIRE$^{-/-}$ mice for three different AIRE-regulated TSAs; (1) collagen (Col2a)-induced arthritis (*Arthritis Rheum 60: 1683-1693, 2009*), (2) myelin oligonucleotide glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (*Eur J Immunol 40: 3499-3509, 2010*), and (3) acetylcholine receptor (AChR)-induced myasthenia gravis (MG) (*J Autoimmun 36: 16-24, 2010*). This has generated new models of rheumatoid arthritis, multiple sclerosis and MG for investigation of disease pathogenesis and experimental therapeutic intervention.



Outcomes for the community

We continue to show that studies of what are rare inherited conditions, such as predispositions to cancers and autoimmunity, not only have immediate benefits for affected families in genetic diagnosis, counselling and choice of therapy, but open new avenues of research into the basic biology of normal biological and disease processes. The long term benefit of generating new test tube and animal models of disease is having a profound effect on the understanding of sporadic, non-familial forms of these diseases and will ultimately result in new therapeutic strategies.

Molecular Regulation Laboratory

Professor Sharad Kumar MSc, PhD

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.

Our broad research focus is on cellular and molecular biology of disease, with an emphasis on cancer biology. Our two major interests are (1) the study of programmed cell death of normal and cancer cells and (2) understanding the regulation of cellular homeostasis by ubiquitination. 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 (the Nedd4 family of ubiquitin ligases), which are implicated in the ubiquitination of a number of proteins mentioned above (*Nature Rev Mol Cell Biol 10: 398-409, 2009*). 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.

KEY DISCOVERIES IN 2009-2010

A TUMOUR SUPPRESSOR FUNCTION FOR CASPASE-2

The function of caspase-2, one of the first discovered and most conserved of caspases, has long remained an enigma. In a recent paper (*Proc Natl Acad Sci USA 106: 5336-5341, 2009*) we provided the first evidence that loss of caspase-2 in mice makes them more susceptible to lymphoma induced by the expression of Myc oncoprotein. We also found that caspase-2 deficiency results in an increased ability of cells to acquire a transformed phenotype. Furthermore, we showed that caspase-2-deficient MEFs have defective cell cycle regulation following DNA damage. These results thus suggest that caspase-2 is a potential tumour suppressor. This discovery has clear implications in understanding tumourigenesis (*Nature Rev Cancer 9: 897-903, 2009*).

A NOVEL MECHANISM OF DEVELOPMENTAL CELL DEATH

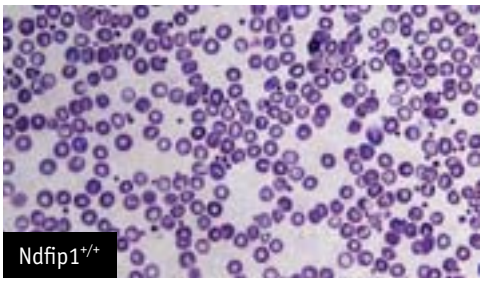
Most cell death during animal development is mediated by caspase-dependent apoptosis. Using *Drosophila* as a model system we made a surprising discovery that the larval midguts undergo normal programmed deletion even when most of the apoptotic execution machinery was genetically ablated or inhibited (*Current Biology 19: 1741-1746, 2009*). We further found that the disruption of autophagy inhibited midgut deletion, suggesting that autophagy was required for programmed cell death in the midgut. Our studies provide evidence for the existence of a novel developmental cell death mechanism where apoptotic machinery seems to be dispensable, but autophagy is critical.

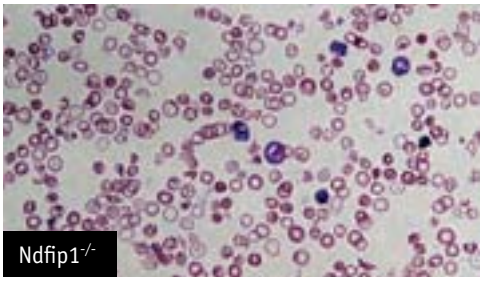
1 Kathryn Mills
2 Natalie Foot
3 Joey Puccini
4 Shannon Nicolson
5 Jantina Manning
6 Hazel Dalton
7 Wenying (Layla) Zhu
8 Krupa Krishnaprasad
9 Sonia Shalini
10 Natasha Boase
11 Loretta Dorstyn
12 Scott Townley
13 Donna Denton
14 Kristen Ho
Inset: Sharad Kumar

A NOVEL INTERPLAY BETWEEN IRON ABSORPTION, INFLAMMATION AND ANAEMIA

In 2008, we reported 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* (*Blood 112: 4268-4275, 2008*), previously identified by us as Nedd4 WW domain interacting proteins. Consistent with these observations *Ndfip1*$^{-/-}$ mice fed a normal diet showed increased accumulation of iron stores in the liver and spleen. In further studies, we found that in *Ndfip1*$^{-/-}$ 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*$^{-/-}$ mice developed severe anaemia due to a combined effect of iron deficiency and inflammatory disease in these animals.

Ndfip1$^{-/-}$ mice are known to develop severe inflammatory disease, and our new observations suggest that iron deficiency may accentuate this phenotype (*Blood 117: 638-646, 2011*). Our results thus provide evidence that *Ndfip1* is a key regulator of DMT1 and iron homeostasis and this regulation may be critical under iron-limiting conditions.





Outcomes for the community

The main anticipated outcomes from our research are (1) better understanding of the disease mechanisms, (2) discovery of new disease markers, and (3) discovery of potentially novel therapeutic targets.

Molecular Signalling Laboratory

Associate Professor Stuart Pitson PhD

THE MOLECULAR Signalling Laboratory examines sphingolipid-mediated cell signalling pathways and how they contribute to cancer and other diseases.

In particular, the primary focus of our work is the enzyme sphingosine kinase, which 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, while sphingosine 1-phosphate also acts as a ligand for a family of sphingosine 1-phosphate-specific cell surface receptors. Of greatest interest to our laboratory are findings that elevated cellular sphingosine kinase prevents programmed cell death (apoptosis), enhances cell proliferation, and leads to neoplastic cell transformation. This indicates an oncogenic role for sphingosine kinase, which is further supported by recent data showing elevated sphingosine kinase in a variety of human cancer cells and inhibition of tumour growth *in vivo* by genetic or chemical suppression of sphingosine kinase.

In addition to this role in tumourigenesis, sphingosine kinase and sphingosine 1-phosphate appear to be 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 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 anti-sphingosine kinase therapeutics. Much of our work to date on sphingosine kinase has focused on the post-translational regulation of this enzyme.

Sphingosine kinase is activated in cells in response to certain growth factors and other agonists. We have shown that activation of sphingosine kinase 1 occurs through phosphorylation, which not only enhances its catalyic activity, but also results in its translocation to the plasma membrane. We have made a major breakthrough by demonstrating that this phosphorylation, and especially the subsequent translocation, mediates the pro-proliferative, pro-survival and oncogenic effects of sphingosine kinase 1. Understanding the mechanism(s) regulating the phosphorylation status of sphingosine kinase 1 and its translocation are likely to provide therapeutic targets to control cancer.

1 Watson Chan
2 Julia Dobbins
3 Kristy Alexander
4 Carl Coolen
5 Stuart Pitson
6 Jo Woodcock
7 Briony Gliddon
8 Melissa Pitman
9 Heidi Neubauer
10 Paul Moretti
11 Duyen Pham

KEY DISCOVERIES IN 2009-2010

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 indicate that targeting this enzyme is a therapeutic option for these EF1A-induced cancers (*Oncogene 30: 372-378, 2011*).

CIB1 CONTROLS ONCOGENIC SIGNALLING BY SPHINGOSINE KINASE

We have revealed a crucial mechanism by which sphingosine kinase is regulated via its interaction with another protein called CIB1. We found that CIB1 binds to sphingosine kinase and transports this protein complex to the cell membrane, a localisation that we have previously shown to be a major factor in the ability of sphingosine kinase to lead to tumour formation. These findings provide us with the unique opportunity to develop potential anti-cancer therapies to specifically target this pathway (*J Biol Chem 285: 483-492, 2010*).

PRO-SURVIVAL 14-3-3 PROTEINS ARE REGULATED BY SPHINGOSINE AND FTY720

We have discovered that a family of 14-3-3 proteins that are critical for maintaining cell survival, bind to and are functionally altered by sphingosine. Sphingosine disrupts the pro-survival function of 14-3-3 proteins, leading ultimately to cell death. Additionally a new drug, FTY720 mimics the effect of sphingosine on 14-3-3 proteins suggesting that FTY720's anti-cancer effects are mediated by its effect on 14-3-3 proteins (*Cellular Signalling 22: 1291–1299, 2010*).

Outcomes for the community

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

Myeloma Research Laboratory

Professor Andrew Zannettino PhD

MULTIPLE myeloma (MM) is an incurable haematological cancer of the antibody-producing plasma cell. The estimated frequency of this disease in our community is estimated to be 5-6 new cases per 100,000 persons per year.

MM is unique amongst haematological malignancies in its capacity to cause massive destruction of the skeleton. The focal osteolytic lesions result in a range of debilitating clinical symptoms including bone pain, pathological fractures, spinal cord compression, hypocalcaemia and renal failure.

The Myeloma Research Laboratory's (MRL) efforts centre on identifying the molecular and cellular mechanisms responsible for myeloma disease progression. Current projects are focused on (1) determining the role played by hypoxia in MM disease progression; (2) identifying novel bone marrow (BM) microenvironmental factors that may contribute to MM disease progression; (3) identifying novel agents to inhibit osteoclast-mediated bone loss and/or stimulate osteoblast-mediated bone formation; (4) identifying novel signalling pathways with roles in mesenchymal stem cell differentiation that may be manipulated to increase bone formation in MM patients; (5) examining the skeletal and metabolic effects of tyrosine kinase inhibitor (TKI) compounds.

KEY DISCOVERIES IN 2009-2010

- long-term imatinib therapy promotes bone formation in CML patients
- disruption of the CXCL12/CXCR4 axis inhibits osteolysis in a murine model of myeloma-associated bone loss
- hypoxia-inducible factor-2 is a novel regulator of aberrant CXCL12 expression in multiple myeloma plasma cells
- NVP-BEZ235, a dual pan class I PI3 kinase and mTOR inhibitor, promotes osteogenic differentiation in human mesenchymal stromal cells and may be a novel treatment modality for myeloma-associated bone loss
- plasma adiponectin levels are markedly elevated in imatinib-treated chronic myeloid leukaemia (CML) patients and represent a mechanism for improved insulin sensitivity in Type 2 diabetic CML patients.

CONTRIBUTION TO MYELOMA TREATMENT

We have provided guidance on both myeloma and supportive treatment strategies and have co-authored guidelines for the safe use of bisphosphonates (*Intern Med J 39: 304-316, 2009*) and Clinical Practice Guidelines. Furthermore, our work has raised awareness amongst clinicians of the importance of routine examination of CTX levels in patients. CTX (the C-telopeptide of the α1 chain of collagen type 1), a reliable marker of bone turnover, is now being used locally as a routine test for all myeloma patients at diagnosis and disease restaging. It is now known that CTX, when used in conjunction with paraprotein levels and bone marrow assessment, can detect early progression of myeloma.

1 Sharon Paton
2 Peter Diamond
3 Mary Matthews
4 Sharon Williams
5 James Richardson
6 Shriram Nath
7 Andrew Zannettino
8 Catherine Gan
9 Jenny Drew
10 Manami Ito
11 Sally Martin
12 Stephen Fitter
13 Hongsheng Wang
14 Kate Vandyke

IMATINIB AND SKELETAL METABOLISM

We have discovered that tyrosine kinase inhibitors (TKIs) affect key kinase enzymes with pivotal roles in both skeletal (*J Bone Miner Res 25: 2126-2137, 2010; J Bone Miner Res 25: 1759-1770, 2010; Blood 115: 766-774, 2010; Bone 44 878-885, 2009; Leukemia 23: 994-997, 2009*) and glucose metabolism (*J Clin Endocrinol Metab 95: 3763-3767, 2010*). In particular, our laboratory was the first to report a potential mechanism for the observed perturbation of growth seen in juvenile patients undergoing imatinib therapy. Our studies highlight the importance of monitoring growth plate morphology in these patients. The increasing use of imatinib as a front-line treatment for CML in the paediatric setting makes our studies of great significance.

IMATINIB, ADIPONECTIN AND TYPE 2 DIABETES

In addition to its anti-neoplastic activity, imatinib therapy is also associated with an improvement in glucose and lipid metabolism in CML patients with concurrent Type 2 diabetes. These improvements occur in the absence of significant dietary or lifestyle changes suggesting imatinib therapy improves insulin sensitivity.

We have shown that imatinib therapy induces a 2-4 fold increase in the plasma concentration of adiponectin, an adipose-secreted adipokine that plays an important role in insulin sensitivity. Low adiponectin levels are an important risk factor in the development of Type 2 diabetes and current anti-diabetic medications (e.g. TZDs) work, at least in part, by elevating plasma adiponectin levels 2-3 fold. Our observed increase in adiponectin levels occurred within a time frame that is coincident with reports of improved glucose and lipid metabolism in diabetic and non-diabetic CML patients that are responsive to imatinib therapy.

STEM CELL THERAPIES

As a co-inventor (in collaboration with Professor Stan Gronthos) of the mesenchymal progenitor cell (MPC) cellular therapy, which is now being commercialised by **Mesoblast Ltd**, we have been instrumental in developing a stem cell-based therapy that is likely to have significant impact in the areas of spinal fusion, osteoarthritis, congestive heart failure, heart attacks, eye diseases, diabetes, and bone marrow repair. In mid-2010, the Australian/New Zealand Therapeutic Goods Administration approved the use of autologous MPC for the repair of skeletal tissues.

Outcomes for the community

With a broad research focus encompassing myeloma disease progression, stem cell biology, bone biology and the makeup of the bone marrow microenvironment, our aim is to unravel the intricate mechanisms which underlie a number of normal and disease processes. With this information, our work has aided the development and/or assessment of targeted therapeutic strategies to treat diseases associated with bone destruction (such as myeloma and osteoporosis), diabetes, spinal fusion, osteoarthritis, cardiac disease and bone marrow repair.

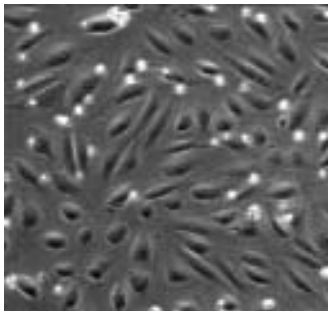
Vascular Biology and Cell Trafficking Laboratory

Dr Claudine Bonder PhD

BLOOD VESSELS contribute to life threatening diseases but are also essential for tissue regeneration and organ transplantation.

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, coronary artery disease and stroke patients have ~40% less circulating EPCs when compared to age-matched healthy controls. Recruitment of EPCs may also be a mechanism by which cancer progresses, as reduced EPC mobilisation has been associated with impaired tumour vasculogenesis, reduced tumour formation and increased cancer patient survival.



Because of the worldwide recognition that EPCs are key determinants of many life threatening and fatal diseases, there are currently over 150 clinical trials registered involving EPCs. 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 (1) investigate the blood vasculature in normal and disease states and (2) identify markers that define a purified population of cells with postnatal vasculogenic potential as well as the genetic profile that regulates their differentiation, survival and recruitment. Our work may provide new opportunities to augment blood vessel development in patients with cardiovascular disease, and also ablate blood vessel development in cancer patients.

KEY DISCOVERIES IN 2009-2010

A NEW MECHANISM BY WHICH NEUTROPHILS ADHERE TO THE VASCULATURE

Leukocytes are recruited from the circulation to combat inflammation and immune responses via a complex cascade of adhesion events. Despite our significant progress in the knowledge of the leukocyte adhesion cascade, there are still several gaps in our understanding which manifest as a conglomerate of currently ineffective therapeutic targets. We recently demonstrated that tumour necrosis factor (TNF)α activates the integrin $\alpha_5\beta_1$ without altering total expression levels on human umbilical vein endothelial cells, and that this process is dependent on sphingosine kinase (SK)-1. We have shown that neutrophil adhesion to TNFα-activated endothelium can be attenuated by blocking SK-1, $\alpha_5\beta_1$ or its ligand angiopoietin (Ang)-2 (*Am J Path 177: 436-446, 2010*). These observations add new complexities that broaden the accepted concept of cellular trafficking and suggest that SK-1 may be a significant target for an effective broad spectrum approach to combat inflammation and immune disorders.

DESCRIPTION OF A NEW SURVIVAL PATHWAY BY ENDOTHELIAL CELLS

We recently demonstrated that under basal conditions sphingosine kinase (SK)-1, integrin $\alpha_v\beta_3$ and CD31 (platelet endothelial cell adhesion molecule; PECAM-1) exist as a heterotrimeric complex, and that in conditions that impact on EC survival, increased formation of this complex occurs. Over-expression studies demonstrate a requirement of SK-1 phosphorylation at serine 225 for increased heterotrimeric complex formation, activation of $\alpha_v\beta_3$ and EC survival signals, including Bcl-X and NFκB pathways. Moreover, β_3 integrin depletion confirmed the requirement for

1 Kate Parham
2 Minky Cockshell
3 Sarah Brice
4 Jyotsna Pippal
5 Wai Yan (Kiwi) Sun
6 Claudine Bonder
7 Lisa Ebert
8 Emma Thompson
Absent:
Samantha Escarbe

this heterotrimeric complex in SK-1 mediated EC survival. Thus, with $\alpha_v\beta_3$ integrin identifiable primarily on angiogenic ECs, and SK-1 being highly expressed in tumours, we hypothesise that targeting SK-1 may impact on multiple survival pathways and its inhibition may be highly efficacious in controlling pathological EC survival.

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-1 (SK-1) regulates the rate and direction of EPC differentiation without effect on the haematopoietic compartment (*Blood 113: 2108-2117, 2009*). Briefly, EPCs from SK-1 knockout mice form more adherent EC units and acquire a mature EC phenotype more rapidly, while conversely, EPCs from mice over-expressing SK-1 in the EC compartment are retarded in their differentiation.

Using this skill set, 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 **Co-operative Research Centre for Biomarker Translation**, these proteins are being investigated for diagnostic and therapeutic potential. 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.

BLOOD VESSELS ARE CRITICAL FOR PANCREATIC ISLET FUNCTION

Pancreatic islet transplantation is limited by extensive apoptosis and suboptimal function of the implanted islets in the longer term. Endothelial progenitor cells (EPC) may be ideal for enhancing both the survival and function of transplanted islets. Our current work (in collaboration with Dr Claire Jessup and Associate Professor Toby Coates at the **Royal Adelaide Hospital**) investigates the *in vitro* formation of rat mosaic pseudoislets comprised of pancreatic beta cells with interspersed vasculogenic EPCs. New and exciting data suggest that mosaic pseudoislets maintain function *in vitro* and may represent an enhanced cell therapy delivery approach for the survival and revascularisation of transplanted islets.

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 the 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 augment blood vessel development in patients with cardiovascular disease and also reduce blood vessel development in cancer patients.

Publications 2009 – 2010

Al-Mawali A, Gillis D and Lewis I. The role of multiparameter flow cytometry for detection of minimal residual disease in acute myeloid leukemia. *Am J Clin Pathol* 131(1):16-26, 2009.

Al-Mawali A, Gillis D and Lewis I. The use of receiver operating characteristic analysis for detection of minimal residual disease using five-color multiparameter flow cytometry in acute myeloid leukemia identifies patients with high risk of relapse. *Cytometry B Clin Cytom* 76(2):91-101, 2009.

Al-Mawali A, To LB, Gillis D, Hissaria P, Mundy J and Lewis I. The presence of leukaemia-associated phenotypes is an independent predictor of induction failure in acute myeloid leukaemia. *Int J Lab Hematol* 31(1):61-8, 2009.

Aricha R, Feferman T, Scott HS, Souroujon MC, Berrih-Aknin S and Fuchs S. The susceptibility of Aire(-/-) mice to experimental myasthenia gravis involves alterations in regulatory T cells. *J Autoimmun* 36:16-24, 2010.

Arthur A, Shi S, Zannettino AC, Fujii N, Gronthos S and Koblar SA. Implanted adult human dental pulp stem cells induce endogenous axon guidance. *Stem Cells* 27(9):2229-37, 2009.

Arthur A, Zannettino A and Gronthos S. The therapeutic applications of multipotential mesenchymal/stromal stem cells in skeletal tissue repair. *J Cell Physiol* 218(2):237-45, 2009.

Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guilhot F, Hochhaus A, Horowitz M, Hughes T, Kantarjian H, Larson R, Radich J, Simonsson B, Silver RT, Goldman J and Hehlmann R. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol* 27(35):6041-51, 2009.

Barry EF, Felquer FA, Powell JA, Biggs L, Stomski FC, Urbani A, Ramshaw H, Hoffmann P, Wilce MC, Grimbaldeston MA, Lopez AF and Guthridge MA. 14-3-3:Shc scaffolds integrate phosphoserine and phosphotyrosine signaling to regulate phosphatidylinositol 3-kinase activation and cell survival. *J Biol Chem* 284(18):12080-90, 2009.

Bartley PA, Ross DM, Latham S, Martin-Harris MH, Budgen B, Wilczek V, Branford S, Hughes TP and Morley AA. Sensitive detection and quantification of minimal residual disease in chronic myeloid leukaemia using nested quantitative PCR for BCR-ABL DNA. *Int J Lab Hematol* 32(6 Pt 1): e222-8, 2010.

Batlle A, Papadopoulou V, Gomes AR, Willimott S, Melo JV, Naresh K, Lam EW and Wagner SD. CD40 and B-cell receptor signalling induce MAPK family members that can either induce or repress Bcl-6 expression. *Mol Immunol* 46(8-9):1727-35, 2009.

Berzsenyi MD, Roberts SK, Preiss S, Woollard DJ, Beard MR, Skinner NA, Bowden DS and Visvanathan K. Hepatic TLR2 & TLR4 expression correlates with hepatic inflammation and TNF-α in HCV & HCV/HIV infection. *J Viral Hepat*, E-pub 6-11-2010.

Biggs L, Yu C, Fedoric B, Lopez AF, Galli SJ and Grimbaldeston MA. Evidence that vitamin D(3) promotes mast cell-dependent reduction of chronic UVB-induced skin pathology in mice. *J Exp Med* 207(3):455-63, 2010.

Blake SJ, Lyons AB and Hughes TP. Nilotinib inhibits the Src-family kinase LCK and T-cell function in vitro. *J Cell Mol Med* 13(3):599-601, 2009.

Bonder CS, Sun WY, Matthews T, Cassano C, Li X, Ramshaw HS, Pitson SM, Lopez AF, Coates PT, Proia RL, Vadas MA and Gamble JR. Sphingosine kinase regulates the rate of endothelial progenitor cell differentiation. *Blood* 113(9):2108-17, 2009.

Bracken CP, Gregory PA, Khew-Goodall Y and Goodall GJ. The role of microRNAs in metastasis and epithelial-mesenchymal transition. *Cell Mol Life Sci* 66(10):1682-99, 2009.

Branford S and Hughes TP. Practical considerations for monitoring patients with chronic myeloid leukemia. *Semin Hematol* 47(4):327-34, 2010.

Branford S, Melo JV and Hughes TP. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter? *Blood* 114(27):5426-35, 2009.

Campbell IK, Kinkel SA, Drake SF, van Nieuwenhuijze A, Hubert FX, Tarlinton DM, Heath WR, Scott HS and Wicks IP. Autoimmune Regulator Controls T Cell Help for Pathogenetic Autoantibody Production in Collagen-Induced *Arthritis. Arthritis Rheum-US* 60(6):1683-1693, 2009.

Carmichael CL, Majewski IJ, Alexander WS, Metcalf D, Hilton DJ, Hewitt CA and Scott HS. Hematopoietic defects in the Ts1Cje mouse model of Down syndrome. *Blood* 113(9):1929-1937, 2009.

Carmichael CL, Wilkins EJ, Bengtsson H, Horwitz MS, Speed TP, Vincent PC, Young G, Hahn CN, Escher R and Scott HS. Poor prognosis in familial acute myeloid leukaemia with combined biallelic CEBPA mutations and downstream events affecting the ATM, FLT3 and CDX2 genes. *Br J Haematol* 150(3):382-385, 2010.

Caruso M, Moore J, Goodall GJ, Thomas M, Phillis S, Tyskin A, Cheetham G, Lerda N, Takahashi H and Ruszkiewicz A. Over-expression of cathepsin E and trefoil factor 1 in sessile serrated adenomas of the colorectum identified by gene expression analysis. *Virchows Arch* 454(3):291-302, 2009.

Castrechini NM, Murthi P, Gude NM, Erwich JJ, Gronthos S, Zannettino A, Brennecke SP and Kalionis B. Mesenchymal stem cells in human placental chorionic villi reside in a vascular Niche. *Placenta* 31(3):203-12, 2010.

Chase A, Schultheis B, Kreil S, Baxter J, Hidalgo-Curtis C, Jones A, Zhang L, Grand FH, Melo JV and Cross NC. Imatinib sensitivity as a consequence of a CSF1R-Y571D mutation and CSF1/CSF1R signaling abnormalities in the cell line GDM1. *Leukemia* 23(2):358-64, 2009.

Chuah C and Melo JV. Targeted treatment of imatinib-resistant chronic myeloid leukemia: Focus on dasatinib. *Onco Targets Ther* 2:83-94, 2009.

Colavita I, Esposito N, Martinelli R, Catanzano F, Melo JV, Pane F, Ruoppolo M and Salvatore F. Gaining insights into the Bcr-Abl activity-independent mechanisms of resistance to imatinib mesylate in KCL22 cells: a comparative proteomic approach. *Biochim Biophys Acta* 1804(10):1974-87, 2010.

Condina MR, Guthridge MA, McColl SR and Hoffmann P. A sensitive magnetic bead method for the detection and identification of tyrosine phosphorylation in proteins by MALDI-TOF/TOF MS. *Proteomics* 9(11):3047-57, 2009.

Cortes JE, Baccarani M, Guilhot F, Druker BJ, Branford S, Kim DW, Pane F, Pasquini R, Goldberg SL, Kalaycio M, Moiraghi B, Rowe JM, Tothova E, De Souza C, Rudoltz M, Yu R, Krahnke T, Kantarjian HM, Radich JP and Hughes TP. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. *J Clin Oncol* 28(3):424-30, 2010.

Cowin PA, Gold E, Aleksova J, O'Bryan MK, Foster PMD, Scott HS and Risbridger GP. Vinclozolin Exposure in Utero Induces Postpubertal Prostatitis and Reduces Sperm Production via a Reversible Hormone-Regulated Mechanism. *Endocrinology* 151(2):783-792, 2010.

Crawford LJ, Windrum P, Magill L, Melo JV, McCallum L, McMullin MF, Ovaa H, Walker B and Irvine AE. Proteasome proteolytic profile is linked to Bcr-Abl expression. *Exp Hematol* 37(3):357-66, 2009.

Dalton HE, Denton D, Foot NJ, Ho K, Mills K, Brou C and Kumar S. Drosophila Ndfip is a novel regulator of Notch signaling. *Cell Death Differ*, E-pub 23-10-2010.

Dawson MA, Opat SS, Taouk Y, Donovan M, Zammit M, Monaghan K, Horvath N, Roberts AW, Prince HM, Hertzberg M, McLean CA and Spencer A. Clinical and immunohistochemical features associated with a response to bortezomib in patients with multiple myeloma. *Clin Cancer Res* 15(2):714-22, 2009.

de Melo JV, Jones GW, Berry C, Vasconcelos RH, de Oliveira CM, Furtado AF, Peixoto CA and Silva-Filha MH. Cytopathological effects of Bacillus sphaericus Cry48Aa/Cry49Aa toxin on binary toxin-susceptible and –resistant Culex quinquefasciatus larvae. *Appl Environ Microbiol* 75(14):4782-9, 2009.

Denton D, Shravage B, Simin R, Baehrecke EH and Kumar S. Larval midgut destruction in Drosophila: not dependent on caspases but suppressed by the loss of autophagy. *Autophagy* 6(1):163-5, 2010.

Denton D, Shravage B, Simin R, Mills K, Berry DL, Baehrecke EH and Kumar S. Autophagy, not apoptosis, is essential for midgut cell death in Drosophila. *Curr Biol* 19(20):1741-6, 2009.

Diamond P, Labrinidis A, Martin SK, Farrugia AN, Gronthos S, To LB, Fujii N, O'Loughlin PD, Evdokiou A and Zannettino AC. Targeted disruption of the CXCL12/CXCR4 axis inhibits osteolysis in a murine model of myeloma-associated bone loss. *J Bone Miner Res* 24(7):1150-61, 2009.

Dickinson M, Prince HM, Kirsa S, Zannettino A, Gibbs SD, Mileshkin L, O'Grady J, Seymour JF, Szer J, Horvath N and Joshua DE. Osteonecrosis of the jaw complicating bisphosphonate treatment for bone disease in multiple myeloma: an overview with recommendations for prevention and treatment. *Intern Med* J 39(5):304-16, 2009.

Dorstyn L and Kumar S. Putative functions of caspase-2. *F1000 Biol Rep* 1, 2009.

Drummond MW, Heaney N, Kaeda J, Nicolini FE, Clark RE, Wilson G, Shepherd P, Tighe J, McLintock L, Hughes T and Holyoake TL. A pilot study of continuous imatinib vs pulsed imatinib with or without G-CSF in CML patients who have achieved a complete cytogenetic response. *Leukemia* 23(6):1199-201, 2009.

Eadie L, Hughes TP and White DL. Nilotinib does not significantly reduce imatinib OCT-1 activity in either cell lines or primary CML cells. *Leukemia* 24(4):855-7, 2010.

Engler JR, Frede A, Saunders V, Zannettino A, White DL and Hughes TP. The poor response to imatinib observed in CML patients with low OCT-1 activity is not attributable to lower uptake of imatinib into their CD34+ cells. *Blood* 116(15):2776-8, 2010.

Engler JR, Frede A, Saunders VA, Zannettino AC, Hughes TP and White DL. Chronic myeloid leukemia CD34+ cells have reduced uptake of imatinib due to low OCT-1 activity. *Leukemia* 24(4):765-70, 2010.

Eyre NS, Baumert TF and Beard MR. Closing the gap: the tight junction protein occludin and hepatitis C virus entry. *Hepatology* 49(5):1770-2, 2009.

Eyre NS and Beard MR. Hepatitis C virus infection in living colour. *Hepatology* 51(5):1852-5, 2010.

Eyre NS, Drummer HE and Beard MR. The SR-BI partner PDZK1 facilitates hepatitis C virus entry. *PLoS Pathog* 6(10), 2010.

Eyre NS, Phillips RJ, Bowden S, Yip E, Dewar B, Locarnini SA and Beard MR. Hepatitis B virus and hepatitis C virus interaction in Huh-7 cells. *J Hepatol* 51(3):446-57, 2009.

Fitter S, Vandyke K, Schultz CG, White D, Hughes TP and Zannettino AC. Plasma adiponectin levels are markedly elevated in imatinib-treated chronic myeloid leukemia (CML) patients: a mechanism for improved insulin sensitivity in type 2 diabetic CML patients? *J Clin Endocrinol Metab* 95(8):3763-7, 2010.

Fletcher AL, Lowen TE, Sakkal S, Reiseger JJ, Hammett MV, Seach N, Scott HS, Boyd RL and Chidgey AP. Ablation and Regeneration of Tolerance-Inducing Medullary Thymic Epithelial Cells after Cyclosporine, Cyclophosphamide, and Dexamethasone Treatment. J Immunol 183(2):823-831, 2009.

Fletcher AL, Seach N, Reiseger JJ, Lowen TE, Hammett MV, Scott HS and Boyd RL. Reduced Thymic Aire Expression and Abnormal NF-κB2 Signaling in a Model of Systemic Autoimmunity. *J Immunol* 182(5):2690-2699, 2009.

Foot NJ, Leong YA, Dorstyn LE, Dalton HE, Ho K, Zhao L, Garrick MD, Yang B, Hiwase D and Kumar S. Ndfip1-deficient mice have impaired DMT1 regulation and iron homeostasis. *Blood* 117(2):638-46, 2011.

Fraser CK, Lousberg EL, Guerin LR, Hughes TP, Brown MP, Diener KR and Hayball JD. Dasatinib alters the metastatic phenotype of B16-OVA melanoma in vivo. *Cancer Biol Ther* 10(7):715-27, 2010.

Fraser CK, Lousberg EL, Kumar R, Hughes TP, Diener KR and Hayball JD. Dasatinib inhibits the secretion of TNF-α following TLR stimulation *in vitro* and *in vivo*. *Exp Hematol* 37(12):1435-44, 2009.

Fritzsch B, Dillard M, Lavado A, Harvey NL and Jahan I. Canal cristae growth and fiber extension to the outer hair cells of the mouse ear require Prox1 activity. *PLoS One* 5(2):e9377, 2010.

Gagliardi L, Hotu C, Casey G, Braund WJ, Ling KH, Dodd T, Manavis J, Devitt PG, Cutfield R, Rudzki Z, Scott HS and Torpy DJ. Familial vasopressin-sensitive ACTH-independent macronodular adrenal hyperplasia (VPs-AIMAH): clinical studies of three kindreds. *Clin Endocrinol* 70(6):883-891, 2009.

Galluzzi L, Aaronson SA, Abrams J, Alnemri ES, Andrews DW, Baehrecke EH, Bazan NG, Blagosklonny MV, Blomgren K, Borner C, Bredesen DE, Brenner C, Castedo M, Cidlowski JA, Ciechanover A, Cohen GM, De Laurenzi V, De Maria R, Deshmukh M, Dynlacht BD, El-Deiry WS, Flavell RA, Fulda S, Garrido C, Golstein P, Gougeon ML, Green DR, Gronemeyer H, Hajnoczky G, Hardwick JM, Hengartner MO, Ichijo H, Jaattela M, Kepp O, Kimchi A, Klionsky DJ, Knight RA, Kornbluth S, Kumar S, Levine B, Lipton SA, Lugli E, Madeo F, Malomi W, Marine JC, Martin SJ, Medema JP, Mehlen P, Melino G, Moll UM, Morselli E, Nagata S, Nicholson DW, Nicotera P, Nunez G, Oren M, Penninger J, Pervaiz S, Peter ME, Piacentini M, Prehn JH, Puthalakath H, Rabinovich GA, Rizzuto R, Rodrigues CM, Rubinsztein DC, Rudel T, Scorrano L, Simon HU, Steller H, Tschopp J, Tsujimoto Y, Vandenabeele P, Vitale I, Vousden KH, Youle RJ, Yuan J, Zhivotovsky B and Kroemer G. Guidelines for the use and interpretation of assays for monitoring cell death in higher eukaryotes. *Cell Death Differ* 16(8):1093-107, 2009.

Gamble JR, Sun WY, Li X, Hahn CN, Pitson SM, Vadas MA and Bonder CS. Sphingosine kinase-1 associates with integrin $\alpha_V\beta_3$ to mediate endothelial cell survival. *Am J Pathol* 175(5):2217-25, 2009.

Ghosh P, Wu J, Shimmon S, Zannettino AC, Gronthos S and Itescu S. Pentosan polysulfate promotes proliferation and chondrogenic differentiation of adult human bone marrow-derived mesenchymal precursor cells. *Arthritis Res Ther* 12(1):R28, 2010.

Gibbons DL, Lin W, Creighton CJ, Rizvi ZH, Gregory PA, Goodall GJ, Thilaganathan N, Du L, Zhang Y, Pertsemlidis A and Kurie JM. Contextual extracellular cues promote tumor cell EMT and metastasis by regulating miR-200 family expression. *Genes Dev* 23(18):2140-51, 2009.

Gibson NS, Schellong SM, Kheir DY, Beyer-Westendorf J, Gallus AS, McRae S, Schutgens RE, Piovella F, Gerdes VE and Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. *J Thromb Haemost* 7(12):2035-41, 2009.

Goldschlager T, Ghosh P, Zannettino A, Gronthos S, Rosenfeld JV, Itescu S and Jenkin G. Cervical motion preservation using mesenchymal progenitor cells and pentosan polysulfate, a novel chondrogenic agent: preliminary study in an ovine model. *Neurosurg Focus* 28(6):E4, 2010.

Goldschlager T, Jenkin G, Ghosh P, Zannettino A and Rosenfeld JV. Potential applications for using stem cells in spine surgery. *Curr Stem Cell Res Ther* 5(4):345-55, 2010.

Gordon EJ, Rao S, Pollard JW, Nutt SL, Lang RA and Harvey NL. Macrophages define dermal lymphatic vessel calibre during development by regulating lymphatic endothelial cell proliferation. *Development* 137(22):3899-910, 2010.

Gronthos S, McCarty R, Mrozik K, Fitter S, Paton S, Menicanin D, Itescu S, Bartold PM, Xian C and Zannettino AC. Heat shock protein-90 beta is expressed at the surface of multipotential mesenchymal precursor cells: generation of a novel monoclonal antibody, STRO-4, with specificity for mesenchymal precursor cells from human and ovine tissues. *Stem Cells Dev* 18(9):1253-62, 2009.

Guipponi M, Li QX, Hyde L, Beissbarth T, Smyth GK, Masters CL and Scott HS. SAGE Analysis of Genes Differentially Expressed in Presymptomatic TgSOD1(G93A) Transgenic Mice Identified Cellular Processes Involved in Early Stage of ALS Pathology. *J Mol Neurosci* 41(1):172-182, 2010.

Hanifa S, Scott HS, Crewther P, Guipponi M and Tan J. Thyroxine treatments do not correct inner ear defects in tmprss1 mutant mice. *Neuroreport* 21(13):897-901, 2010.

Hari PN, Zhang MJ, Roy V, Perez WS, Bashey A, To LB, Elfenbein G, Freytes CO, Gale RP, Gibson J, Kyle RA, Lazarus HM, McCarthy PL, Milone GA, Pavlovsky S, Reece DE, Schiller G, Vela-Ojeda J, Weisdorf D and Vesole D. Is the International Staging System superior to the Durie-Salmon staging system? A comparison in multiple myeloma patients undergoing autologous transplant. *Leukemia* 23(8):1528-34, 2009.

Helbig KJ, Ruszkiewicz A, Lanford RE, Berzsenyi MD, Harley HA, McColl SR and Beard MR. Differential expression of the CXCR3 ligands in chronic hepatitis C virus (HCV) infection and their modulation by HCV in vitro. *J Virol* 83(2):836-46, 2009.

Hercus TR, Thomas D, Guthridge MA, Ekert PG, King-Scott J, Parker MW and Lopez AF. The granulocyte-macrophage colony-stimulating factor receptor: linking its structure to cell signaling and its role in disease. *Blood* 114(7):1289-98, 2009.

Hewitt CA, Ling KH, Merson TD, Simpson KM, Ritchie ME, King SL, Pritchard MA, Smyth GK, Thomas T, Scott HS and Voss AK. Gene Network Disruptions and Neurogenesis Defects in the Adult Ts1Cje Mouse Model of Down Syndrome. *Plos One* 5(7):e11561, 2010.

Hiwase DK, White D, Zrim S, Saunders V, Melo JV and Hughes TP. Nilotinib-mediated inhibition of ABCB1 increases intracellular concentration of dasatinib in CML cells: implications for combination TKI therapy. *Leukemia* 24(3):658-60, 2010.

Hiwase DK, White DL, Powell JA, Saunders VA, Zrim SA, Frede AK, Guthridge MA, Lopez AF, D'Andrea RJ, To LB, Melo JV, Kumar S and Hughes TP. Blocking cytokine signaling along with intense Bcr-Abl kinase inhibition induces apoptosis in primary CML progenitors. *Leukemia* 24(4):771-8, 2010.

Hiwase DK, White DL, Saunders VA, Kumar S, Melo JV and Hughes TP. Short-term intense Bcr-Abl kinase inhibition with nilotinib is adequate to trigger cell death in BCR-ABL(+) cells. *Leukemia* 23(6):1205-6, 2009.

Hiwase SD, Dyson PG, To LB and Lewis ID. Cotransplantation of placental mesenchymal stromal cells enhances single and double cord blood engraftment in nonobese diabetic/severe combined immune deficient mice. *Stem Cells* 27(9):2293-300, 2009.

Ho LH, Taylor R, Dorstyn L, Cakouros D, Bouillet P and Kumar S. A tumor suppressor function for caspase-2. *Proc Natl Acad Sci USA* 106(13):5336-41, 2009.

Hochhaus A, Muller MC, Radich J, Branford S, Kantarjian HM, Hanfstein B, Rousselot P, Kim DW, Lipton JH, Bleickardt E, Lambert A and Hughes TP. Dasatinib-associated major molecular responses in patients with chronic myeloid leukemia in chronic phase following imatinib failure: response dynamics and predictive value. *Leukemia* 23(9):1628-33, 2009.

Hochhaus A, O'Brien SG, Guilhot F, Druker BJ, Branford S, Foroni L, Goldman JM, Muller MC, Radich JP, Rudoltz M, Mone M, Gathmann I, Hughes TP and Larson RA. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. *Leukemia* 23(6):1054-61, 2009.

Howitt J, Putz U, Lackovic J, Doan A, Dorstyn L, Cheng H, Yang B, Chan-Ling T, Silke J, Kumar S and Tan SS. Divalent metal transporter 1 (DMT1) regulation by Ndfip1 prevents metal toxicity in human neurons. *Proc Natl Acad Sci USA* 106(36):15489-94, 2009.

Hubert FX, Kinkel SA, Crewther PE, Cannon PZF, Webster KE, Link M, Uibo R, O'Bryan MK, Meager A, Forehan SP, Smyth GK, Mittaz L, Antonarakis SE, Peterson P, Heath WR and Scott HS. Aire-Deficient C57BL/6 Mice Mimicking the Common Human 13-Base Pair Deletion Mutation Present with Only a Mild Autoimmune Phenotype. *J Immunol* 182(6):3902-3918, 2009.

Hughes T, Saglio G, Branford S, Soverini S, Kim DW, Muller MC, Martinelli G, Cortes J, Beppu L, Gottardi E, Kim D, Erben P, Shou Y, Haque A, Gallagher N, Radich J and Hochhaus A. Impact of baseline BCR-ABL mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. *J Clin Oncol* 27(25):4204-10, 2009.

Hughes TP and Hochhaus, A. Clinical strategies to achieve an early and successful response to tyrosine kinase inhibitor therapy. *Seminars in Hematology* 46(2):Supp 3:S11-S15, 2009.

Hughes TP and Branford S. Monitoring disease response to tyrosine kinase inhibitor therapy in CML. *Hematology Am Soc Hematol Educ Program* 477-87, 2009.

Hughes TP and Branford S. Measuring minimal residual disease in chronic myeloid leukemia: fluorescence in situ hybridization and polymerase chain reaction. *Clin Lymphoma Myeloma* 9(3): S266-71, 2009.

Hughes TP, Hochhaus A, Branford S, Muller MC, Kaeda JS, Foroni L, Druker BJ, Guilhot F, Larson RA, O'Brien SG, Rudoltz MS, Mone M, Wehrle E, Modur V, Goldman JM and Radich JP. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). *Blood* 116(19):3758-65, 2010.

Hutton JF, Gargett T, Sadlon TJ, Bresatz S, Brown CY, Zola H, Shannon MF, D'Andrea RJ and Barry SC. Development of CD4+CD25+FoxP3+ regulatory T cells from cord blood hematopoietic progenitor cells. *J Leukoc Biol* 85(3):445-51, 2009.

Isenmann S, Arthur A, Zannettino AC, Turner JL, Shi S, Glackin CA and Gronthos S. TWIST family of basic helix-loop-helix transcription factors mediate human mesenchymal stem cell growth and commitment. *Stem Cells* 27(10):2457-68, 2009.

Jabbour AM, Heraud JE, Daunt CP, Kaufmann T, Sandow J, O'Reilly LA, Callus BA, Lopez A, Strasser A, Vaux DL and Ekert PG. Puma indirectly activates Bax to cause apoptosis in the absence of Bid or Bim. *Cell Death Differ* 16(4):555-63, 2009.

Jabbour E, Branford S, Saglio G, Jones D, Cortes JE and Kantarjian HM. Practical advice for determining the role of BCR-ABL mutations in guiding tyrosine kinase inhibitor therapy in patients with chronic myeloid leukemia. *Cancer*, E-pub 1-12-2010.

Jarman KE, Moretti PA, Zebol JR and Pitson SM. Translocation of sphingosine kinase 1 to the plasma membrane is mediated by calcium- and integrin-binding protein 1. *J Biol Chem* 285(1):483-92, 2010.

Jin L, Lee EM, Ramshaw HS, Busfield SJ, Peoppl AG, Wilkinson L, Guthridge MA, Thomas D, Barry EF, Boyd A, Gearing DP, Vairo G, Lopez AF, Dick JE and Lock RB. Monoclonal antibody-mediated targeting of CD123, IL-3 receptor α chain, eliminates human acute myeloid leukemic stem cells. *Cell Stem Cell* 5(1):31-42, 2009.

Jongmans MCJ, Kuiper RP, Carmichael CL, Wilkins EJ, Dors N, Carmagnac A, Schouten-van Meeteren AYN, Li X, Stankovic M, Kamping E, Bengtsson H, Schoenmakers E, van Kessel AG, Hoogerbrugge PM, Hahn CN, Brons PP, Scott HS and Hoogerbrugge N. Novel RUNX1 mutations in familial platelet disorder with enhanced risk for acute myeloid leukemia: clues for improved identification of the FPD/AML syndrome. *Leukemia* 24(1):242-246, 2010.

Kantarjian H, Pasquini R, Levy V, Jootar S, Holowiecki J, Hamerschlak N, Hughes T, Bleickardt E, Dejardin D, Cortes J and Shah NP. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R). *Cancer* 115(18):4136-47, 2009.

Kazenwadel J, Michael MZ and Harvey NL. Prox1 expression is negatively regulated by miR-181 in endothelial cells. *Blood* 116(13):2395-401, 2010.

Kedzierska K, Valkenburg SA, Guillonneau C, Hubert FX, Cukalac T, Curtis JM, Stambas J, Scott HS, Kedzierski L, Venturi V and Davenport MP. Diversity and clonotypic composition of influenza-specific CD8(+) TCR repertoires remain unaltered in the absence of Aire. *Eur J Immunol* 40(3):849-858, 2010.

Kelly RM, Goren EM, Taylor PA, Mueller SN, Stefanski HE, Osborn MJ, Scott HS, Komarova EA, Gudkov AV, Hollander GA and Blazar BR. Short-term inhibition of p53 combined with keratinocyte growth factor improves thymic epithelial cell recovery and enhances T-cell reconstitution after murine bone marrow transplantation. *Blood* 115(5):1088-1097, 2010.

Khew-Goodall Y and Goodall GJ. Myc-modulated miR-9 makes more metastases. *Nat Cell Biol* 12(3):209-11, 2010.

Khorashad JS, Wagner S, Greener L, Marin D, Reid A, Milojkovic D, Patel H, Willimott S, Rezvani K, Gerrard G, Loaiza S, Davis J, Goldman J, Melo J, Apperley J and Foroni L. The level of BCR-ABL1 kinase activity before treatment does not identify chronic myeloid leukemia patients who fail to achieve a complete cytogenetic response on imatinib. *Haematologica* 94(6):861-4, 2009.

Khoury HJ, Guilhot F, Hughes TP, Kim DW and Cortes JE. Dasatinib treatment for Philadelphia chromosome-positive leukemias: practical considerations. *Cancer* 115(7):1381-94, 2009.

Kim M, Park SW, Pitson SM and Lee HT. Isoflurane protects human kidney proximal tubule cells against necrosis via sphingosine kinase and sphingosine-1-phosphate generation. *Am J Nephrol* 31(4):353-62, 2010.

Kim S, Prout M, Ramshaw H, Lopez AF, LeGros G and Min B. Cutting edge: Basophils are transiently recruited into the draining lymph nodes during helminth infection via IL-3, but infection-induced Th2 immunity can develop without basophil lymph node recruitment or IL-3. *J Immunol* 184(3):1143-7, 2009.

Klawitter J, Kominsky DJ, Brown JL, Christians U, Leibfritz D, Melo JV, Eckhardt SG and Serkova NJ. Metabolic characteristics of imatinib resistance in chronic myeloid leukaemia cells. *Br J Pharmacol* 158(2):588-600, 2009.

Ko HJ, Kinkel SA, Hubert FX, Nasa Z, Chan J, Siatskas C, Hirubalan P, Toh BH, Scott HS and Alderuccio F. Transplantation of autoimmune regulator-encoding bone marrow cells delays the onset of experimental autoimmune encephalomyelitis. *Eur J Immunol* 40:3499-509, 2010.

Kochetkova M, Kumar S and McColl SR. Chemokine receptors CXCR4 and CCR7 promote metastasis by preventing anoikis in cancer cells. *Cell Death Differ* 16(5):664-73, 2009.

Kok CH, Brown AL, Ekert PG, D'Andrea RJ. Gene expression analysis reveals HOX gene upregulation in trisomy 8 AML. *Leukemia* 24:1239-1243, 2010.

Kominsky DJ, Klawitter J, Brown JL, Boros LG, Melo JV, Eckhardt SG and Serkova NJ. Abnormalities in glucose uptake and metabolism in imatinib-resistant human BCR-ABL-positive cells. *Clin Cancer Res* 15(10):3442-50, 2009.

Kroemer G, Galluzzi L, Vandenabeele P, Abrams J, Alnemri ES, Baehrecke EH, Blagosklonny MV, El-Deiry WS, Golstein P, Green DR, Hengartner M, Knight RA, Kumar S, Lipton SA, Malorni W, Nunez G, Peter ME, Tschopp J, Yuan J, Piacentini M, Zhivotovsky B and Melino G. Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009. *Cell Death Differ* 16(1):3-11, 2009.

Kumar S. Caspase 2 in apoptosis, the DNA damage response and tumour suppression: enigma no more? *Nat Rev Cancer* 9(12):897-903, 2009.

Kumar S and Dorstyn L. Analysing caspase activation and caspase activity in apoptotic cells. *Methods Mol Biol* 559:3-17, 2009.

Laan M, Kisand K, Kont V, Moll K, Tserel L, Scott HS and Peterson P. Autoimmune Regulator Deficiency Results in Decreased Expression of CCR4 and CCR7 Ligands and in Delayed Migration of CD4(+) Thymocytes. *J Immunol* 183(12):7682-7691, 2009.

Labrinidis A, Diamond P, Martin S, Hay S, Liapis V, Zinonos I, Sims NA, Atkins GJ, Vincent C, Ponomarev V, Findlay DM, Zannettino AC and Evdokiou A. Apo2L/TRAIL inhibits tumor growth and bone destruction in a murine model of multiple myeloma. *Clin Cancer Res* 15(6):1998-2009, 2009.

Lee IH, Campbell CR, Song SH, Day ML, Kumar S, Cook DI and Dinudom A. The activity of the epithelial sodium channels is regulated by caveolin-1 via a Nedd4-2-dependent mechanism. *J Biol Chem* 284(19):12663-9, 2009.

Lidington D, Peter BF, Meissner A, Kroetsch JT, Pitson SM, Pohl U and Bolz SS. The phosphorylation motif at serine 225 governs the localization and function of sphingosine kinase 1 in resistance arteries. *Arterioscler Thromb Vasc Biol* 29(11):1916-22, 2009.

Limaye V, Vadas MA, Pitson SM and Gamble JR. The effects of markedly raised intracellular sphingosine kinase-1 activity in endothelial cells. *Cell Mol Biol Lett* 14(3):411-23, 2009.

Limaye V, Xia P, Hahn C, Smith M, Vadas MA, Pitson SM and Gamble JR. Chronic increases in sphingosine kinase-1 activity induce a pro-inflammatory, pro-angiogenic phenotype in endothelial cells. *Cell Mol Biol Lett* 14(3):424-41, 2009.

Ling KH, Hewitt CA, Beissbarth T, Hyde L, Banerjee K, Cheah PS, Cannon PZ, Hahn CN, Thomas PQ, Smyth GK, Tan SS, Thomas T and Scott HS. Molecular networks involved in mouse cerebral corticogenesis and spatio-temporal regulation of Sox4 and Sox11 novel antisense transcripts revealed by transcriptome profiling. *Genome Biol* 10(10), 2009.

Ling KH, Hewitt CA, Beissbarth T, Hyde L, Cheah PS, Smyth GK, Tan SS, Hahn CN, Thomas T, Thomas PQ and Scott HS. Spatiotemporal Regulation of Multiple Overlapping Sense and Novel Natural Antisense Transcripts at the Nrgn and Camk2n1 Gene Loci during Mouse Cerebral Corticogenesis. *Cereb Cortex*, Aug 2010.

Liu B, Li J, Tsykin A, Liu L, Gaur AB and Goodall GJ. Exploring complex miRNA-mRNA interactions with Bayesian networks by splitting-averaging strategy. *BMC Bioinformatics* 10:408, 2009.

Liu B, Liu L, Tsykin A, Goodall GJ, Green JE, Zhu M, Kim CH and Li J. Identifying functional miRNA-mRNA regulatory modules with correspondence latent dirichlet allocation. *Bioinformatics* 26(24):3105-11, 2010.

Lopez AF, Hercus TR, Ekert P, Littler DR, Guthridge M, Thomas D, Ramshaw HS, Stomski F, Perugini M, D'Andrea R, Grimbaldeston M and Parker MW. Molecular basis of cytokine receptor activation. *IUBMB Life* 62(7):509-18, 2010.

Loveridge C, Tonelli F, Leclercq T, Lim KG, Long JS, Berdyshev E, Tate RJ, Natarajan V, Pitson SM, Pyne NJ and Pyne S. The sphingosine kinase 1 inhibitor 2-(p-hydroxyanilino)-4-(p-chlorophenyl)thiazole induces proteasomal degradation of sphingosine kinase 1 in mammalian cells. *J Biol Chem* 285(50):38841-52, 2010.

Malavaud B, Pchejetski D, Mazerolles C, de Paiva GR, Calvet C, Doumerc N, Pitson S, Rischmann P and Cuvillier O. Sphingosine kinase-1 activity and expression in human prostate cancer resection specimens. *Eur J Cancer* 46(18):3417-24, 2010.

Manning JA and Kumar S. A potential role for NEDD1 and the centrosome in senescence of mouse embryonic fibroblasts. *Cell Death Dis* 1(4):e35, 2010.

Manning JA, Lewis M, Koblar SA and Kumar S. An essential function for the centrosomal protein NEDD1 in zebrafish development. *Cell Death Differ* 17(8):1302-14, 2010.

Manning JA, Shalini S, Risk JM, Day CL and Kumar S. A direct interaction with NEDD1 regulates gamma-tubulin recruitment to the centrosome. *PLoS One* 5(3):e9618, 2010.

Markova B, Albers C, Breitenbuecher F, Melo JV, Brummendorf TH, Heidel F, Lipka D, Duyster J, Huber C and Fischer T. Novel pathway in Bcr-Abl signal transduction involves Akt-independent, PLC-gamma1-driven activation of mTOR/p70S6-kinase pathway. *Oncogene* 29(5):739-51, 2010.

Martin SK, Diamond P, Williams SA, To LB, Peet DJ, Fujii N, Gronthos S, Harris AL and Zannettino AC. Hypoxia-inducible factor-2 is a novel regulator of aberrant CXCL12 expression in multiple myeloma plasma cells. *Haematologica* 95(5):776-84, 2010.

Martin SK, Fitter S, Bong LF, Drew JJ, Gronthos S, Shepherd PR and Zannettino AC. NVP-BEZ235, a dual pan class I PI3 kinase and mTOR inhibitor, promotes osteogenic differentiation in human mesenchymal stromal cells. *J Bone Miner Res* 25(10):2126-37, 2010.

McCartney EM and Beard MR. Impact of alcohol on hepatitis C virus replication and interferon signaling. *World J Gastroenterol* 16(11):1337-43, 2010.

McCarty RC, Gronthos S, Zannettino AC, Foster BK and Xian CJ. Characterisation and developmental potential of ovine bone marrow derived mesenchymal stem cells. *J Cell Physiol* 219(2):324-33, 2009.

McCook LJ, Ayling T, Cappo M, Choat JH, Evans RD, De Freitas DM, Heupel M, Hughes TP, Jones GP, Mapstone B, Marsh H, Mills M, Molloy FJ, Pitcher CR, Pressey RL, Russ GR, Sutton S, Sweatman H, Tobin R, Wachenfeld DR and Williamson DH. Adaptive management of the Great Barrier Reef: a globally significant demonstration of the benefits of networks of marine reserves. *Proc Natl Acad Sci USA* 107(43):18278-85, 2010.

McWeeney SK, Pemberton LC, Loriaux MM, Vartanian K, Willis SG, Yochum G, Wilmot B, Turpaz Y, Pillai R, Druker BJ, Snead JL, MacPartlin M, O'Brien SG, Melo JV, Lange T, Harrington CA and Deininger MW. A gene expression signature of CD34+ cells to predict major cytogenetic response in chronic-phase chronic myeloid leukemia patients treated with imatinib. *Blood* 115(2):315-25, 2010.

Melo JV and Hewett DR. Wrapping BCR-ABL: it's in the bag. *Blood* 116(18):3382-3, 2010.

Menicanin D, Bartold PM, Zannettino AC and Gronthos S. Genomic profiling of mesenchymal stem cells. *Stem Cell Rev* 5(1):36-50, 2009.

Mercer TR, Dinger ME, Bracken CP, Kolle G, Szubert JM, Korbie DJ, Askarian-Amiri ME, Gardiner BB, Goodall GJ, Grimmond SM and Mattick JS. Regulated post-transcriptional RNA cleavage diversifies the eukaryotic transcriptome. *Genome Res* 20(12):1639-50, 2010.

Milicevic NM, Milicevic Z, Miljkovic MD, Labudovic-Borovic M, Laan M, Peterson P, Kisand K, Scott H, Qu N and Westermann J. Metallophilic macrophages are fully developed in the thymus of autoimmune regulator (Aire)-deficient mice. *Histochem Cell Biol* 131(5):643-649, 2009.

Milicevic Z, Milicevic NM, Laan M, Peterson P, Kisand K, Scott HS and Westermann J. Ultrastructure of medullary thymic epithelial cells of autoimmune regulator (Aire)-deficient mice. *Immunol Cell Biol* 88(1):50-56, 2010.

Muller MC, Cortes JE, Kim DW, Druker BJ, Erben P, Pasquini R, Branford S, Hughes TP, Radich JP, Ploughman L, Mukhopadhyay J and Hochhaus A. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations. *Blood* 114(24):4944-53, 2009.

Muller MC, Cross NC, Erben P, Schenk T, Hanfstein B, Ernst T, Hehlmann R, Branford S, Saglio G and Hochhaus A. Harmonization of molecular monitoring of CML therapy in Europe. *Leukemia* 23(11):1957-63, 2009.

Osborn M, Horvath N and To LB. New drugs in multiple myeloma. *Australian Prescriber* 32(4):95-98, 2009.

Osborn M and Hughes TP. Managing imatinib resistance in chronic myeloid leukaemia. *Curr Opin Hematol* 17(97-103, 2010.

Osna NA, White RL, Donohue TM, Jr., Beard MR, Tuma DJ and Kharbanda KK. Impaired methylation as a novel mechanism for proteasome suppression in liver cells. *Biochem Biophys Res Co* 391(2):1291-6, 2010.

Paquet-Fifield S, Schluter H, Li A, Aitken T, Gangatirkar P, Blashki D, Koelmeyer R, Pouliot N, Palatsides M, Ellis S, Brouard N, Zannettino A, Saunders N, Thompson N, Li J and Kaur P. A role for pericytes as microenvironmental regulators of human skin tissue regeneration. *J Clin Invest* 119(9):2795-806, 2009.

Patil S, Spencer A, Schwarer A, Lewis I, Hertzberg M, Avery S, Wei A, Noutsos T, Paul E, Taouk Y and Muirhead J. Reduced-intensity conditioned allogeneic haematopoietic stem cell transplantation results in durable disease-free and overall survival in patients with poor prognosis myeloid and lymphoid malignancies: eighty-month follow-up. *Bone Marrow Transplant* 45(7):1154-60, 2010.

Perugini M, Brown AL, Salerno DG, Booker GW, Stojkoski C, Hercus TR, Lopez AF, Hibbs ML, Gonda TJ and D'Andrea RJ. Alternative modes of GM-CSF receptor activation revealed using activated mutants of the common beta-subunit. *Blood* 115(16):3346-53, 2010.

Perugini M, Kok CH, Brown AL, Wilkinson CR, Salerno DG, Young SM, Diakiw SM, Lewis ID, Gonda TJ and D'Andrea RJ. Repression of Gadd45α by activated FLT3 and GM-CSF receptor mutants contributes to growth, survival and blocked differentiation. *Leukemia* 23(4):729-38, 2009.

Perugini M, Lee H, McRae S, D'Andrea RJ. Pharmacotherapy of chronic immune thrombocytopenia purpura (ITP) with Romiplostim. Clin Med Rev Thera 2:1-7, 2010.

Perugini M, Varelias A, Sadlon T, D'Andrea RJ. Hematopoietic growth factor mimetics: from concept to clinic. Cytokine Growth Factor Rev 20(1):87-94, 2009.

Piliponsky AM, Chen CC, Grimbaldeston MA, Burns-Guydish SM, Hardy J, Kalesnikoff J, Contag CH, Tsai M and Galli SJ. Mast cell-derived TNF can exacerbate mortality during severe bacterial infections in C57BL/6-KitW-sh/W-sh mice. *Am J Pathol* 176(2):926-38, 2010.

Pitman MR and Pitson SM. Inhibitors of the sphingosine kinase pathway as potential therapeutics. *Curr Cancer Drug Targets* 10(4):354-67, 2010.

Pitson SM and Pebay A. Regulation of stem cell pluripotency and neural differentiation by lysophospholipids. *Neurosignals* 17(4):242-54, 2009.

Powell JA, Thomas D, Barry EF, Kok CH, McClure BJ, Tsykin A, To LB, Brown A, Lewis ID, Herbert K, Goodall GJ, Speed TP, Asou N, Jacob B, Osato M, Haylock DN, Nilsson SK, D'Andrea RJ, Lopez AF and Guthridge MA. Expression profiling of a hemopoietic cell survival transcriptome implicates osteopontin as a functional prognostic factor in AML. *Blood* 114(23):4859-70, 2009.

Psaltis PJ, Carbone A, Leong DP, Lau DH, Nelson AJ, Kuchel T, Jantzen T, Manavis J, Williams K, Sanders P, Gronthos S, Zannettino AC and Worthley SG. Assessment of myocardial fibrosis by endoventricular electromechanical mapping in experimental nonischemic cardiomyopathy. *Int J Cardiovasc Imaging* 27(1):25-37, 2011.

Psaltis PJ, Carbone A, Nelson AJ, Lau DH, Jantzen T, Manavis J, Williams K, Itescu S, Sanders P, Gronthos S, Zannettino AC and Worthley SG. Reparative effects of allogeneic mesenchymal precursor cells delivered transendocardially in experimental nonischemic cardiomyopathy. *JACC Cardiovasc Interv* 3(9):974-83, 2010.

Psaltis PJ, Paton S, See F, Arthur A, Martin S, Itescu S, Worthley SG, Gronthos S and Zannettino AC. Enrichment for STRO-1 expression enhances the cardiovascular paracrine activity of human bone marrow-derived mesenchymal cell populations. *J Cell Physiol* 223(2):530-40, 2010.

Psaltis PJ, Zannettino AC, Gronthos S and Worthley SG. Intramyocardial navigation and mapping for stem cell delivery. *J Cardiovasc Transl Res* 3(2):135-46, 2010.

Rawat VPS, Arseni N, Ahmed F, Mulaw MA, Thoene S, Heilmeier B, Sadlon T, D'Andrea RJ, Hiddemann W, Bohlander SK, Buske C and Feuring-Buske M. The Vent-like homeobox gene VENTX promotes human myeloid development in vitro and in vivo and is highly expressed in acute myeloid leukemia. Proc Natl Acad Sci U S A 107(39):16946-16951, 2010.

Risebro CA, Searles RG, Melville AA, Ehler E, Jina N, Shah S, Pallas J, Hubank M, Dillard M, Harvey NL, Schwartz RJ, Chien KR, Oliver G and Riley PR. Prox1 maintains muscle structure and growth in the developing heart. *Development* 136(3):495-505, 2009.

Roberts KG, Smith AM, McDougall F, Carpenter H, Horan M, Neviani P, Powell JA, Thomas D, Guthridge MA, Perrotti D, Sim AT, Ashman LK and Verrills NM. Essential requirement for PP2A inhibition by the oncogenic receptor c-KIT suggests PP2A reactivation as a strategy to treat c-KIT+ cancers. *Cancer Res* 70(13):5438-47, 2010.

Roberts NA, Desanti GE, Withers DR, Scott HR, Jenkinson WE, Lane PJL, Jenkinson EJ and Anderson G. Absence of thymus crosstalk in the fetus does not preclude hematopoietic induction of a functional thymus in the adult. *Eur J Immunology* 39(9):2395-2402, 2009.

Ross DM, Branford S, Melo JV and Hughes TP. Reply to 'What do we mean by sensitivity when we talk about detecting minimal residual disease?' by Steinbach and Debatin. *Leukemia* 23(4):819-20; Author reply 820, 2009.

Ross DM, Branford S, Seymour JF, Schwarer AP, Arthur C, Bartley PA, Slader C, Field C, Dang P, Filshie RJ, Mills AK, Grigg AP, Melo JV and Hughes TP. Patients with chronic myeloid leukemia who maintain a complete molecular response after stopping imatinib treatment have evidence of persistent leukemia by DNA PCR. *Leukemia* 24(10):1719-24, 2010.

Ross DM, Schafranek L, Hughes TP, Nicola M, Branford S and Score J. Genomic translocation breakpoint sequences are conserved in BCR-ABL1 cell lines despite the presence of amplification. *Cancer Genet Cytogenet* 189(2):138-9, 2009.

Rotin D and Kumar S. Physiological functions of the HECT family of ubiquitin ligases. *Nat Rev Mol Cell Biol* 10(6):398-409, 2009.

Sadlon TJ, Wilkinson BG, Pederson S, Brown CY, Bresatz S, Gargett T, Melville EL, Peng K, D'Andrea RJ, Glonek GG, Goodall GJ, Zola H, Shannon MF and Barry SC. Genome-wide identification of human FOXP3 target genes in natural regulatory T cells. *J Immunol* 185(2):1071-81, 2010.

Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, Pasquini R, Clark RE, Hochhaus A, Hughes TP, Gallagher N, Hoenekopp A, Dong M, Haque A, Larson RA and Kantarjian HM. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 362(24):2251-9, 2010.

Score J, Calasanz MJ, Ottman O, Pane F, Yeh RF, Sobrinho-Simoes MA, Kreil S, Ward D, Hidalgo-Curtis C, Melo JV, Wiemels J, Nadel B, Cross NC and Grand FH. Analysis of genomic breakpoints in p190 and p210 BCR-ABL indicate distinct mechanisms of formation. *Leukemia* 24(10):1742-50, 2010.

Scott HS. Is that a pathogenic mutation, a rare non-pathogenic variant, or don't you know? *Hum Mutat* 30(5):vii, 2009.

Scott HS. One of the reasons why humans, and not sponges or worms, get psychiatric disorders? *Hum Mutat* 31(11):v, 2010.

Sears D, Luong P, Yuan M, Nteliopoulos G, Man YK, Melo JV and Basu S. Functional phosphoproteomic analysis reveals cold-shock domain protein A to be a Bcr-Abl effector-regulating proliferation and transformation in chronic myeloid leukemia. *Cell Death Dis* 1(11):e93, 2010.

See F, Seki T, Psaltis PJ, Sondermeijer HP, Gronthos S, Zannettino AC, Govaert KM, Schuster MD, Kurlansky PA, Kelly DJ, Krum H and Itescu S. Therapeutic Effects of Human STRO-3-Selected Mesenchymal Precursor Cells and their Soluble Factors in Experimental Myocardial Ischemia. *J Cell Mol Med*, E-pub 16-12-2010.

Shi W, de Graaf CA, Kinkel SA, Achtman AH, Baldwin T, Schofield L, Scott HS, Hilton DJ and Smyth GK. Estimating the proportion of microarray probes expressed in an RNA sample. *Nucleic Acids Res* 38(7):2168-2176, 2010.

Siow DL, Anderson CD, Berdyshev EV, Skobeleva A, Natarajan V, Pitson SM and Wattenberg BW. Sphingosine kinase localization in the control of sphingolipid metabolism. *Adv Enzyme Regul*, E-pub 16-11-2010.

Siow DL, Anderson CD, Berdyshev EV, Skobeleva A, Pitson SM and Wattenberg BW. Intracellular localization of sphingosine kinase 1 alters access to substrate pools but does not affect the degradative fate of sphingosine-1-phosphate. *J Lipid Res* 51(9):2546-59, 2010.

Sobrinho-Simoes M, Wilczek V, Score J, Cross NC, Apperley JF and Melo JV. In search of the original leukemic clone in chronic myeloid leukemia patients in complete molecular remission after stem cell transplantation or imatinib. *Blood* 116(8):1329-35, 2010.

Song JH, Kim M, Park SW, Chen SW, Pitson SM and Lee HT. Isoflurane via TGFβ,1 release increases caveolae formation and organizes sphingosine kinase signaling in renal proximal tubules. *Am J Physiol Renal Physiol* 298(4):F1041-50, 2010.

Spencer A, Prince HM, Roberts AW, Prosser IW, Bradstock KF, Coyle L, Gill DS, Horvath N, Reynolds J and Kennedy N. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. *J Clin Oncol* 27(11):1788-93, 2009.

Sun WY, Pitson SM and Bonder CS. Tumor necrosis factor-induced neutrophil adhesion occurs via sphingosine kinase-1-dependent activation of endothelial $\alpha_5\beta_1$ integrin. *Am J Pathol* 177(1):436-46, 2010.

Tay L, Duncan E, Singhal D, Al-Qunfoidi R, Coghlan D, Jaksic W, Szabo F, McRae S and Lloyd J. Twelve years of experience of acquired hemophilia A: trials and tribulations in South Australia. *Semin Thromb Hemost* 35(8):769-77, 2009.

ter Braak M, Danneberg K, Lichte K, Liphardt K, Ktistakis NT, Pitson SM, Hla T, Jakobs KH and Meyer zu Heringdorf D. Gα(q)-mediated plasma membrane translocation of sphingosine kinase-1 and cross-activation of S1P receptors. *Biochim Biophys Acta* 1791(5):357-70, 2009.

Tojo A, Usuki K, Urabe A, Maeda Y, Kobayashi Y, Jinnai I, Ohyashiki K, Nishimura M, Kawaguchi T, Tanaka H, Miyamura K, Miyazaki Y, Hughes T, Branford S, Okamoto S, Ishikawa J, Okada M, Usui N, Tanii H, Amagasaki T, Natori H and Naoe T. A Phase I/II study of nilotinib in Japanese patients with imatinib-resistant or -intolerant Ph+ CML or relapsed/refractory Ph+ ALL. *Int J Hematol* 89(5):679-88, 2009.

Tonelli F, Lim KG, Loveridge C, Long J, Pitson SM, Tigyi G, Bittman R, Pyne S and Pyne NJ. FTY720 and (S)-FTY720 vinylphosphonate inhibit sphingosine kinase 1 and promote its proteasomal degradation in human pulmonary artery smooth muscle, breast cancer and androgen-independent prostate cancer cells. *Cell Signal* 22(10):1536-42, 2010.

Vandyke K, Dewar AL, Farrugia AN, Fitter S, Bik To L, Hughes TP and Zannettino AC. Therapeutic concentrations of dasatinib inhibit in vitro osteoclastogenesis. *Leukemia* 23(5):994-7, 2009.

Vandyke K, Dewar AL, Fitter S, Menicanin D, To LB, Hughes TP and Zannettino AC. Imatinib mesylate causes growth plate closure in vivo. *Leukemia* 23(11):2155-9, 2009.

Vandyke K, Fitter S, Dewar AL, Hughes TP and Zannettino AC. Dysregulation of bone remodeling by imatinib mesylate. *Blood* 115(4):766-74, 2010.

Vij R, Horvath N, Spencer A, Taylor K, Vadhan-Raj S, Vescio R, Smith J, Qian Y, Yeh H and Jun S. An open-label, phase 2 trial of denosumab in the treatment of relapsed or plateau-phase multiple myeloma. *Am J Hematol* 84(10):650-6, 2009.

Viswanathan SR, Powers JT, Einhorn W, Hoshida Y, Ng TL, Toffanin S, O'Sullivan M, Lu J, Phillips LA, Lockhart VL, Shah SP, Tanwar PS, Mermel CH, Beroukhim R, Azam M, Teixeira J, Meyerson M, Hughes TP, Llovet JM, Radich J, Mullighan CG, Golub TR, Sorensen PH and Daley GQ. Lin28 promotes transformation and is associated with advanced human malignancies. Nat Genet 41(7):843-8, 2009.

Wang B, Herman-Edelstein M, Koh P, Burns W, Jandeleit-Dahm K, Watson A, Saleem M, Goodall GJ, Twigg SM, Cooper ME and Kantharidis P. E-cadherin expression is regulated by miR-192/215 by a mechanism that is independent of the profibrotic effects of transforming growth factor-beta. *Diabetes* 59(7):1794-802, 2010.

Wang H, Paton JC, Thorpe CM, Bonder CS, Sun WY and Paton AW. Tissue factor-dependent procoagulant activity of subtilase cytotoxin, a potent AB5 toxin produced by shiga toxigenic Escherichia coli. *J Infect Dis* 202(9):1415-23, 2010.

Wati S, Rawlinson SM, Ivanov RA, Dorstyn L, Beard MR, Jans DA, Pitson SM, Burrell CJ, Li P and Carr JM. TNF-α stimulation of cells with established dengue virus type 2 (DENV-2) infection induces cell death that is accompanied by reduced ability of TNF-α to activate NF-κB and reduced sphingosine kinase-1 activity. *J Gen Virol*, E-pub 15-12-2010.

Weisberg E, Choi HG, Ray A, Barrett R, Zhang J, Sim T, Zhou W, Seeliger M, Cameron M, Azam M, Fletcher JA, Debiec-Rychter M, Mayeda M, Moreno D, Kung AL, Janne PA, Khosravi-Far R, Melo JV, Manley PW, Adamia S, Wu C, Gray N and Griffin JD. Discovery of a small-molecule type II inhibitor of wild-type and gatekeeper mutants of BCR-ABL, PDGFRα, Kit, and Src kinases: novel type II inhibitor of gatekeeper mutants. *Blood* 115(21):4206-16, 2010.

White DL, Dang P, Engler J, Frede A, Zrim S, Osborn M, Saunders VA, Manley PW and Hughes TP. Functional activity of the OCT-1 protein is predictive of long-term outcome in patients with chronic-phase chronic myeloid leukemia treated with imatinib. *J Clin Oncol* 28(16):2761-7, 2010.

White DL and Hughes TP. Predicting the response of CML patients to tyrosine kinase inhibitor therapy. Curr Hematol Malig Rep 4(2):59-65, 2009.

White DL, Saunders VA, Dang P, Engler J and Hughes TP. OCT-1 activity measurement provides a superior imatinib response predictor than screening for single-nucleotide polymorphisms of OCT-1. *Leukemia* 24(11):1962-5, 2010.

White HE, Matejtschuk P, Rigsby P, Gabert J, Lin F, Lynn Wang Y, Branford S, Muller MC, Beaufils N, Beillard E, Colomer D, Dvorakova D, Ehrencrona H, Goh HG, El Housni H, Jones D, Kairisto V, Kamel-Reid S, Kim DW, Langabeer S, Ma ES, Press RD, Romeo G, Wang L, Zoi K, Hughes T, Saglio G, Hochhaus A, Goldman JM, Metcalfe P and Cross NC. Establishment of the first World Health Organization International Genetic Reference Panel for quantitation of BCR-ABL mRNA. *Blood* 116(22):e111-7, 2010.

Williams SA, Martin SK, Vincent C, Gronthos S, Zheng T, Atkins GJ and Zannettino AC. Circulating levels of TWEAK correlate with bone erosion in multiple myeloma patients. Br J Haematol 150(3):373-6, 2010.

Williams SL, Milne IR, Bagley CJ, Gamble JR, Vadas MA, Pitson SM and Khew-Goodall Y. A proinflammatory role for proteolytically cleaved annexin A1 in neutrophil transendothelial migration. *J Immunol* 185(5):3057-63, 2010.

Winkler IG, Barbier V, Wadley R, Zannettino AC, Williams S and Levesque JP. Positioning of bone marrow hematopoietic and stromal cells relative to blood flow in vivo: serially reconstituting hematopoietic stem cells reside in distinct nonperfused niches. *Blood* 116(3):375-85, 2010.

Woodcock JM, Ma Y, Coolen C, Pham D, Jones C, Lopez AF and Pitson SM. Sphingosine and FTY720 directly bind pro-survival 14-3-3 proteins to regulate their function. *Cell Signal* 22(9):1291-9, 2010.

Worthley DL, Ruszkiewicz A, Davies R, Moore S, Nivison-Smith I, Bik To L, Browett P, Western R, Durrant S, So J, Young GP, Mullighan CG, Bardy PG and Michael MZ. Human gastrointestinal neoplasia-associated myofibroblasts can develop from bone marrow-derived cells following allogeneic stem cell transplantation. *Stem Cells* 27(6):1463-8, 2009.

Wright JA, Richer JK and Goodall GJ. microRNAs and EMT in mammary cells and breast cancer. *J Mammary Gland Biol Neoplasia* 15(2):213-23, 2010.

Yang B and Kumar S. Nedd4 and Nedd4-2: closely related ubiquitin-protein ligases with distinct physiological functions. *Cell Death Differ* 17(1):68-77, 2010.

Yong AS and Melo JV. The impact of gene profiling in chronic myeloid leukaemia. *Best Pract Res Clin Haematol* 22(2):181-90, 2009.

Zannettino AC, Paton S, Arthur A, Khor F, Itescu S, Gimble JM and Gronthos S. Multipotential human adipose-derived stromal stem cells exhibit a perivascular phenotype in vitro and in vivo. *J Cell Physiol* 214(2):413-21, 2008.

Zebol JR, Hewitt NM, Moretti PA, Lynn HE, Lake JA, Li P, Vadas MA, Wattenberg BW and Pitson SM. The CCT/TRiC chaperonin is required for maturation of sphingosine kinase 1. *Int J Biochem Cell Biol* 41(4):822-7, 2009.

Zhao F, Mancuso A, Bui TV, Tong X, Gruber JJ, Swider CR, Sanchez PV, Lum JJ, Sayed N, Melo JV, Perl AE, Carroll M, Tuttle SW and Thompson CB. Imatinib resistance associated with BCR-ABL upregulation is dependent on HIF-1α-induced metabolic reprogramming. *Oncogene* 29(20):2962-72, 2010.

Zinonos I, Labrinidis A, Lee M, Liapis V, Hay S, Ponomarev V, Diamond P, Zannettino AC, Findlay DM and Evdokiou A. Apomab, a fully human agonistic antibody to DR5, exhibits potent antitumor activity against primary and metastatic breast cancer. *Mol Cancer Ther* 8(10):2969-80, 2009.

Major Awards 2009 – 2010

Acute Leukaemia Laboratory

- Dr Michelle Perugini was awarded the 3 year Shahin Early Career Research Fellowship.
- Ms Nur Hezrin Shahrin and Ms Jackie Mao were awarded Robinson Institute Honours Scholarships.
- Ms Teresa Sadras was awarded a Robinson Institute Postgraduate Scholarship and a Poster Prize from the Centre for Stem Cell Research.
- Ms Sonya Diakiw was awarded the International Society for Experimental Haematology Conference Poster Discussion Panel Award, the Acute Leukaemia Short-Term Scholarship, a Cancer Council SA Travel Grant and a Lorne Conference Travel Award.
- Dr Michelle Perugini, Ms Sonya Diakiw and Ms Teresa Sadras were also awarded with International Society for Experimental Haematology Conference Travel Awards.

Cytokine Receptor Laboratory

- Professor Angel Lopez won the 2010 South Australian Scientist of the Year Award from the Government of South Australia.
- Professor Angel Lopez won the 2010 South Australian of the Year – Science Category Award from the Government of South Australia.
- Dr Tim Hercus won the 2009 Hanson Institute Best Publication Award.

Cytokine Research Laboratory

- Dr Philip Gregory won the 2009 Hanson Institute Basic Science New Investigator Award.

Hepatitis C Virus Research Laboratory

- Sumudu Narayana won the Zonta Club of Adelaide Inc Honours Scholarship 2010 and the Siemens Silver Medal Award at ACH2 2010.
- Dr Nick Eyre won the Gilead Sciences Pty Ltd Hepatitis Early Career Investigator Medal.

Mast Cell Laboratory

- Ms Anastasia Yu won the Best Poster Prize at the 4th Barossa Meeting "Science Amongst the Vines" (2009).
- Ms Anastasia Yu won second prize for Best PhD Presentation at the Adelaide Immunology Retreat (2010).
- Ms Anastasia Yu won an Australasian Society for Immunology Travel Bursary to attend the 41st ASI conference convened in Perth, WA (2010)

Melissa White Memorial Laboratory

- Dr Deborah White won the 2009 Hanson Institute Clinical Researcher of the Year Award.

Molecular Pathology Research Laboratory

- Dr Chris Hahn was awarded the 2010 New Directions in Leukaemia Research Prize for Excellence in Leukaemia Research.
- Dr Brita Ardesjo Lundgren was awarded a 2010 Swedish Endocrine Society Award.
- Dr Brita Ardesjo Lundgren was awarded a 2010 Swedish Society of Medicine Award.
- Mr Chan-Eng Chong won second prize for Best PhD Poster Presentation at the 2010 Faculty of Health Sciences (University of Adelaide) Post-graduate Research Conference.
- Mr Chan-Eng Chong was awarded a 2009 Adelaide Scholarship International Award, University of Adelaide.
- Mr King Hwa (Michael) Ling was awarded a 2009 FHS Postgraduate Travelling Fellowship Award and Discipline of Medicine Travelling Fund, University of Adelaide, to attend the Keystone Symposia, USA.
- Mr King Hwa (Michael) Ling was awarded the Best Poster Presentation Award, Australian Society for Medical Research, 2009 SA Scientific Meeting.

Molecular Regulation Laboratory

- Mr Joey Puccini received an Australian Postgraduate Award.
- Professor Kumar was elected an international member of the European Research Institute for Integrated Cellular Pathology (ERI-ICP).
- Dr Jantina Manning was awarded an Early Career Fellowship from the RAH/IMVS Research Committee.
- Professor Kumar won the 2009 Ranbaxy Research Award (Medical Sciences-Basic Research).

Myeloma Research Laboratory

- Dr Sally Martin won the University Medal for her PhD, and HSANZ Albert Baikie Memorial Medal.
- Dr Kate Vandyke won the University of Adelaide Medal for her PhD.
- Dr Peter Psaltis won the Hugh Gilmore Prize, Ross Wishart Memorial Award and the Nimmo Prize.

Vascular Biology and Cell Trafficking Laboratory

- Dr Claudine Bonder won the 2009 Tall Poppy for South Australia Award.
- Dr Sarah Brice won Best Early Career Award at the 2010 Australian Vascular Biology Conference.
- Ms Kate Parham received a 2009 Australian Postgraduate Award, University of Adelaide.
- Ms Wai Sun won first prize for best poster at the 2010 Centre for Stem Cell Research Annual Meeting, and at the 2010 Faculty of Health Sciences Post-graduate Research Day.

Research Staff and Students 2009 – 2010

Acute Leukaemia Laboratory

Research Staff
Richard D'Andrea
Ian Lewis
Anna Brown
Petra Neufing
Michelle Perugini
Sarah Bray
Carolyn Butcher
Grant Engler
Lena Eriksson
Monika Kutyna
Marianne Oosterwegel
Diana Salerno

Students
Sonya Diakiw (PhD)
Chung Hoow Kok (PhD)
Nisha Rao (PhD)
Teresa Sadras (PhD)
Nur Hezrin Shahrin (PhD)
(BSc, Hons)
Jackie Mao (BSc, Hons)

Students who completed their degrees in 2009 and 2010
Chung Hoow Kok (PhD)
Nur Hezrin Shahrin (Hons)
Jackie Mao (Hons)

Cell Growth and Differentiation Laboratory

Research Staff
Mark Guthridge
Emma Barry
Ana Lonic
Jason Powell

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

Students who completed their degrees in 2009 and 2010
None

Cell Signalling Laboratory

Research Staff
Yeesim Khew-Goodall
Lesley Crocker
Xiaochun Li

Students
Leila Belle (nee Wyatt) (PhD)
Samuel Dyer (PhD)
Jin Jau Liau (PhD)
Asanthi Perera (PhD)

Students who completed their degrees in 2009 and 2010
Samantha Williams (PhD)
Asanthi Perera (1st Class Hons)

Cytokine Receptor Laboratory

Research Staff
Angel Lopez
Tim Hercus
Hayley Ramshaw
Frank Stomski
Joanna Woodcock
Carl Coolen
Mara Dottore
Rebecca Krake
Barbara McClure
Melanie Pudney
Anna Sapa

Students
Jarrod Sandow (PhD)

Students who have completed their degrees in 2009-2010
None

Cytokine Research Laboratory

Research Staff
Greg Goodall
Matthew Anderson
Andrew Bert
Cameron Bracken
Philip Gregory
Narelle Mancini
Suraya Roslan
Rosemary Sladic
Anna Tsykin
Josephine Wright

Students
Natasha Kolesnikoff (PhD)
Yat Yuen (Eddie) Lim (PhD)
Emily Paterson (PhD)
Daniel Thomson (PhD)
Stuti Srivastava (Hons)

Students who completed their degrees in 2009 and 2010
Emily Paterson (PhD)
Stuti Srivastava (Hons)

Haematology Clinical Research Unit

Laboratory Heads
L Bik To
Ian Lewis

Clinical Staff
Peter Bardy
Pratyush Giri
Noemi Horvath
Cindy Lee
Simon McRae
Sarah Roberts
David Ross
Lay Tay

Scientific Staff
Tony Cambareri
Malgorzata (Gosha) Badowicz
Elizabeth Duncan
Pam Dyson
Peter Harrison
Kate Harrison
Monica Kutyna
Kerry Munro
Thanh Nguyen
Trevor Rawling
Judy Stevens
Rick Tocchetti
Michael Vo

Students who completed their degrees in 2009-2010
Smita Hiwase (PhD)

Hepatitis C Virus Research Laboratory

Research Staff
Michael Beard
Jill Carr
Nicholas Eyre
Karla Helbig
Gemma Sharp
Kylie Van der Hoek

Students
Renee Phillips (PhD)
Erin McCartney (PhD)
Edmund Tse (PhD)
Kate Muller (PhD)
Geerapong Tanongsaksrikun
(visiting international student)
Guillaume Fiches (visiting
international student)
Clarissa Ling Tan (Hons)
Sumudu Narayana (Hons)

Students who completed their degrees in 2009 and 2010
Renee Phillips (PhD)
Clarissa Ling Tan (Hons)
Sumudu Narayana (Hons)

Leukaemia Biology Group

Research Staff
Junia V. Melo
Debora Casolari
Duncan Hewett
Jun Ishiko
Brett Johnson
Angela Kleeman
Ljiljana Vidovic
Vicki Wilczek

Students
Bradley Chereda (PhD)
Ka Chung Cheung (PhD)
Daniel Sears (PhD)
Mark Cutting (BSc/Hons)
Tess Peer (BSc/Hons)

Students who completed their degrees in 2009 and 2010
None

Leukaemia Unit

Research Staff
Sue Branford
Emma Channon
Chani Field
Linda Fletcher
Jasmina Georgievski
Wendy Parker
Stuart Phillis
Haley Prime
Jodi Prime
Brad Sullivan
Alex Yeoman
Goldy Yong

Students
David Ross (PhD)
Ng Chan Thiam (BSc)
Zoe Donaldson (Hons)

Students who completed their degrees in 2009 and 2010
David Ross (PhD)

Lymphatic Development Laboratory

Research Staff
Natasha Harvey
Jan Kazenwadel
Genevieve Secker

Students
Emma Gordon (PhD)
Kelly Betterman (PhD)

Students who completed their degrees in 2009 and 2010
None

Mast Cell Laboratory

Research Staff
Michele Grimbaldeston
Lisa Biggs
Boris Fedoric
Emma Gordon

Students
Zhen Liu (Hons)
Anastasia Yu (PhD)

Students who completed their degrees in 2009 and 2010
Zhen Liu (1st Class Hons)

Melissa White Memorial Laboratory

Research Staff
Timothy Hughes
Deborah White
Chung Hoow Kok
Verity Saunders
Phuong Dang
Amity Frede
Kelvin GrootObbink
Jarrad Goyne
Eva Nievergall
David Yeung
Stephanie Arbon
Bronwyn Cambareri
Sasha Wheeler

Students
David Ross (PhD)
Devendra Hiwase (PhD)
Jane Engler (PhD)
Carine Tang (PhD)
Jackie Wong (PhD)
Laura Eadie (PhD)
Dale Watkins (PhD)
Lisa Schafranek (PhD)

Students who completed their degrees in 2009 and 2010
David Ross (PhD)
Devendra Hiwase (PhD)
Lisa Schafranek (1st Class Hons)
Dale Watkins (1st Class Hons)

Molecular Pathology Research Laboratory

Research Staff
Hamish Scott
Christopher Hahn
Brita Ardesjö Lundgren
Wendy Parker
Peter J Brautigan
Joseph Carolan
Zoe Kilpatrick
Jacqueline Rossini
Milena Stankovic

Students
King-Hwa (Michael) (PhD)
Lucia Gagliardi (PhD)
Chan Eng Chong (PhD)
Sarah Kinkel (PhD)
Ming Lin (Hons)

Students who completed their degrees in 2009 and 2010
Sarah Kinkel (PhD)

Molecular Regulation Laboratory

Research Staff
Sharad Kumar
Loretta Dostyn
Donna Denton
Natasha Boase
Hazel Dalton
Natalie Foot
Nirmal Lorensuhewa
Balazs Bajka
Jantina Manning
Sonia Shalini
Yew Ann Leong
Kristen Ho
Scott Townley
Kathryn Mills
Daniel Lachini

Students
Jantina Manning (PhD)
Joey Puccini (Hons 2009, PhD 2010)
Katherine Adriaanse (Hons)

Students who completed their degrees in 2009 and 2010
Jantina Manning (PhD)
Joey Puccini (1st Class Hons)
Katherine Adriaanse (1st Class Hons)

Molecular Signalling Laboratory

Research Staff
Stuart Pitson
Renae Barr
Briony Gliddon
Tamara Leclercq
Melissa Pitman
Samantha Williams
Joanna Woodcock
Kristy Alexander
Carl Coolen
Julia Dobbins
Ruby Ivanov
Paul Moretti
Duyen Pham

Student
Huasheng Chan (PhD)

Students who completed their degrees in 2009 and 2010
Tamara Leclercq (PhD)
Kate Jarman (PhD)
Huasheng Chan (1st Class Hons 2009)

Myeloma Research Laboratory

Research Staff
Andrew Zannettino
Peter Diamond
Stephen Fitter
Sharon Williams
Sally Martin
Jenny Drew
Sharon Paton
Hongsheng Wang
Manami Ito

Students
Catherine Gan (PhD)
Shriram Nath (PhD)
Mary Matthews (PhD)
James Richardson (PhD)

Students who completed their degrees in 2009 and 2010
Sally Martin (PhD – Winner of University of Adelaide Medal)
Peter Psaltis (PhD)
Kate Vandyke (PhD)

Vascular Biology and Cell Trafficking Laboratory

Research Staff
Claudine Bonder
Jeff Barrett
Sarah Brice
Jyotsna Pippal
Michaelia (Minky) Cockshell
Samantha Escarbe

Students
Wai Yan (Kiwi) Sun (PhD)
Kate Parham (PhD)
Shaundeep Sen (PhD)

Students who completed their degrees in 2009 and 2010
Emma Thompson (1st Class Hons)
Kate Parham (1st Class Hons)

Seminar Program 2009 – 2010

2009

Dr Guy Heathers

Chief Business Officer, Cancer Therapeutics CRC Pty Ltd, Australia
Creating new cancer drugs from your research: a new company dedicated to discovering new cancer drugs from Australia's research efforts (2/3/09)

Dr Ching-Cheng Chen

Dept of Pathology, Stanford University School of Medicine, USA
Cell lineage specification at the single cell level (11/3/09)

Professor David Vaux

La Trobe University, Australia
Truth lies in Science, or true lies in Science (12/3/09)

Professor Andrew McMahon

Frank B Baird Jr. Prof of Science, Harvard University, USA
Sonic hedgehog morphogen signaling and the regulation of neural diversity (16/3/09)

Dr Quenten Schwarz

Centre for Cancer Biology, Australia
Coordinating neural crest stem cell migration with cell specification (19/3/09)

Professor Jean Paul Thiery

Institute of Molecular and Cell Biology, A*STAR, Singapore
The neural crest ontogeny, adhesion and migration (23/3/09)

Associate Professor Chris Ormandy

Garvan Institute of Medical Research, Australia
Elf5 is essential for mammary development, but is it also a tumour suppressor during cancinogenesis? (26/3/09)

Professor Emma Whitelaw

Queensland Institute of Medical Research, Australia
The role of epigenetics in development (2/4/09)

Dr Michele Grimbaldeston

Centre for Cancer Biology, Australia
Mast Cells: 'Tunable' regulators of inflammation? (9/4/09)

Professor Ian Frazer, FAA

Director, Diamantina Institute for Cancer, Immunology and Metabolic Medicine, The University of Queensland, Australia
Immunoprophylaxis and Immunotherapy for HPV-associated cancer (16/4/09)

Dr Anthony Borneman

Senior Research Scientist, The Australian Wine Research Institute, Australia
Comparative genomics in yeast – from chIP chip to whole genome sequencing (29/4/09)

Professor Nick Fazzalari

Bone and Joint Research Laboratory, SA Pathology and Hanson Institute, Australia
Does the skeleton have a heartbeat and does it influence skeletal integrity? (30/4/09)

Associate Professor Ygal Haput

Tumour Suppression Laboratory, Peter MacCallum Cancer Centre, Australia
Regulation of the tumour suppressors p53 and PML: clues for anti-cancer targets (7/5/09)

Dr Matthias Ernst

Colon Molecular and Cell Biology Laboratory, Ludwig Institute for Cancer Research, Australia
Linking inflammation to Cancer: A novel role for Stat3 (14/5/09)

Associate Professor Ricky Johnstone

Gene Regulation Laboratory, Cancer Therapeutics Program, Peter MacCallum Cancer Centre, Australia
Anti-cancer activities of HDAC inhibitors used alone and in combination with other pro-apoptotic agents (21/5/09)

Professor Alan Mackay-Sim

Director, National Centre for Adult Stem Cell Research, Griffith University, Australia
Stem cells from olfactory mucosa: naris to nosology (28/5/09)

Dr Tim Kuchel

Veterinary Services Division, SA Pathology, Australia, and
Dr Emma Parkinson-Lawrence

Pharmacy and Medical Sciences, University of South Australia, Australia
Core Facilities in the Frome Road Precinct – Veterinary Services Division and the Biophysical Characterisation Facility (11/6/09)

Dr Gethin Thomas

Lions Medical Research Foundation Fellow, Musculoskeletal Genetics Group, Diamantina Institute for Cancer, Immunology and Metabolic Medicine, The University of Queensland, Australia
Gene discovery in bone and joint disease (16/6/09)

Associate Professor Jiake Xu

Orthopaedic Surgery, QEH Medical Centre, University of Western Australia, Australia
Regulation of Vesicular Trafficking pathways in osteoclasts (25/6/09)

Dr Kate Stacey

Institute for Molecular Bioscience and School of Chemistry and Molecular Biosciences, The University of Queensland, Australia
DNA can be deadly: Host defence against pathogen DNA (9/7/09)

Professor Bill Heath

Federation Fellow, Department of Microbiology and Immunology, University of Melbourne, Australia
Initiation and maintenance of killer T cell immunity to viral infections (16/7/09)

Associate Professor Michael Hickey

NHMRC Senior Research Fellow, Centre for Inflammatory Diseases, Monash University, and Department of Medicine, Monash Medical Centre, Australia
Using in vivo imaging to understand the mechanisms of leukocyte recruitment (23/7/09)

Professor Steve Krillis

Centre for Infection and Inflammation Research, University of New South Wales, Australia
Autoantibody induced thrombosis; current aspects on molecular, clinical and therapeutic aspects (30/7/09)

Professor Shaun Jackson

Head, Thrombosis Research Laboratory, Monash University, Australia
Human and experimental thrombosis (6/8/09)

Dr Jorg Heierhorst

Head, Molecular Genetics Unit, St Vincent's Institute of Medical Research, Australia
Roles of phospho-regulated protein interaction domains in the DNA damage response (13/8/09)

Associate Professor Susie Nilsson

Australian Stem Cell Centre, Australia
The role of Osteopontin in HSC biology (20/8/09)

Associate Professor David Haylock

Australian Stem Cell Centre, Australia
Development of thrombopoietin mimics for ex vivo expansion of haemopoietic stem cells (21/8/09)

Dr Anne Thompson

Executive Director, Victorian Cancer Biobank, Australia
Sound planning, governance and management can unite a consortium (27/8/09)

Dr Agnes Yong

Hematology Branch, National Heart, Lung and Blood Institute, National Institutes of Health, USA
Tackling the leukaemic stem cell in CML from the immunological perspective (2/9/09)

Dr Tonya Bliss

Department of Neurosurgery, Stanford University of Medicine, USA
The role of transplanted human neural stem cells in brain repair after stroke (3/9/09)

Dr Paul Foster

University of Newcastle, Australia
Regulating allergic inflammation by manipulating miRNA (8/9/09)

Dr Leigh Coultas

Cancer and Haematology Division, Walter and Eliza Hall Institute, Australia
Hedgehog signaling in development of the early blood vascular system (10/9/09)

Professor Tom Gonda

Diamantina Institute for Cancer, Immunology and Metabolic Medicine, The University of Queensland, Australia
MYB in myeloid cell transformation and breast cancer (18/9/09)

Professor Christina Mitchell

Monash University, Australia
Regulation of PI3-kinase signalling by lipid phosphatises (1/10/09)

Professor David Brindley

Signal Transduction Research Group, Department of Biochemistry, University of Alberta, Canada
Autotaxin and lysophosphatidate release breast cancer cells from the chemotherapeutic actions of Taxol (8/10/09)

Dr Ross Dickins

Nossal Fellow, VESKI Fellow, Division of Molecular Medicine, Walter and Eliza Hall Institute, Australia
Modeling targeted cancer therapy using RNA interference in mice (15/10/09)

Dr Krasimir Vasilev

School of Advanced Manufacturing and Mechanical Engineering, Mawson Institute, University of South Australia, Australia
Functional nanoengineered plasma polymer films for biomaterials applications (21/10/09)

Professor Patrick Tam

Head, Embryology Research Unit, Children's Medical Research Institute, University of Sydney, Australia
Mouse endoderm development: Lineage allocation and morphogenetic function (22/10/09)

Associate Professor Tony Tiganis

Department of Biochemistry and Molecular Biology, School of Biomedical Sciences, Monash University, Australia
Reactive oxygen species, protein tyrosine phosphatases and type 2 diabetes (29/10/09)

Dr Robin Anderson

Head, Metastasis Research Laboratory, Peter MacCallum Cancer Centre, Australia
Regulation of Breast Cancer Metastasis by BMP4 (5/11/09)

Professor Melissa Little

The University of Queensland, Australia
Renal organogenesis: What can it tell us about renal repair and regeneration options? (12/11/09)

Professor Joe Trapani

Head, Cancer Immunology Program, Peter MacCallum Cancer Centre, Australia
Structure function analysis of lymphocyte perforin, and its role in cancer susceptibility (26/11/09)

Dr Martin Ashdown

University of Melbourne and Royal Women's Hospital, Australia, and
Associate Professor Brendon Coventry

Tumour Immunology Laboratory, University of Adelaide; Royal Adelaide Hospital, Hanson Institute, Australia
'The Capture of Fire' – Therapeutic modulation and reversal of immune suppression in cancer (30/11/09)

2010

Dr Christina Kurts
Institute of Experimental Immunology, University of Bonn, Germany
Role of chemokines in cross-presentation and glomerular injury (21/1/10)

Dr Kimi Honma
National Cancer Center Research Institute, Tokyo
Ribophorin II (RPN2) confers docetaxel resistance in breast cancer (18/2/10)

Dr Michael Samuel
Beatson Institute for Cancer Research, Scotland
Novel insights into Rho/ROCK signalling in skin cancer (25/2/10)

Professor Jack Bennink
Laboratory of Viral Diseases, NIAID, National Institutes of Health, USA
(I) Intraviral imaging of the anti-viral immune response and (II) Antigenic drift: Mechanisms of influenza A virus hemaglutinin immune escape (2/3/10)

Professor Phil Hogg
Director, Lowry Cancer Research Centre, University of New South Wales, Australia
From the bench to the bedside with a novel class of anti-mitochondrial cancer drugs (18/3/10)

Associate Professor Paul Thomas
School of Molecular and Biomedical Science, University of Adelaide, Australia
Identifying mechanisms of brain and gonad development using Sox3 transgenic mice (25/3/10)

Dr Toby Coates
Renal Unit, Royal Adelaide Hospital, Australia
Clinical and experimental cellular transplantation therapy – the new frontier in organ replacement therapy (1/4/10)

Professor Kerin O'Dea
Director, Sansom Institute for Health Research, University of South Australia, Australia
Diabetes and vascular disease risk in Indigenous Australian populations (8/4/10)

Dr Andreas Strasser
NHMRC Australia Fellow, Molecular Genetics of Cancer Division, Walter and Eliza Hall Institute, Australia
Targeting apoptosis regulators for cancer therapy (15/4/10)

Dr Grant Buchanan
Prostate Cancer Foundation of Australia, BHP Billiton, Research Fellow, Head, Molecular Ageing Laboratory, University of Adelaide, Australia
Molecular dynamics of steroid signaling in the breast and prostate cancer microenvironment (22/4/10)

Professor Sharon D Ricardo
Director, MBio Graduate School, and Renal Regeneration Laboratory, Monash Immunology and Stem Cell Laboratories (MISCL), Australia
Therapeutic strategies for kidney development, growth and repair (29/4/10)

Professor Antony Braithwaite
Children's Medical Research Institute, Sydney, Australia
Mouse models of p53 tumour suppressor gene function (6/5/10)

Professor Paul Hertzog
Director, Centre for Innate Immunity and Infectious Disease, Monash University, Australia
Innate immune responses in homeostasis, inflammation and cancer (13/5/10)

Dr Jose A Villadangos
NHMRC Senior Research Fellow, Immunology Division, Walter and Eliza Hall Institute, Australia
Regulation of antigen presentation in the dendritic cell network (27/5/10)

Dr Shane Grey
ARC Future Fellow, Gene Therapy and Autoimmunity Group, Garvan Institute of Medical Research, Australia
Behind every great T cell lies a B cell; B and T cell interactions that drive autoimmune diabetes (3/6/10)

Dr Anthony Don
UNSW Cancer Research Centre, Faculty of Medicine, University of New South Wales, Australia
Immunosuppressive sphingosine analogues, and 2-dimensional sphingolipid profiling using mass and relative polarity (10/6/10)

Dr Gordon K Smyth
Bioinformatics Division, Walter and Eliza Hall Institute, Australia
Detecting transcriptional signatures for cell populations and pathways (17/6/10)

Dr Nicole Verrills
NHMRC Peter Doherty (Biomedical) Fellow, Medical Biochemistry, Faculty of Health, University of Newcastle, Australia
Activating the tumour suppressor, PP2A, as a novel strategy for leukaemia therapy (24/6/10)

Dr Matt McCormack
Bone Marrow Research Laboratories, Royal Melbourne Hospital, Australia
Identification of self-renewing thymocytes that are the cell-of-origin in a mouse model of T-cell leukaemia (1/7/10)

Professor Shaun McColl
Head Chemokine Biology, Discipline of Microbiology and Immunology, School of Molecular and Biomedical Science University of Adelaide, Australia
Novel insights into regulation of chemokine function: Focus on the atypical chemokine receptor, CCX-CKR (8/7/10)

Dr Tony Papenfuss
Bioinformatics Division, Walter and Eliza Hall Institute, Australia
Using genomics to understand the Tasmanian Devil facial tumour disease (15/7/10)

Associate Professor Hong Zhou

Bone Research, ANZAC Research Institute, University of Sydney, Australia
Glucocorticoids and osteoblast (29/7/10)

Associate Professor Katharina Gaus

Centre for Vascular Research, University of New South Wales, Australia
Membrane organising and signal transduction in T cells (5/8/10)

Professor Richard Boyd

Director, Monash Immunology and Stem Cell Laboratories (MISCL), Australia
Combining stem cells and hormonal therapy to restore immunity in cancer patients (12/8/10)

Professor John Rasko

Cell and Molecular Therapies, Royal Prince Alfred Hospital and Centenary Institute, Australia
A new dimension to the hemopoietic stem cell niche (26/8/10)

Professor Joseph A Trapani

Director of Research, Head, Cancer Immunology Program, Peter MacCallum Cancer Centre, Australia
Structure function analysis of lymphocyte perforin, and its role in cancer susceptibility (2/9/10)

Dr Paul Neilsen

Breast Cancer Genetics Laboratory, Hanson Institute, Australia
Mutant p53 drives cancer cell invasion in breast tumours (16/9/10)

Associate Professor Allison Cowin

NHMRC Research Fellow, Head, Wound Healing Laboratory, Women's and Children's Health Research Institute, Australia
The function of the cytoskeletal protein, Flightless I, in would healing (23/9/10)

Professor John Schrader

Director, the Biomedical Research Centre, University of British Columbia, Canada
The human antibody repertoire and the rapid generation of monoclonal antibodies for the therapy of pandemic H1N1 influenza and other, non-infectious diseases (30/9/10)

Professor Matthew Gillespie

Director, Prince Henry's Institute, Australia
Immune cell functions in bone (7/10/10)

Dr Mark Shackleton

Melanoma Research Laboratory, Peter MacCallum Cancer Centre, Australia
Understanding melanoma progression (28/10/10)

Professor Keryn Williams

NHMRC Principal Research Fellow, Department of Ophthalmology, Flinders University, Australia
Heritable influences in oxygen-induced retinopathy (4/11/10)

Professor Daniel Bikle

Professor of Medicine and Dermatology, University of California, Australia
The interaction between vitamin D and calcium on keratinocyte differentiation (18/11/10)

Dr Ben Hogan

Institute for Molecular Bioscience, The University of Queensland, Australia
Molecular genetics and development (25/11/10)

Invited Presentations 2009 – 2010

Cell Growth and Differentiation Laboratory

Dr Mark Guthridge
Invited Speaker

- Queensland Institute of Medical Research Seminar. 2009, Brisbane, Australia.
- 5th Garvan Signalling Symposium. October 2010, Sydney, Australia.

Cell Signalling Laboratory

Dr Yeesim Khew-Goodall
Invited Speaker

- 6th International Conference on Pathophysiology. September 2010, Montreal, Canada.
- The International EMT Conference. September 2009, Tucson, USA.

Cytokine Receptor Laboratory

Professor Angel Lopez
Invited Speaker

- Royal Brisbane and Women's Hospital Health Care Symposium. October 2010, Brisbane, Australia.
- OzBio 2010. September/October 2010, Melbourne, Australia.
- 1st Italy-Australia Symposium. September 2010, Prato, Italy.
- EMBO Conference. May 2010, Dubrovnik, Croatia.
- Institute of Molecular Bioscience, University of Queensland. March 2010, Brisbane, Australia.
- 8th Australian Peptide Conference. October 2009, South Stradbroke Island, Australia.
- WEHI, Prof D Metcalf's 80th Birthday Celebrations/Symposium. March 2009, Melbourne, Australia.

Cytokine Research Laboratory

Associate Professor Greg Goodall
Invited Speaker and/or Session Chair

- Monash Institute of Medical Research Seminar. 2009, Melbourne, Australia.
- Dept of Molecular and Cellular Biology, University of Arizona. 2009, Tucson, USA.
- RNAi-2009 Meeting. Boston, USA.
- Lorne Protein Conference. 2009, Lorne, Australia.
- Hunter Cellular Biology Meeting. 2009, Hunter Valley, Australia.
- AIMS National Scientific Meeting. 2009, Adelaide, Australia.
- 4th International Epithelial-Mesenchymal Transition Meeting. 2009, Tucson, USA.
- Lorne Cancer Conference. 2010, Lorne, Australia.
- OzBio2010. Melbourne, Australia.
- Australian Health and Medical Research Congress. 2010, Melbourne, Australia.

Haematology Clinical Research Unit

Professor L Bik To
Invited Speaker and/or Session Chair

- Haematology Society of Australia & New Zealand Conference. October 2009, Adelaide, Australia.
- Novartis Oncology Educational Meeting. August 2010, Perth, Australia.
- Novartis Oncology Meeting. August 2010, Melbourne, Australia.
- Genzyme Transplant Oncology Meeting. August 2010, Sydney, Australia.
- Haematology Oncology Grand Round, Queen Mary Hospital. November 2010, Hong Kong.

Hepatitis C Virus Research Laboratory

Associate Professor Michael Beard
Invited Speaker

- American Association for the Study of Liver Disease. (Presidential Plenary). November 2010, Boston, USA.

Leukaemia Biology Group

Professor Junia V. Melo
Invited Speaker and/or Session Chair

- Novartis Correlative Studies Workshop. March 2009, Paris, France.
- Novartis Educational Symposia on CML. April 2009, Nagoya, Fukuoka and Tokyo, Japan.
- Annual Meeting of the Haematology Society of Taiwan. April 2009, Taipei, Taiwan.
- Update from ASH2008. April 2009, Singapore.
- Novartis Haematology GET Weekend. May 2009, Melbourne, Australia.
- 14th Congress of the Asia-Pacific Society of Bone Marrow Transplantation. August 2009, Seoul, South Korea.
- Hong Kong Society of Haematology. September 2009, Hong Kong.
- 11th European Society of Haematology International Conference on CML. September 2009, Bordeaux, France.
- Advanced Course on CML for Spanish doctors. September 2009, Adelaide, Australia.
- Haematology Society of New Zealand & Australia Conference. October 2009, Adelaide, Australia.
- 51st Annual Meeting of the American Society of Hematology. December 2009, New Orleans, USA.
- 15th Congress of the European Hematology Association. June 2010, Barcelona, Spain.
- 12th European Society of Haematology International Conference on CML. September 2010, Washington DC, USA.
- BMS-sponsored educational symposia at Siriraj Hospital and the Army Hospital. October 2010, Bangkok, Thailand.
- 15th Congress of the Asia-Pacific Society of Bone Marrow Transplantation. October 2010, Phuket, Thailand.
- 52nd Annual Meeting of the American Society of Hematology, December 2010, Orlando, USA.

Leukaemia Unit

Associate Professor Susan Branford
Invited Speaker and/or Session Chair

- Latin American Chronic Myeloid Leukemia Global Opinion Leaders Summit. October 2010, Porta Vallarta, Mexico.
- Latin American Nilotinib Investigator meeting. October 2010, Porta Vallarta, Mexico.
- Bcr-Abl Meeting. September 2010, Washington, USA.
- European School of Haematology 12th International Conference on CML. September 2010, Washington, USA.
- Federation of South African Societies of Pathology Conference. September 2010, Cape Town, South Africa.
- South America CML Tour. May 2010, Colombia and Venezuela.
- BCR-ABL Methods Meeting. May 2010, Taiwan and Hong Kong.
- Chronic Myeloid Leukaemia Global Opinion Leaders Summit. March 2010, Dresden, Germany.
- ENESTxtnd Investigator Workshop. November 2010, Melbourne, Australia.
- Novartis Oncology Research and Development Meeting. May 2010, Melbourne, Australia.
- Australasian Society of Cytogeneticists (ASoC) 16th Interim Scientific Meeting. March 2010, Canberra, Australia.
- Haematology Society of Australia & New Zealand Conference. October 2009, Adelaide, Australia.
- Australian Institute of Medical Scientists National Scientific Meeting. October 2009, Adelaide, Australia.

Lymphatic Development Laboratory

Dr Natasha Harvey
Invited Speaker and/or Session Chair

- First Australian Conference on Lymphatic Biology in Health and Disease. October 2010, Melbourne, Australia.
- Ozbio2010. September 2010, Melbourne, Australia.
- Ludwig Institute for Cancer Research Seminar. October 2009, Melbourne, Australia.
- International Society of Lymphology Congress. (Keynote). September 2009, Sydney, Australia.
- 14th Australia and New Zealand Microcirculation Society Meeting. August 2009, Queenstown, New Zealand.
- Monash University Seminar. August 2009, Melbourne, Australia.
- ESH Angiogenesis Conference. June 2009, Helsinki, Finland.
- WEHI, Postgraduate Lecture Series Seminar. May 2009, Melbourne, Australia.

Mast Cell Laboratory

Dr Michele Grimbaldeston
Invited Speaker and/or Session Chair

- 4th Barossa Meeting. November 2009, Barossa Valley, Australia.
- 13th Australasian Autoimmunity Workshop. October/November 2009, Adelaide, Australia.
- Mutagenesis and Experimental Pathology Society of Australia
- (MEPSA) Annual Scientific Meeting. December 2009, Sydney, Australia.
- 20th Australian Society of Clinical Immunology and Allergy Annual Conference. September 2009, Adelaide, Australia.
- Australian Society for Medical Research, SA Annual Scientific
- Meeting. 2010, Adelaide, Australia.
- The Ludwig and Melbourne Health 2010 Seminar. July 2010, Melbourne, Australia.
- 11th Brisbane Immunology Group Annual Retreat. August 2010, Sunshine Coast, Australia.
- Monash Centre for Inflammatory Diseases Seminar. October 2010, Melbourne, Australia.
- 5th Australian Health & Medical Research Congress. November 2010, Melbourne, Australia.

Melissa White Memorial Laboratory

Professor Timothy Hughes
Invitations to International Speaker Faculties

- 52nd ASH Meeting. 2010, Orlando, USA.
- Hematologic Malignancies. 2010, Houston, USA.
- ELN Frontiers Meeting. 2010, Vienna, Austria.
- 7th Global Nilotinib Investigator Meeting / Novartis Oncology Asia Pacific Summit. 2010, Hong Kong.
- EHA 2010 Novartis Satellite Symposium. 2010, Barcelona, Spain
- ASH CML Educational Session. 2009, New Orleans, USA.
- Hematologic Malignancies. 2009, Brussels, Belgium
- ELN Frontiers. 2009, Barcelona, Spain.
- New Horizons in Treating Cancer. 2009, Lisbon, Portugal.
- Seminars in Hematological Oncology – Fourth International Educational Forum. 2009, Herzlia, Israel.
- GOLS on CML. 2009, Paris, France.
- 6th Symposium of the European Leukaemia Net. 2009, Mannheim, Germany.
- ISEH 2010. 39TH Annual Scientific Meeting. 2010, Melbourne, Australia.
- New Directions in Leukaemia Research. 2010, Sunshine Coast, Australia.
- Haematology Society of Australia & New Zealand Conference. October 2009, Adelaide, Australia.

Associate Professor Deborah White
Invitations to International Speaker Faculties

- Faculty TKI BLT. 2009, Bordeaux, France.
- Faculty CML GOLS. 2010, Dresden, Germany.
- Faculty CML: Biological Basis of Therapy. 2010, Washington, USA.

Molecular Pathology Research Laboratory

Professor Hamish Scott
Invited Speaker

- Royal College of Pathologists of Australasia (RCPA): Pathology Update. February 2010, Melbourne, Australia.
- 13th Australasian Autoimmunity Workshop. October 2009, Adelaide, Australia.
- Australian Institute of Medical Scientists Conference. October 2009, Adelaide, Australia.
- Australasian Society of Clinical Immunology and Allergy (ASCIA), 20th Annual Scientific Meeting. September 2009, Adelaide, Australia.

Molecular Regulation Laboratory

Professor Sharad Kumar
Invited Speaker and/or Session Chair

- 34th Lorne Protein Conference. February 2009, Lorne, Australia.
- 21st Lorne Cancer Conference. February 2009, Lorne, Australia.
- Peter McCallum Cancer Institute Seminar. May 2009, Melbourne, Australia.
- ASBMB Adelaide Protein Group AGM. (Keynote). June 2009, Adelaide, Australia.
- 6th General Meeting of the International Proteolysis Society. (Keynote). October 2009, Surfers Paradise, Australia.
- LIMS Cell Death and Cancer Symposium, La Trobe University. November 2009, Melbourne, Australia.
- 4th Barossa Meeting. November 2009, Barossa Valley, Australia.
- National Centre for Biological Science. December 2009, Bangalore, India.
- Signaling 2010. February 2010, Rio Das Pedras, Brazil.
- 2010 Hunter Cell Biology Meeting. March 2010, Pokolbin, Australia.
- Institute of Molecular Biosciences Seminar, University of Queensland. April 2010, Brisbane, Australia.
- OzBio 2010. September/October 2010, Melbourne, Australia.

Molecular Signalling Laboratory

Associate Professor Stuart Pitson
Invited Speaker and/or Session Chair:

- FASEB Summer Research Conference. June/July 2009, Carefree, USA.
- International Federation of Placental Associations Conference. October 2009, Adelaide, Australia.
- Gordon Research Conference. February 2010, Ventura, USA.
- St Vincent's Institute for Medical Research Seminar. October 2009, Melbourne, Australia.

Myeloma Research Laboratory

Professor Andrew Zannettino
Invited Speaker and/or Session Chair

- Asia Pacific Oncology Symposium. (Plenary). March 2009, Hong Kong.
- Janssen Cilag, Multiple Myeloma 3 (MM3) meeting. May 2009, Sydney, Australia.
- Asia Pacific Haematology Summit. (Plenary). August 2009, Kuala Lumpur, Malaysia.
- HAA 2009. 2009 Annual Scientific Meeting of HSANZ, ANZSBT, ASTH. (Plenary). October 2009, Adelaide, Australia.
- Leukaemia Foundation of Australia. May 2010, Adelaide, Australia.
- Myeloma-Pathophysiology and Preclinical studies excluding Therapy session, 52nd Annual Meeting of the American Society of Hematology. December 2010, Florida, USA.

Vascular Biology and Cell Trafficking Laboratory

Dr Claudine Bonder
Invited Speaker

- 9th World Congress for Microcirculation. September 2010, Paris, France.
- Australian and New Zealand Microcirculation Society. August 2009, Queenstown, New Zealand.

Grants and Fellowships Awarded 2009 – 2010

Investigator	Title	Granting Body
F Alderuccio, H Scott, F-X Hubert	The role of Aire in immunological tolerance and autoimmunity	NHMRC
R Anderson, Y Khew-Goodall, P Gregory, C Johnstone	Identification and functional evaluation of microRNAs and their target genes that regulatebreast cancer metastasis	NHMRC
G Atkins, D Findlay, D Haynes, T Zheng, A Zannettino	The role of TNF family members TWEAK and TNF-alpha in bone remodelling	NHMRC
S Barry, MF Shannon, H Zola, R D'Andrea	Functional validation of FoxP3 target genes in human regulatory T cells	NHMRC
S Barry, H Zola, R D'Andrea, I Lewis	Differentiation of cord blood stem cells into thymus (T) function cells with regulatory phenotype and	Australian Research Council
S Barry, R D'Andrea, I Lewis	Optimisation of cord blood stem cell differentiation into T cells with regulatory phenotype	Inner Wheel Australia
M Beard	Senior Research Fellowship	NHMRC
M Beard, K Helbig	Identification of interferon stimulated genes that limit HCV replication and predict therapeutic outcome	NHMRC
M Beard, S Locarnini	Development of a laboratory based platform to manage patients who develop antiviral drug-resistance to the STAT-C compounds	ACH2
C Bonder	Florey Fellowship	Royal Adelaide Hospital
C Bonder	Role for sphingosine kinase-1 in endothelial progenitor cell survival and differentiation	NHMRC
C Bonder, A Lopez	Identification of new biomarkers on human endothelial progenitor cells	CRC for Biomarker Translation
C Bonder, S Pitson	A novel pathway controlling endothelial progenitor cell (EPC) fate	Cancer Council SA
C Bracken	Postdoctoral Training Fellowship: Investigating the role of microRNAs in breast cancer metastasis and proliferation	National Breast Cancer Foundation
D Cooper, M Beard, G Dore, S Emery, M French, T Kelleher, S Kent, A Lloyd, D Purcell	HIV and HCV Vaccines and Immunopathogenesis (program grant)	NHMRC
R D'Andrea, A Brown, I Lewis, C Mullighan, P Bardy	Klf5 function in Acute Myeloid Leukaemia	Cancer Council SA
R D'Andrea, C Mullighan, I Lewis, N Jenkins	Klf5 function in normal and leukaemic haemopoiesis	NHMRC
R D'Andrea, H Ramshaw, P Ekert, I Lewis, S Barry	Dissecting the role of the IL-3 receptor alpha subunit and beta-catenin in Acute Myeloid Leukaemia	NHMRC
R D'Andrea, H Scott, P Bardy, J.V. Melo	Molecular genetics of Polycythemia Vera	NHMRC
P Ekert, H Scott	The role of Hox genes in myeloid cell development and myeloid leukaemias	NHMRC
A Evdokiou, D Findlay, A Zannettino	Antitumour efficacy of TRAIL: an immunotherapeutic approach for the treatment of skeletal malignancies	NHMRC
P Foster, A Lopez	Targeting the β subunit of the IL-3, IL-5 and GM-CSF receptors as therapy for allergic inflammation	NHMRC
S Fuller, C Hahn, M Bahlo, H Scott, J Wiley	Using familial predisposition to CLL to follow disease progression	Leukaemia Foundation of Australia
G Goodall, G Farshid	miR-200 and other microRNAs in breast cancer	Cancer Council SA
G Goodall, P Gregory, Y Khew-Goodall	Identification of microRNAs that regulate the properties of breast cancer tumour initiating cells	Cancer Council SA
G Goodall, Y Khew-Goodall	Development Grant	NHMRC
G Goodall, MF Shannon, Y Khew-Goodall, A Ruskiewicz	Regulation of expression of the microRNA-200 family	NHMRC
P Gregory	Early Career Fellowship: Identification and functional evaluation of microRNAs in breast cancer metastasis and proliferation	National Breast Cancer Foundation
M Grimbaldeston	Career Development Award Fellowship	NHMRC
M Grimbaldeston	Does Vitamin D3 potentiate IgG-induced interleukin 10 production by human mast cells?	Royal Adelaide Hospital

Investigator	Title	Granting Body
M Grimbaldeston	Florey Fellowship (relinquished after 7 months to take up NHMRC CDA Fellowship)	Royal Adelaide Hospital
M Grimbaldeston	Mary Overton Fellowship	Royal Adelaide Hospital
M Grimbaldeston	Mast cells limit chronic UVB-induced skin pathology	NHMRC
S Gronthos, A Zannettino	Twist-1 mediated regulation of multipotential mesenchymal stem cell self-renewal and cell fate determination	NHMRC
S Gronthos, A Zannettino, N Fazzalari	The role of TWIST family basic helix-loop-helix transcription factors in bone cell commitment, function and repair	NHMRC
M Guthridge	The regulation of pleiotropic responses by bidentate motifs embedded in growth factor receptors	NHMRC
M Guthridge, P Ekert	Identifying the critical components of growth factor-mediated survival pathways	NHMRC
M Guthridge, T Hughes	A novel cytokine-receptor survival axis in chronic myeloid leukaemia	NHMRC
C Hahn, H Scott, R D'Andrea, P Ekert	GATA2 is a new predisposition gene for familial acute myeloid leukaemia	Cancer Council SA
N Harvey	Defining the role of macrophages in lymphatic vascular development	Cancer Council SA
N Harvey, M Francois	Defining the molecular events that initiate the genesis of lymphatic vessels	NHMRC
P Hissaria, Y Khew-Goodall, S Proudman	Identification of microRNAs in Scleroderma	Arthritis Australia
P Hissaria, C Bonder, S Proudman, Patterson	Systemic sclerosis serum microenvironment dysregulates endothelial progenitor cell migration	Arthritis Australia
N Horvath, A Zannettino, C Lee, LB To	Seed grant for the establishment of a multiple myeloma and related disorders database	Cancer Council SA
T Hughes	Practitioner Research Fellowship	NHMRC
T Hughes, J.V. Melo, S Branford, D White	Development and assessment of novel assays to predict response to second-line TKI therapy in imatinib resistant CML	NHMRC
Y Khew-Goodall	Senior Research Fellowship	Cancer Council SA
Y Khew-Goodall, G Goodall, G Farshid	The Pez-TGFbeta-miR200-ZEB1/2 axis in breast cancer	NHMRC
Y Khew-Goodall, G Goodall, S Proudman, P Hissaria	The identification of microRNAs in Scleroderma	NHMRC
S Kumar	Caspase-2 function in cell death and disease	NHMRC
S Kumar	Caspase function in animal development	NHMRC
S Kumar	Characterisation of the tumour suppressor function of caspase-2	NHMRC
S Kumar	Regulation of cell death and proliferation by histone demethylases	NHMRC
S Kumar	Roles of Ndfips as adaptors for the Nedd4 family	NHMRC
S Kumar	Senior Principal Research Fellowship	NHMRC
S Kumar, E Baehrecke, L Dorstyn	Apoptosis and autophagy in developmentally programmed cell death	NHMRC
S Kumar, D Cakouros	Controlling gene expression in normal and cancer cells	Cancer Council SA
S Kumar, D Cook	Nedd4-2 function in ENaC regulation	NHMRC
I Lewis, R D'Andrea	Novel somatic mutations causing acute myeloid leukaemia	Contributing Haematologists' Committee
A Lopez, S Kumar, T Hughes, H Scott, G Goodall, W Tilley, S McColl, J Paton, D Adelson, J Gécz, J.V. Melo, B To	Infrastructure grant for the South Australian Cancer Genome Facility, Centre for Cancer Biology and University of Adelaide	Australian Cancer Research Foundation
A Lopez, M Parker	Structural Biology of Cytokine Receptor Signalling – Program grant	NHMRC
A Lopez, H Ramshaw, C Mullighan	Eradicating the leukaemic stem cell with specific therapy	Cancer Council SA
S McColl, A Lopez	Structure and function of PI-3 kinase	Australian Research Council

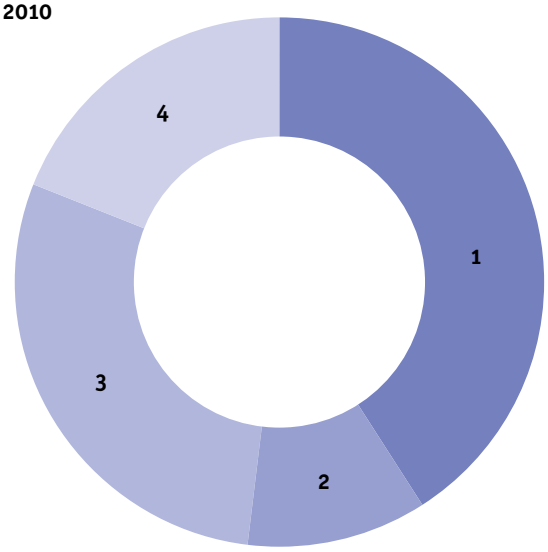
Investigator	Title	Granting Body
J.V. Melo, D Hewett, B Johnson	Control of expression of Bcr-Abl oncogene, the causative lesion of chronic myeloid leukaemia	Cancer Council SA
S Pitson	Mechanisms of regulation and biological roles of sphingosine kinase 2	NHMRC
S Pitson	Mechanisms of regulation and biological roles of sphingosine kinase 2	Cancer Council SA
S Pitson	Regulation of sphingosine kinase 2	Medvet
S Pitson	Role of sphingosine kinase 1 in PP2A-associated tumorigenesis	NHMRC
S Pitson	Senior Research Fellowship	NHMRC
S Pitson	Sphingosine kinase and signalling	Fay Fuller Foundation
S Pitson	The molecular mechanisms regulating oncogenic signalling by sphingosine kinase 1 phosphorylation and localisation	NHMRC
S Pitson	The role of SKAM and sphingosine kinase in wound healing	NHMRC
P Poronnik, S Kumar	Discovery grant. Assessing the physiological roles of ubiquitination in regulating neuronal ion channels, receptors and transporters	Australian Research Council
B Powell, P Anderson, A Zannettino, S Gronthos, D David	Mechanisms of premature granial fusion: role of retinol binding protein 4 in osteogenesis and suture fusion	NHMRC
H Ramshaw	Peter Nelson Fellowship	Cancer Council SA
R Saint, S Kumar, H Richardson, R Richards, G Hime, S O'Neill	Enabling grant. Australian Drosophila Biomedical Research Facility (OzDros)	NHMRC
Q Schwarz	Career Development Award	NHMRC
Q Schwarz	How does VEGF control heart development?	Channel 7 Children's Research Fund
H Scott	Senior Research Fellowship	NHMRC
H Scott, R D'Andrea, G Suthers, P Bardy, T Hughes, I Lewis, C Mullighan, C Hahn	Using familial predispositions to haematological malignancies to follow disease progression	Cancer Council SA
S-S Tan, S Kumar, D Vaux, C Morganti-Kossmann, J Silke, T Kossmann	Preventing neuronal cell death following brain trauma	Victorian Neurotrauma Initiative
E Thompson, G Goodall, A Fabra Fres, M Henderson, P Hill	Novel microRNA regulators in the breast cancer EMT	Cancer Australia
E Thompson, G Goodall, C Saunders, R Anderson, A Yap, I Street, K Stanley, A Dowling	National Collaborative Breast Cancer Research Grant: Targeting Breast Cancer Recurrence through epithelial Mesenchymal Plasticity	National Breast Cancer Foundation
D White, T Hughes, R D'Andrea, A Somogyi, J.V. Melo	The role of OCT-1 activity enhancers in improving the response of patients with low OCT-1 activity to imatinib	Leukemia & Lymphoma Society of USA – Translational Research Program
A Zannettino	Abl kinase inhibition as a novel therapy for myeloma-associated bone loss	Leukemia & Lymphoma Society of USA – Translational Research Program
A Zannettino, S Gronthos, J-P Levesque, D Peet, LB To	Is hypoxia inducible factor 2 the trigger of the angiogenic switch and a driver of disease progression in myeloma?	NHMRC
A Zannettino, S Gronthos, D Peet, L To, A Evdokiou	The role of CXCL12 (SDF-1)/CXCR4 in pathological angiogenesis and osteolytic bone disease in multiple myeloma	NHMRC
A Zannettino, T Hughes, A Evdokiou	Abl kinase inhibition as a novel therapy for malignancy-associated bone loss	Cancer Council SA

Financial Highlights

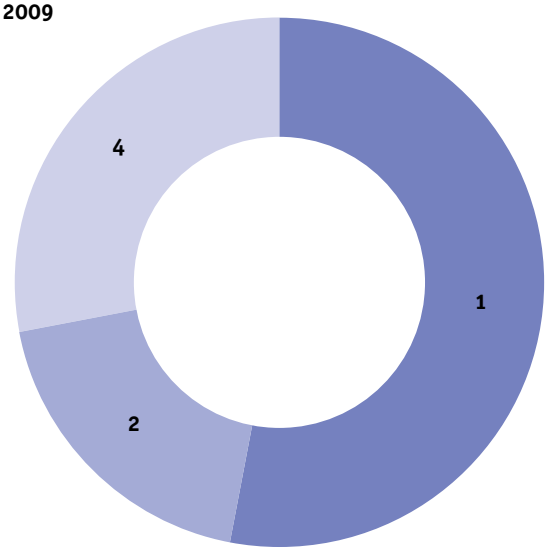
Research Income

		2010	2009
1	Federal (NHMRC and ARC) Grants	$7,101,972	$5,443,022
2	Other Research Grants	$2,013,772	$1,896,214
3	Establishment of ACRF Cancer Genome Facility	$5,025,000	0
4	Commercial Grants	$3,397,257	$2,867,257

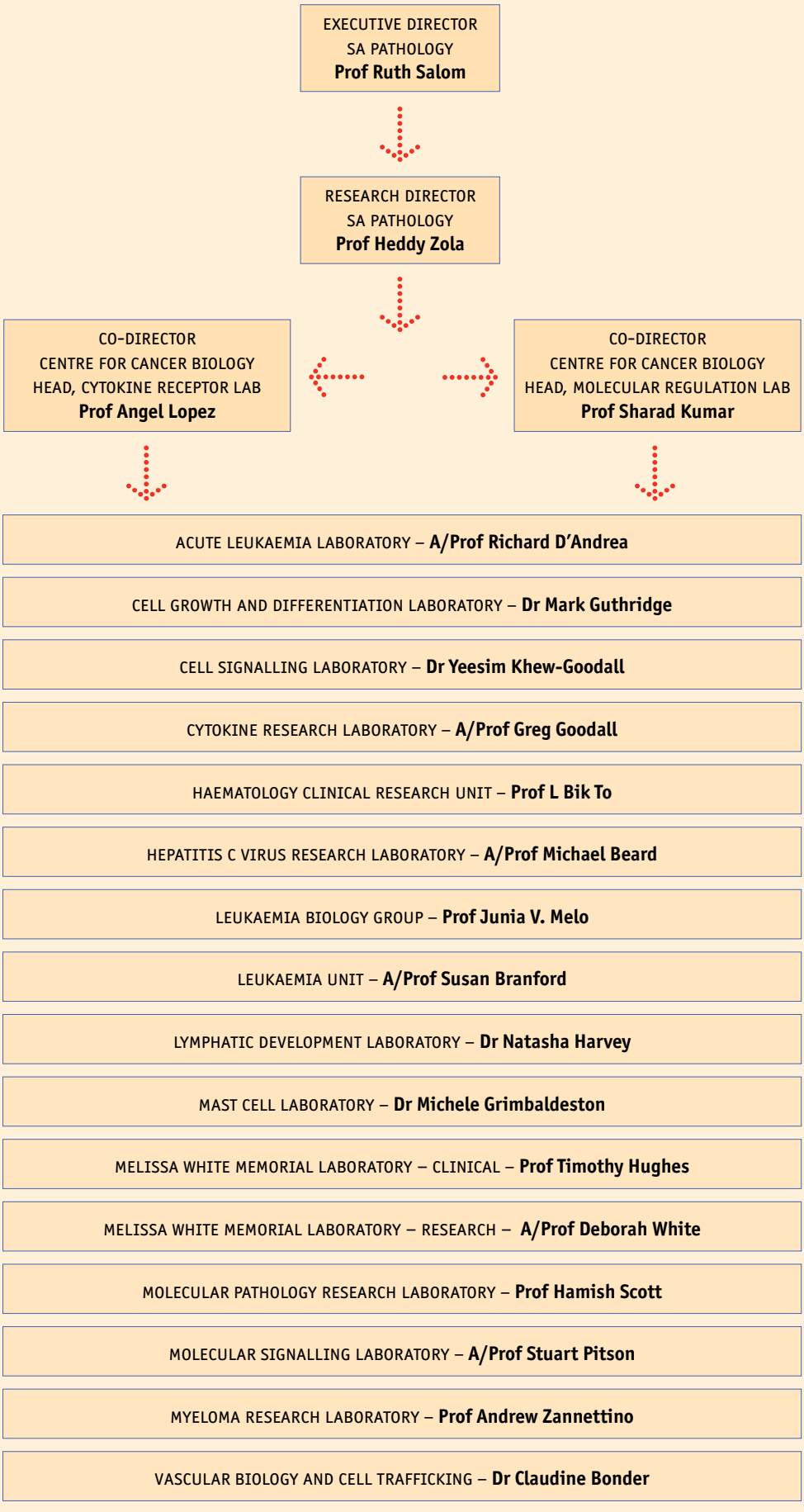
2010



2009



Organisational Chart



Our Supporters

The Centre for Cancer Biology wishes to thank all of our supporters and sponsors, as well as members of the public who donate to support our work.

Private Benefactors

Mr Michael and Mrs Andrea White and extended family
The Fay Fuller Foundation
The Matthew Roberts Foundation
Mr Steven Literacki
The Shahin Family

We also acknowledge the support of the following organisations that provided substantial financial or in-kind support during our first two years of operation

Our Primary Supporter

SA PATHOLOGY

IMVS PATHOLOGY

Our Other Supporters

Government of South Australia
SA Health

Australian Government
National Health and Medical Research Council
NHMRC

Australian Cancer Research Foundation

The Cancer Council South Australia

Medvet LABORATORIES

CRC BIOMARKER TRANSLATION

National Breast Cancer Foundation

The University of Adelaide

RAH Research Fund

BioInnovationSA

Government of South Australia

Research Australia

Australian Government
Australian Research Council

Leukaemia Foundation
VISION TO CURE
MISSION TO CARE

The Leukemia & Lymphoma Society
Fighting Blood Cancers

HOW YOU CAN SUPPORT 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

You can make a donation at any time by sending a cheque or money order. All donations are greatly appreciated and are fully tax deductable. No administrative fees or overheads are deducted when you donate; one hundred percent of your donation goes directly to research.

Make a donation in memoriam and in honour

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

Build a corporate partnership

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

Sponsorship

Companies or individuals may wish to sponsor a research project or individual Fellowships. These can be from 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 or mail:

Centre for Cancer Biology
SA Pathology
PO Box 14 Rundle Mall
Adelaide South Australia 5000
Australia

Centre for Cancer Biology

Centre for Cancer Biology
SA Pathology
Frome Road
Adelaide South Australia 5000
Australia
Tel: +61 8 8222 3422
Fax: +61 8 8232 4092

General Enquiries
Ms Anna Nitschke
Executive Assistant to Professor Angel Lopez
Email: Anna.Nitschke@health.sa.gov.au

Postal Address
PO Box 14 Rundle Mall
Adelaide South Australia 5000
Australia

Website
www.centreforcancerbiology.org.au

www.centreforcancerbiology.org.au