mMCP4 protects against chronic UVB-induced ulceration and neoplasia development

Cross-section of chronically UVB-irradiated ear of mast cell-deficient c-KitW/W-v mouse. Section stained with Masson’s trichrome.
It gives me great pleasure to present the third Annual Report of the Centre for Cancer Biology (CCB) of SA Pathology and to reflect on its successes in 2012.

Since its establishment in 2009 as a hub of cancer research excellence, the Centre for Cancer Biology has steadily grown. New laboratory heads have been recruited, new technologies brought in and new facilities have been established. This growth has energised a virtuous cycle with a significant rise in competitive research grants, Fellowships and infrastructure funding for the CCB.

As you will see in this Annual Report, 2012 has been yet another highly successful year for the CCB. The membership of its Faculty has grown, several new Fellowships and research grants have been won, and the CCB has earned and received donations for much needed state-of-the-art equipment that ensures our researchers continue to be competitive which facilitates the translation of discoveries into better cancer treatments.

Having arrived last year from the National Health Service in the UK where health care is strongly linked to excellence in scientific research, I have been impressed with the integration of the CCB with the rest of SA Pathology. The close association of our pathologists with CCB researchers helps maintain the high quality of our diagnostic pathology services whilst giving our CCB researchers access to the most relevant pathology samples needed to make their cancer discoveries. The further integration of the CCB work with our own clinicians and clinicians at the Royal Adelaide Hospital provides reciprocal benefits to research and clinical care.

This close association between diagnostic and research activities is further boosted with the opening of the ACRF Cancer Genomics Facility, creating a wonderful formula that is already helping further advance the personalised cancer care provided by SA Pathology in South Australia, as well as boosting cancer, genomics and bioinformatics research for the CCB, our University of Adelaide partner and the SA research community in general.

As you will also see in this Annual Report the CCB enjoys a wonderful association with the rest of the research community and in particular with the two neighbouring universities: the University of Adelaide and the University of South Australia, with which it shares students, equipment, library facilities and seminar programs. Of note also are the CCB links to industry that facilitate the commercialisation of many of its inventions and their development for clinical use.

As I reflect on the future of health care for the State, I cannot fail to appreciate how well SA Pathology and the CCB fit with the recently released McKeon report and its Strategic Review of Health and Medical Research commissioned by our Federal Government. Its motto of ‘Better health through research’ could not better epitomise what we are doing in SA Pathology today. The McKeon Report mirrors our vision and gives us further considered evidence of the benefits to be gained by facilitating and strengthening the excellent work of the CCB.

Ken Barr
Executive Director, SA Pathology
We are delighted to present the third Annual Report of the Centre for Cancer Biology. As in previous years, the CCB continued to achieve significant landmarks in 2012, with the opening of the $8.5 million ACPF Cancer Genomics Facility being one of the highlights. This new facility was inaugurated on October 2 by the Right Honourable Minister John Hill, SA Minister for Health and Ageing, and Mr Tom Dery, Chairman of the Australian Cancer Research Foundation Board of Directors. This unique facility in South Australia is already being used to annotate the DNA of patients’ cancers to enable researchers and physicians to categorize and define cancers more accurately for better and more personalized ways of treating each patient. This is being used by South Australian and CCB investigators in discovery, translational research (eg clinical trials) and standard cancer care.

Research at the CCB continued to encompass basic understanding of why and how cells become malignant, how they spread, what keeps them alive and sometimes makes them resistant to killing by therapeutic drugs, as well as advanced translational and clinical work focused on improving treatments. Given the wide scope of cancer research being performed at the CCB, our scientists made significant advancements in the fundamental understanding of tumorigenesis as well as in personalised treatment of certain cancers.

CCB researchers published 110 scientific articles in the 2012 calendar year. There were many research highlights and we include a small selection here. In a collaborative study published in the Journal of Clinical Investigation, Professor Greg Goodall and colleagues from the MD Anderson Cancer Centre in the US (Dr Don Gibbons and Dr Jonathan Kune) identified several miR-34a target genes required for tumour cell invasion. Their findings provide a strong rationale to develop miR-34a as a therapeutic agent in a distinct group of cancer patients. In a study published in the prestigious Journal of Clinical Oncology, Associate Professor Susan Boyd and her colleagues provided new data on the optimal response to therapy after diagnosis of CML, which has direct implications in the clinical management of this blood cancer. In a publication in Molecular Psychiatry, Dr Quentin Schwarz and Professor Angel Lopez discovered that 14-3-3 proteins, previously shown to be important for regulating blood cell signalling, are central players in schizophrenia. In another high profile paper in the Journal of Clinical Investigation, Dr Michael Samuel, in collaboration with colleagues at the Beatson Institute for Cancer Research in the UK and the Ludwig Maximilians Universität in Germany, showed that the genetic ablation or pharmacological inhibition of the chemokine receptor CXCR2 suppresses tumour growth in several mouse models of skin and intestinal cancer. Their work suggests that targeting of CXCR2 may have therapeutic utility in the treatment of intestinal and skin cancers.

One of the key thrusts of the CCB is to maintain cancer research excellence. This can be measured in high quality publications, as well as in public health outcomes. The research excellence is also evident in the success of CCB scientists in obtaining peer reviewed funding and fellowships from local, national and international sources. We were delighted to see many of our new investigators receiving project grants as well as the more established ones. In the latest round of the highly competitive NHMRC Project Grants, CCB researchers won eight. They also won 31 grants from several other funding bodies. Those who were awarded project grants in the 2012 NHMRC round included Professor Sharad Kumar and Dr Hayley Rasmussen, two grants each; Associate Professor Richard D’Andrea, Associate Professor Stuart Pitson, Professor Andrew Zannettino, and Dr Quenten Schwarz, awarded project grants in the 2012 NHMRC round included Professor Sharad Kumar and Dr Hayley Ramshaw, two grants each; and colleagues from the MD Anderson Cancer Centre in the US (Dr Don Gibbons and Dr Jonathan Kune) identified several miR-34a target genes required for tumour cell invasion. Their findings provide a strong rationale to develop miR-34a as a therapeutic agent in a distinct group of cancer patients. In a study published in the prestigious Journal of Clinical Investigation, Dr Michael Samuel, in collaboration with colleagues at the Beatson Institute for Cancer Research in the UK and the Ludwig Maximilians Universität in Germany, showed that the genetic ablation or pharmacological inhibition of the chemokine receptor CXCR2 suppresses tumour growth in several mouse models of skin and intestinal cancer. Their work suggests that targeting of CXCR2 may have therapeutic utility in the treatment of intestinal and skin cancers.

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In 2012 we welcomed three new members to the CCB Faculty: Professor Michael Brown, Dr Michael Samuel and Associate Professor Andrew Ruszkiewicz. These members greatly enrich both basic and clinical research capabilities of the CCB and we look forward to new productive collaborations as a result of these appointments.

On 14 June 2012, the CCB held its Annual General Meeting. Professor David Vaux, Assistant Director of Walter and Eliza Hall Institute, Melbourne, presented a special guest lecture where he praised the research efforts of the scientists at the CCB and outlined the importance of fundamental and discovery research in the development of new diagnostics and more tailored types of treatment for cancer patients. Professor Vaux presented a number of research excellence awards to the staff and students of the CCB, including the Best Primary Research Publication Award to Dr Chris Hahn; the Best Student Primary Research Publication Award to Ms Tamarra Leckcox, and the CCB Early Career Investigator Award to Dr Sally Martin. The CCB takes special pride in training and mentoring junior scientists and graduate students. As Directors of the CCB, the achievements of our younger scientists always give us great delight.

CCB scientists played a major role in the organization of ComBio 2012, the major annual combined conferences of the Australian Society for Biochemistry and Molecular Biology (ASBMB), the Australia and New Zealand Society for Cell and Development Biology and other scientific societies. Associate Professor Stuart Pitson was the convenor of a highly successful ASBMB meeting, whereas Professors Greg Goodall and Sharad Kumar served as the Program Chair and Deputy Program Chair, respectively. Many other CCB members served as members of the organising committee, thematic or session chairs and speakers.

This report gives us an opportunity to thank our supporters and collaborators including the Australian Cancer Research Foundation, Novartis, the Cooperative Research Centre for Biomarker Translation, CSL Ltd, Therapeutic Innovation Australia, Health Services Charitable Gift Board, eSearch SA, The University of Adelaide and The University of South Australia. Keeping up with the state-of-the-art technological platforms that facilitate our research is a key part of our strategy. To this end, we are grateful for the provision of $900,000 that helped us expand our Imaging Facility with the installation of a 2-photon microscope.

As in previous years, we have had strong support from SA Pathology and this is an opportunity for both of us to thank Mr Kon Barr, Executive Director of SA Pathology and Professor Heddy Zola, Research Director of SA Pathology, for their continued commitment to cancer research and the CCB Faculty. Professor Zola has greatly facilitated the smooth running of the CCB with great attention to detail and ever present good humour. Our thanks also go to the RAH Research Foundation, led by Mr Mark Goldsmith, for their enthusiasm in bringing our scientific successes to the South Australian community and for raising valuable funds for the work of the CCB so that it can continue to pursue its main aim of fighting and defeating cancer.

Professors Sharad Kumar and Angel Lopez Co-Directors, Centre for Cancer Biology
A major research focus of the group is the identification and characterisation of genes involved in the myeloid lineage and in myeloid disease including Acute Myeloid Leukaemia (AML) and the Myeloproliferative Neoplasms (MPN).

Utilising myeloid cell line models, we have described a novel role for TCPO1 in specifying macrophage lineage differentiation. Making use of a large cohort of AML patient samples, we have also recently published studies showing the prognostic impact in AML of KLF7 promoter methylation, and silencing of the GADD45A tumour suppressor by promoter methylation. To investigate further the role of KLF7, we are currently characterising a conditional haematopoietic-specific knockout model of KLF7.

Our interest in the molecular genetics of MPN has led us to identify somatic mutations in the JAK2 gene transformation of myeloid cells. In collaboration with other groups, we have investigated the occurrence of JAK2V617F mutations in Chronic Myeloid Leukaemia (CML) and reported the cooperation of Ex17 with AP-1 transcription factors in solid tumours.

We also focus on the mechanisms of cytokine receptor signalling and the role of aberrant signalling in leukaemia. Specifically, we have reported the frequency and prognostic significance of the FLT3-ITD mutation in the core binding factor (CBF) AMLs. In collaboration with other groups, we have described the use of novel systems to dissect signalling pathways associated with GM-CSF and IL3 receptors. In addition, we are exploring the link between IL-3 signalling and β-catenin activity in AML associated with HOX gene over-expression or MLL gene translocations.

We have explored novel treatments for AML and the Philadelphia chromosome negative MPN. For both groups of diseases, we have identified novel pathways that may have potential to induce changes in mitochondrial activity and we are investigating this activity further in xenograft AML models. We have also identified somatic mutations in the EGFR gene in MPN patients suggesting a potential important role for aberrant EGFR signalling in MPN.

We have shown that DECA activity in this subtype is associated with its ability to induce changes in mitochondrial activity and we are investigating this activity further in xenograft AML models. We have also identified somatic mutations in the EGFR gene in MPN patients suggesting a potential important role for aberrant EGFR signalling in MPN.

Prognostic Significance and Role for GADD45A in AML
To test the clinical significance of GADD45A promoter hypermethylation in an AML patient cohort (167 AML patients) we measured DNA methylation at 4 CpG residues previously shown to be methylated in numerous cancers. This showed that GADD45A promoter methylation is predictive of poor survival overall in AML, and particularly in normal karyotype AML. This is the first study to link GADD45A promoter methylation to patient outcome in cancer (Leukemia doi: 10.1038/leu.2012.340 2012). Our analysis also revealed a positive correlation between GADD45A promoter methylation status and the presence of JH1/JH2 and DNMT3A mutations suggesting this mark may be detecting a broader epigenetic phenotype. We also showed that GADD45A promoter methylation segregated outcome in the important intermediate-risk group of patients that are negative for FLT3-ITD, but positive for NPM1 mutations; a group of patients in which it is difficult to determine prognosis and therefore treatment options.

Role of IL-3 mediated β-catenin activation in HOX gene mediated myeloid transformation and AML
β-catenin has previously been shown to be stabilised in AML, however the molecular mechanisms that underlie the β-catenin activity in AML remain poorly understood. We have investigated the link between IL-3 signalling and β-catenin expression/stabilisation in AML. We have now shown that IL-3 signalling induces dose-dependent β-catenin accumulation and activation in murine and human myeloid cell lines. In a murine model of HOX transformation (FDM cells) we have used Cre-mediated deletion of β-catenin to demonstrate a requirement for β-catenin accumulation and activation in murine and human myeloid cell lines. In a murine model of HOX transformation (FDM cells) we have used Cre-mediated deletion of β-catenin to demonstrate a requirement for β-catenin accumulation and activation in murine and human myeloid cell lines. In a murine model of HOX transformation (FDM cells) we have used Cre-mediated deletion of β-catenin to demonstrate a requirement for β-catenin accumulation and activation in murine and human myeloid cell lines.

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

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

An ongoing interest of the Cell Signalling Laboratory is the interactions of the cancer cell with its microenvironment. Cells secrete factors that can act upon themselves or on other cells for normal maintenance or homeostasis. Cancer cells, through mutations, can have an altered composition of secreted factors which can act to alter their immediate microenvironment, turning it from one that supports metastasis and resistance to chemotherapy to one that suppresses cancer progression.

In addition to our interest in breast cancer, the Cell Signalling Laboratory (in collaboration with Professor Greg Goodall, Dr Susanna Proudman and Dr Pravin Hissaria) has also 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 establishing or progression of scleroderma.

Key discoveries 2012

Identification of novel functions of Pez

Mutations to Pez have been identified in various cancers including breast and colorectal cancers, but limited knowledge of its substrates or biological functions has hampered studies to identify how Pez mutations affect cancer progression. We have identified novel functions of Pez that indicate how dysregulation of Pez could affect cancer progression and novel substrates for Pez that could help us understand the normal physiological functions of this protein. Importantly, these findings could be a key to understanding how mutations in this protein that have been identified in cancers may facilitate metastasis or oncogenesis.

Identification of differentially expressed microRNAs

Using scleroderma patient samples, we have identified microRNAs that are differentially expressed between normals and scleroderma patients and between patients with limited and diffuse disease. Consistent with current notions that limited and diffuse forms of scleroderma have different aetiologies, our data suggest that the two different forms of scleroderma have arisen through different mechanisms. Exploring the mechanisms by which the changes in microRNA expression patterns are regulated, we have found correlations between expression of certain microRNAs with pro-inflammatory cytokines that are elevated in scleroderma patients.

Outcomes for the Community

Solid tumours make up the majority of human cancers whereby the progression to metastasis is the main cause of morbidity and mortality in these patients. Currently, there is little effective treatment for metastatic disease. 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.
Abnormalities such as extended cell viability or survival, and enhanced cell proliferation are hallmarks of cancer. Understanding the molecular basis of cytokine receptor signalling in health and disease is vital for the design of new forms of therapy for leukaemia and some chronic and debilitating inflammatory conditions such as asthma and rheumatoid arthritis.

Cytokines or growth factors regulate the function of cells in the body by binding to specific receptors on the cell surface. This initial binding triggers cytokine receptor activation which in turn generates multiple biochemical events that signal the cell how to divide, where to migrate, what to secrete, etc. Our laboratory focuses on a particular set of cytokines named βc cytokines because their receptors share the major signalling subunit called βc. These include GM-CSF, IL-3 and IL-5, cytokines that by and large regulate the function of many blood cells and as such are important in normal blood formation, malignant haemopoiesis (leukaemia) as well as diseases such as rheumatoid arthritis, multiple sclerosis, asthma and autoimmune diseases.

Cytokine receptors are the conduit between the extracellular milieu and the cell’s internal machinery that allows cells to respond in a variety of ways such as maintenance of viability or proliferation.

To understand how the βc cytokines signals, we are studying receptor proximal events, namely how the receptor complex assembles on the cell surface to initiate downstream signalling. In collaboration with Professor Michael Parker and his team (St Vincent’s Institute of Medical Research), we are establishing how GM-CSF and IL-3 interact with their receptors to form a binary complex and how this interaction then dictates how higher order complexes are assembled that initiate signalling.

Defining the key molecular interactions is important to design specific forms of therapeutics. In collaboration with Professor Paul Ekert and his team, we are studying the signalling mechanisms activated following receptor assembly.

A second approach is to understand why some cytokine receptors such as the IL-3 receptor is upregulated in some leukaemias. In collaboration with Professor Richard D’Andrea and Professor Hamish Scott (Centre for Cancer Biology), we are defining the consequences of increased IL-3 receptor expression in terms of genetic programs and the biological advantages that leukaemia cells gain from this. In collaboration with Professor Greg Goodall and Dr Cameron Bracken (Centre for Cancer Biology), we are studying the mechanisms at the microRNA level that control IL-3 receptor expression.

As blood cells are also involved in diseases such as asthma, we are characterizing their role in this disease. In collaboration with Associate Professor Michelle Gilmartin (Grimwade Centre for Cancer Biology) and with CSL Ltd, we are examining how βc cytokines stimulate mast cells and how this stimulation may be tamed. As mast cells are important not only in asthma but in many other inflammatory conditions and in some solid cancers, it may be possible to regulate their function to better control disease.

Interestingly, the actions of βc cytokines do not seem to be restricted to blood cells. In collaboration with Dr Quentin Schwarz (Centre for Cancer Biology), we have found an unexpected role in neuronal development and function, and in collaboration with Dr Claudine Boarder (Centre for Cancer Biology), a possible pathogenic role in breast cancer.

As we learn more about βc cytokines and how their receptors work, opportunities arise to apply this knowledge. A few years ago, we generated a monoclonal antibody that blocks the IL-3 receptor, rapidly being appreciated as a marker of acute myeloid leukaemia stem cells. CSL Ltd has now improved this antibody (CISL362) so that it can kill these stem cells better, a result that has led to clinical trials currently being carried out in Australia and the US to examine the therapeutic potential of CISL362.

In collaboration with Professor Timothy Hughes and Associate Professor Deborah White teams (Centre for Cancer Biology), we are also examining this antibody for its usefulness in chronic myeloid leukaemia.
The emergence of 'serrated' polyps as a class of precursor lesion of CRC presents a major challenge for the early detection and management of colorectal cancer and its precursors. This alternate, so-called 'serrated pathway', of CRC presents added complexity in our attempts to understand disease progression, in particular the transition from premalignant to malignant disease. The serrated polyps are notoriously difficult to visualize endoscopically and may not be detected on routine colonoscopic examination. There is growing evidence that failure to identify serrated polyps during colonoscopy may explain the occurrence of 'interval' colon cancers in patients with previous 'negative' colonoscopic examinations.

Additionally, the serrated polyps with malignant potential often have overlapping morphological features with benign hyperplastic polyps making their recognition in routine histological examination difficult. We are using -omics technologies to detect and characterise the underlying molecular alterations in order to understand the biology of early precursor lesions and the potential factors that influence the rate of progression of these lesions to carcinoma.

Our research requires high quality biological samples from patients with colorectal cancer and clinical data. The Gastroenterology Research Laboratory is responsible for establishing and managing the Colorectal Cancer Tissue Bank which holds samples of colorectal cancers and other gastrointestinal tumours, colorectal polyps and normal tissues, matching blood and clinical data from patients treated in various hospitals in Adelaide. This material is used for research projects conducted by us and other researchers at the Centre for Cancer Biology.

Most colorectal cancers (CRCs) arise from conventional adenomas, however up to 30% of cancers may develop from 'serrated' polyps which until recently were regarded as innocuous lesions without malignant potential.

Key discoveries 2012

We have previously demonstrated over-expression of Cathepsin E and Trefoil Factor 1 in sessile serrated adenomas but not in conventional adenomas of the colorectum which is indicative of molecular differences between these types of colorectal polyps. Our recent gene expression data has shown that a unique molecular profile exists which distinguishes hyperplastic polyps and sessile serrated adenomas at the molecular level. Our gene expression profiling of hyperplastic polyps and sessile serrated adenomas revealed a strong correlation between Claudin1 (CLDN1) expression and BRAF V600E mutation status in a subset of serrated colorectal polyps. Results of our study identify CLDN1 as a potential biomarker of the serrated pathway.

Outcomes for the Community

Our work towards better characterisation of precursor lesions of colorectal cancer results in better understanding of the biology behind serrated polyps and subsequently will enhance early detection, pathological diagnosis and treatment strategies for colorectal cancer.
The majority of solid cancers, including most lung, breast, colon, prostate and liver cancers, arise from epithelial cells. Most deaths from these cancers are due to metastasis, which involves the transition of the cancer to an invasive form.

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

EMT is driven by coordinated changes in the expression of hundreds of structural and regulatory proteins. These changes are determined by integrated gene expression networks that themselves involve numerous components. We have identified microRNAs that play a central role in controlling and coordinating the regulatory networks that underlie EMT in cancer cells.

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

**Key discoveries 2012**

**ZEB1 induces widespread changes in the miRNA transcriptome and controls biological processes other than EMT and stem-ness through repression of miR-34a**

Metastatic cancer is extremely difficult to treat, and the presence of metastases greatly reduces a cancer patient’s likelihood of long-term survival. The ZEB1 transcriptional repressor promotes metastasis through downregulation of miRNAs that are strong inducers of epithelial differentiation and inhibitors of stem cell factors. In collaboration with Don Gibbons and Jonathan Kurie at the MD Anderson Cancer Center, we have investigated additional roles of ZEB1 in metastasis using a mouse model of human lung adenocarcinoma metastasis driven by ZEB1, human lung carcinoma cells, and human breast carcinoma cells. Transcriptional profiling studies revealed that ZEB1 controls the expression of numerous oncogenic and tumour-suppressive miRs, including miR-34a. Ectopic expression of miR-34a decreased tumour cell invasion but is restored at metastatic sites. In contrast, adenomas and adenocarcinomas with strong expression of miR-200, suggesting this family of miRNAs is involved in the recapitulation of the primary tumour phenotype at metastatic sites. In addition, laser capture microdissection and quantitative real-time polymerase chain reaction (qPCR) were employed to quantify levels of miR-200 in the normal epithelium, tumour core, invasive front, and stroma. We found that miR-200 is down-regulated at the invasive front of colorectal cancers with degraded basement membrane and indicates EMT is involved in cancer progression.

**Down-regulation of the miRNA-200 family at the invasive front of colorectal cancers with degraded basement membrane indicates EMT is involved in cancer progression.**

Cancer progression is a complex series of events thought to incorporate the reversible developmental process of epithelial-to-mesenchymal transition (EMT). In vitro, the miR-200 family maintains the epithelial phenotype by post-transcriptionally inhibiting the E-cadherin repressors, ZEB1 and ZEB2. We have used in situ hybridization and immunohistochemistry to assess expression of miR-200 and EMT biomarkers in formalin-fixed paraffin-embedded human colorectal adenocarcinomas. In addition, laser capture microdissection and quantitative real-time polymerase chain reaction (qPCR) were employed to quantify levels of miR-200 in the normal epithelium, tumour core, invasive front, and stroma. We found that miR-200 is down-regulated at the invasive front of colorectal adenocarcinomas that have destroyed and invaded beyond the basement membrane. However, regional lymph node metastases and vascular carcinoma deposits show strong expression of miR-200, suggesting this family of miRNAs is involved in the recapitulation of the primary tumour phenotype at metastatic sites. In contrast, adenomas and adenocarcinomas with intact basement membranes showed uniform miR-200 expression from the tumour core to the tumour-host interface. Taken together, these data support the involvement of EMT and metastasis in the metastatic cascade and show that miR-200 is down-regulated at the initial stages of stromal invasion but is restored at metastatic sites (Neoplasia, accepted 17 Dec 2012).

**Outcomes for the Community**

Our work is identifying new molecules and pathways that drive metastasis, the primary cause of death of cancer sufferers. These discoveries open up new avenues for potential therapeutic exploitation and for development of new diagnostics.
The Clinical Research Unit encompasses a number of research groups in the Royal Adelaide Hospital Department of Haematology, including both cancer and non-cancer related research. The Haemostasis Program studies the laboratory as well as the clinical aspects of bleeding and clotting problems, ranging from diagnostic and monitoring to treatment.

A major new initiative is the South Australian Cancer Research Biobank which was funded by the Beat Cancer Project as well as MedVet Science Pty Ltd. The setting up of a tumour bank to facilitate researchers in SA is a major and far-reaching project. The external funding allows the expansion of the RAH Blood Disease Tumour Bank first set up in the 1980s to cover collection from all major public teaching hospitals in SA. The original bank has already been a significant enabler of research leading to multiple publications. We expect that the new bank will have double the collection rate and will therefore be even more important for discovery research in South Australia.

The investigators in the Clinical Research Unit are also active collaborators with other researchers in the Centre, particularly in the conduct of translational research projects in leukaemias and myeloma.

Through a coordinated research programme, the Haematology Clinical Research Unit has a strong commitment to improving the treatment of patients with blood diseases.

Outcomes for the Community

The clinical research unit has a core focus of improving the treatment of patients with malignant and non-malignant diseases of the blood. This is achieved by a core interest in fundamental research, involvement in clinical trials utilising novel agents and provision of infrastructure to allow these activities to expand. 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.

Key discoveries 2012

Haemostasis Program Report
The Haemostasis Program comprises applied clinical and diagnostic projects. Our broad theme is to introduce new, or improve current, haemostasis tests with the aim of developing better tools to diagnose and manage patients with bleeding or clotting disorders. Currently, the projects include:

- Study of Protein S deficiency (inherited or acquired) as a cause of thrombosis, and its impact on thrombin generation (TGT) in the presence and absence of thrombomodulin. This work has included experiments to assess the impact of various pre-analytical variables on the TGT, a neglected area in the development of this potential diagnostic test.
- Investigation of the coagulation factors that may contribute to thrombosis in patients with myeloma, especially during chemotherapy. Our aim is to determine parameters that predict which patients are more likely to develop thrombosis so that anticoagulants can be prescribed before the thrombosis occurs. Samples have also been collected from patients with MDS (monoclonal gammopathy of unknown significance), a precursor to myeloma, as a patient control group. A future project to study polycythemia vera using a similar approach is also planned.
- The study of methods to diagnose Factor XIII deficiency. This project has identified a novel cause of false positive results in commonly used screening tests and will recommend a change in practice for all laboratories that screen for and manage this rare disorder.
- The study of tests to assess the effect of new oral anticoagulant drugs on the coagulation pathway, and to monitor the effect of reversal agents. This includes introduction of diagnostic tests to measure drug levels and research to investigate their impact on thrombin generation. This work will help those patients with excessive bleeding as a drug side effect, or those requiring emergency surgery.
- The study of pharmacokinetics of Factor VIII treatment products in haemophilia, in order to ascertain half-life and plan for required therapy during and after surgery. This project has the potential to save unnecessary use of expensive products by tailoring dosages to half-life, and also to ensure sufficient dose is given to those patients needing a higher dose.
- The study of pharmacokinetics of new oral anticoagulant drugs in haemophilia. This project aims to improve patient care by providing a comprehensive understanding of drug metabolism and half-life, and to monitor the effect of reversal agents.

The study of thrombin generation in mild haemophilia A, to better understand the different bleeding phenotypes of this disorder and to relate this to genotype. This project is in early completion and shows interesting differences between sub-groups. This may allow better prediction of treatment needs.
Hepatitis C 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.

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

Recent development of direct acting antiviral (DAAs) compounds show great promise in the treatment of hepatitis C, however these are often expensive, have significant side effects and are not available to all infected with HCV. Thus new therapies and a greater understanding of the pathogenesis of hepatitis C are required.

HCV replication in living cells is a complex process that depends on an intact microtubule network. We have demonstrated that NS5A-positive cytoplasmic viral replication complexes (RCs) are highly motile and associated with the microtubule network. We have further shown that STAT3, a transcription factor that controls the expression of genes involved in the host response to infection, is actively phosphorylated in the presence of replicating HCV. Expression of a constitutively active STAT3 leads to significant decreases in HCV RNA levels. We have established that STAT3 is actively phosphorylated in the presence of replicating HCV. Expression of a constitutively active form of STAT3 leads to marked increases in HCV RNA levels, whereas conversely, chemical inhibition and siRNA knockdown of STAT3 leads to significant decreases in HCV RNA levels. As a transcription factor, up-regulation of a distinct set of STAT3 dependent genes may create an environment that is favourable for HCV. However, we have recently shown that STAT3 may exert its antiviral effect through a direct interaction with the HCV NS5A protein and the pro viral host factor VAP-A to disrupt HCV replication within the HCV replication complex. Interestingly, viperin also limits replication of the closely related flavivirus, Dengue. In this instance, viperin interacts with the dengue NS3 protein that is also a key component of the dengue virus replication complex. Furthermore, in collaboration with the Westmead Millennium Institute, Sydney we have also shown that viperin inhibits the replication of HIV (Blood 120:778-88, 2012). Thus, viperin has antiviral activity against a number of important viruses and our work adds to the understanding of how we respond to control viral infections.

Dynamic imaging of the HCV life cycle
Using a combination of fluorescent labeling approaches (tetrasaccharide tags, fluorescent proteins and SNAP tags) we have developed techniques to image the localization and dynamics of the HCV proteins, NS5A and core, HCV RNA and relevant host cell factors in living virus producing cells. Specifically, we are interested in the role of NS5A in the biogenesis and function of HCV replication complexes (RCs) that harbour active replication of HCV RNA and how these structures associate with core-coated cytoplasmic lipid droplets, the sites of infectious virus particle assembly. We have demonstrated that NS5A-positive cytoplasmic structures (putative RCs) traffic throughout the cytoplasm in a process that depends on an intact microtubule network and, at least in part, on the dynamin motor protein complex.

Outcomes for the Community
Chronic hepatitis C often results in serious liver disease including the development of liver cancer and places a significant burden on our health system. Our work investigating the host response to infection with HCV has significant implications in that a greater understanding of how the liver combats HCV infection is essential for the development and implementation of new therapeutic strategies. Furthermore, our work with the new HCV DAAAs will inform therapeutic strategy in particular with HCV genotype 6 that predominates in Asia.

Key discoveries 2012
Host control of viral replication
Viral infection of cells results in a host response that attempts to limit viral replication through the induction of specific antiviral proteins. However, the complete spectrum of these antiviral proteins has not been characterized. Our laboratory specifically focuses on the host interferon stimulated gene, viperin and its role in limiting a number of medically important viruses. We have shown that viperin exerts its antiviral effect through a direct interaction with the HCV NS5A protein and the pro viral host factor VAP-A to disrupt HCV replication within the HCV replication complex. Interestingly, viperin also limits replication of the closely related flavivirus, Dengue. In this instance, viperin interacts with the dengue NS3 protein that is also a key component of the dengue virus replication complex. Furthermore, in collaboration with the Westmead Millennium Institute, Sydney we have also shown that viperin inhibits the replication of HIV (Blood 120:778-88, 2012). Thus, viperin has antiviral activity against a number of important viruses and our work adds to the understanding of how we respond to control viral infections.

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Dynamic imaging of the HCV life cycle
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Outcomes for the Community
Chronic hepatitis C often results in serious liver disease including the development of liver cancer and places a significant burden on our health system. Our work investigating the host response to infection with HCV has significant implications in that a greater understanding of how the liver combats HCV infection is essential for the development and implementation of new therapeutic strategies. Furthermore, our work with the new HCV DAAAs will inform therapeutic strategy in particular with HCV genotype 6 that predominates in Asia.
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. With the introduction of targeted tyrosine kinase inhibitors (TKI), CML has been transformed from a disease with median survival of five years to one compatible with normal life expectancy if patients comply with daily oral medication for life. This is a first in other chronic illnesses. It was the first human disease to be therapeutically targeted.

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), aiming at identifying new molecular targets for the treatment of these diseases.

CML affects all age groups with a median age of onset in the mid-50s. It is not unreasonable to assume that the average life span of these patients after diagnosis is now 30 years. With estimated TKI costs of AUD 30,000–50,000 per annum per patient, each successive year adds at least AUD 900 million in projected costs. Unfortunately, despite the impressive successes of TKIs for CML, a significant proportion of patients do not achieve optimal response, and many more relapse under this form of treatment. The reasons for this are still largely unknown. It is vital therefore to devise a treatment strategy which allows complete eradication of the leukaemic clone, leading ultimately to total cessation of treatment. This can only be achieved through 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. It’s still early days in this investigation, when we are looking broadly at large regions of the genome, before narrowing down to specific parts where we hope to find a cure. Specific questions that are currently being addressed are:

- What comes ‘before’ the BCR-ABL fusion gene: Genetic ‘lesions’ preceding CML?
- What regulates BCR-ABL: how BCR-ABL gene expression is controlled.
- What is regulated by Bcr-Abl: downstream genes/proteins essential for the leukaemic (chronic phase) phenotype.
- What adds to/replaces Bcr-Abl signalling to result in disease progression: mechanisms of blast transformation.
- What determines the difference in disease progression rates and response to treatment: establishment of prognostic and predictive gene expression signatures.
- What determines CML stem cell quiescence and possibilities to reverse it: identification of genes differentially expressed (in comparison with normal stem cells) which can be therapeutically targeted.

Key discoveries 2012

We have dissected the pathway of regulation of the Bach2 gene, which is repressed by BCR-ABL. This repression prevents Bach2 from making sure leukaemic cells with additional genetic abnormalities and, thus, more malignant, are induced to undergo apoptosis (i.e., these cells remain alive, and give rise to an acute transformation of CML). Our work showed that BCR-ABL utilises the Pax5 transcription factor in this regulation, a protein previously linked to other types of leukaemia. Such ‘mapping’ of the network of interactions between proteins in the leukaemic cell helps to pave the way to new forms of therapy. This was published by Debora Casolari and co-workers from the LBG and Imperial College London (Leukemia doi: 10.1038/leu.2012.220, Epub Aug 4 2012).

The cancer stem cell (CSC) concept has important therapeutic implications, but its investigation has been hampered both by a lack of consistency in the terms used for these cells and by how they are defined. Together with a panel of experts in CSC biology, we reviewed several issues related to their phenotype and functional properties, and proposed a conceptual and practical framework for CSC terminology (Nature Reviews in Cancer 12: 767-775, 2012). More precise reporting of the parameters that are used to identify CSCs, and to attribute responses to them was recommended as key to accelerating an understanding of their biology and developing more effective methods for their eradication in patients.

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 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.
Tyrosine kinase inhibitor therapy has remarkably changed the course of disease for patients with chronic myeloid leukaemia (CML) and most achieve long-term remission. However, responses to inhibitor drugs are highly heterogeneous in terms of the rate of clearance of leukaemic cells after the initiation of therapy and some patients develop drug resistance.

The initial molecular response to therapy can indicate the long-term outcome for patients. Studies have demonstrated that the rate of reduction of leukaemia in response to tyrosine kinase inhibitors can determine whether patients will achieve an optimal response to therapy after diagnosis of CML. For patients who develop drug resistance, some of them can be treated with more powerful tyrosine kinase inhibitor drugs. However, only about 50% of the patients respond and identifying which patients were going to respond was not possible for most patients. We examined the initial molecular response for patients who had failed their first therapy and were treated with another drug. Those patients who achieved the most rapid reductions in the first 3 months of therapy had a very good long-term treatment response (J Clin Oncology 30: 4323-29, 2012), whereas those who only had a minor reduction were highly likely to fail therapy. This information has meant that clinicians now examine the initial molecular response to therapy as a guide to the potential outcome for their patient. Those with a rapid reduction can be reassured that their response may be very good. Other patients may benefit from an early change of therapy.

The dynamics of a BCR-ABL1 rise after a response to therapy may help to identify a patient who has stopped taking their medication. A rise in BCR-ABL1 is the molecular marker for potential loss of response. However, we have determined that it can also occur when a patient stops taking their drug. We have found very rapid increases in BCR-ABL1 levels when a patient completely stops response to kinase inhibitor therapy and progresses to the terminal, acute leukaemia phase of the disease, which is also known as blast crisis. We have characterised the rise as the number of days over which the BCR-ABL1 level doubles; the doubling time. With progression to blast crisis, the doubling time is very short and is on average nine days. For patients who relapse but do not have sudden blast crisis, the doubling-time is much longer and is on average 48 days. For these patients there is time to consider therapeutic options for rescue since their relapse is slow. Surprisingly we found that patients who stopped taking their therapy for any reason also had a very rapid rise that was as rapid as the patients who progressed to blast crisis, however, these patients did not develop an acute leukaemia and were responsive when therapy was recommenced (Blood 119: 4264-71, 2012). Some patients stop taking their drug without telling their doctor, but in the long run it can lead to a poor response and possible shortening of life. Our molecular test and assessment of BCR-ABL1 doubling times now provides an indication to clinicians that their patient may have stopped taking their drug. In the absence of blast crisis a fast doubling-time may identify a non-adherent patient.

Key discoveries 2012

Some patients have many BCR-ABL1 mutations below the level of detection by standard techniques and these can cause poor response to therapy.

Using a sensitive mutation analysis technique we searched for mutations within the BCR-ABL1 gene we could not detect using the conventional technique of the laboratory. Surprisingly, we detected many mutations in some patients (up to ten mutations). The most we had detected by standard techniques was four mutations. Most patients only have one mutation, which is sufficient to cause resistance. Usually a change of therapy can overcome the resistance caused by mutations since most are sensitive to more potent tyrosine kinase inhibitors. However, we discovered that patients who had many low level mutations had a very high risk of failing to respond to more potent inhibitors (Blood 119: 2034-38, 2012). This was even though all of their mutations were predicted to be sensitive to the more powerful drugs. This was important information for clinicians to help with their decisions regarding the best therapy for their patients.

Our laboratory investigates the molecular response to therapy by an examination of the BCR-ABL1 oncogene. This abnormal gene causes the leukaemia and can be effectively targeted by drugs that inhibit BCR-ABL1. We investigate factors associated with clinical response and resistance to the targeted therapy. Failure to achieve certain reductions of leukaemia at specific time-points predicts suboptimal response or treatment failure.

Our research has benefited patients by providing guidance for clinicians when determining the most appropriate therapy after drug resistance. We regularly test patients using a sensitive technique to enable us to identify resistance causing mutations, which would otherwise go undetected. This avoids costly and time consuming trials of inappropriate kinase inhibitor drugs. We have also demonstrated the importance of the initial rapid reduction of leukaemia in the first months of therapy and established criteria for determining whether a patient is non-adherent to therapy. It is important that a clinician is alerted to non-adherence since this can lead to long-term suboptimal response for their patient.
Lymphatic Development Laboratory
Associate Professor Natasha Harvey PhD

The cardiovascular system, comprised of the heart, blood vessels and lymphatic vessels, is the first organ network to develop in the vertebrate embryo. While blood vessels are essential for the delivery of oxygen and nutrients to the tissues, lymphatic vessels are crucial for returning tissue fluid and protein to the bloodstream. Lymphatic vessels also play key roles in directing immune cell trafficking throughout the body and absorbing dietary fats from the digestive tract. The growth and development of lymphatic vessels (lymphangiogenesis) “goes wrong” in a large catalogue of human disorders; insufficient or abnormal lymphangiogenesis manifests in conditions including lymphoedema and vascular malformations, while excessive lymphangiogenesis is associated with inflammatory diseases and cancer.

The major goal of research in the Lymphatic Development Laboratory is to identify and characterise signals important for the construction, maturation and function of lymphatic vessels, with the aim that they may prove to be targets for the generation of novel therapeutics able to promote, or inhibit 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.

Key discoveries 2012

The growth factors FGF2 and VEGF-C play distinct roles in lymphangiogenesis

Primary mouse endothelial cells have traditionally proven difficult to culture and as a consequence, few assays have been developed to dissect gene function and signal transduction pathways in these cells ex vivo. Having established methodology for the purification, short-term culture and transfection of primary blood (BEC) and lymphatic (LEC) vascular endothelial cells isolated from embryonic mouse skin, we optimised robust assays able to measure primary embryonic LEC proliferation, migration and three-dimensional tube forming ability in vitro. We then used these assays to dissect the roles of established pro-lymphangiogenic growth factors FGF2 and VEGF-C in cellular processes important for lymphatic vessel development. Our work demonstrated that FGF2 promotes LEC proliferation directly via FGF receptors and independently of VEGF receptors in primary embryonic LEC. Further investigation revealed that FGF receptor 1 (FGFR1) was by far the predominant FGF receptor expressed by primary embryonic LEC and was important for FGF2 mediated LEC proliferation. While FGF2 potently promoted LEC proliferation and migration, three dimensional tube formation assays revealed that VEGF-C primarily promoted LEC sprouting and elongation, illustrating that FGF2 and VEGF-C play distinct, cooperative roles in lymphatic vascular morphogenesis. These assays provide useful tools able to dissect gene function in cellular events important for lymphangiogenesis and implicate FGFR1 as a key player in developmental lymphangiogenesis in vivo. PLoS One 7(7):e40497, 2012.

Defining signals important for lymphatic vessel growth and remodelling in the mouse mammary gland

Despite the key roles of lymphatic vessels in breast cancer metastasis, little is known regarding the cellular sources of signals that drive lymphatic vascular growth and patterning in this tissue. By employing high resolution, three-dimensional imaging technology, we revealed that lymphatic vessels in the postnatal mouse mammary gland share an intimate spatial association with epithelial ducts and large blood vessels. Moreover, we demonstrated that the lymphatic vasculature is dynamically remodelled during mammary gland morphogenesis; growth of the lymphatic vessel network accompanied expansion of the mammary epithelial tree during pregnancy and was followed by regression during involution. Our work found that epithelial cells, in particular myoepithelial cells, are a rich source of growth factors including VEGF-C and VEGF-D that promote lymphatic vessel growth and development and that levels of these growth factors in the mammary gland peaked preceding a burst in lymphatic vessel growth during pregnancy. Our work sheds new light on the location of lymphatic vessels in the mouse mammary gland and the cellular sources of growth factors responsible for patterning the lymphatic vasculature during development. In addition, our work suggests a new explanation for the propensity of metastatic breast tumour cells to gain access to the lymphatic vasculature (Am J Pathol 181: 2225-38, 2012).

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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 often results in secondary lymphoedema, a major problem for many cancer patients. There are currently no effective, curative treatments for lymphoedema. By understanding the signals that control the growth and development of lymphatic vessels, we hope to design new therapeutics that either block, or promote 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 cells are unique immunocytes that normally reside in tissues, particularly those that are exposed to the external environment such as the skin, gut and lung.

Historically, they are depicted as major effector cells of asthma and other IgE-associated allergic disorders and immune responses to parasites. However, in addition to their ability to initiate and amplify inflammation, mast cells can also regulate such responses to protect against pathological effects of excessive inflammation and aid the processes of restoring tissue homeostasis.

Research being undertaken by the Mast Cell Laboratory focuses on the novel regulatory abilities of mast cells, with an emphasis on how this dynamic cell contributes to the regulation of inflammation associated with allergy and skin cancer development. In a recent paper (J Exp Med 2010), we identified the molecular basis for the protective effects of mast cells in this setting, their ability to produce the anti-inflammatory cytokine, IL-10, in response to vitamin D3.

For over 80 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, a component of sunlight. The findings from this study provided the first in vivo evidence of a regulatory axis between vitamin D3 and mast cells.

In collaboration with Dr Michael Samuel (Centre for Cancer Biology) and Professor Gunnar Pejler (Uppsala, Sweden), we are investigating the important question of whether mast cells can also regulate such inflammatory processes. In 2012, CSL Ltd and our laboratory, together with Professor Angel Lopez (Centre for Cancer Biology), set up a collaboration to develop therapeutics that specifically target the overactivity of mast cells without causing loss of their viability. Already, we have identified a number of molecules with such efficacy in vitro and we are now investigating them for their therapeutic potential using humanised mouse models of nasal polyp growth.

Key discoveries 2012

Vitamin D3 suppresses IgE-mediated mast cell activation

Mast cells have long been recognized as active participants of the allergic response at specific sites. Whether in the skin or the lung, the binding and cross-linking of IgE on the surface of mast cells stimulates the release of inflammatory mediators that exacerbate the allergic response. Our new findings demonstrate that the pro-inflammatory properties of certain IgE-dependent immune settings can be reduced upon vitamin D3 administration. Utilizing the powerful tool of mast cell-deficient c-kit mutant mice, that can be successfully repleted of their mast cell deficiency by selective engraftment of bone marrow-derived cultured mast cells, we observed that topical cutaneous application of vitamin D3 significantly curtails ear swelling responses associated with IgE-mediated passive cutaneous anaphylaxis. Notably, this effect required the presence of dermal mast cells and their expression of vitamin D receptors.

Outcomes for the Community

Our research extends from basic discovery in mouse models through to drug development for clinical settings. The emergence of the notion that mast cells also possess ‘anti-inflammatory’ potential and that they exhibit a level of ‘plasticity’ in response to the signals they receive from the tissue in which they reside, points to the possibility that ‘harnessing’ mast cell functions will be clinically beneficial.

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

At the molecular level we have identified that at certain stages of UVB-induced neoplastic progression, mast cells protect against detrimental inflammation and tissue changes by secreting IL-10 and the chymotrypsin-like protease, mast cell protease 4.

Another important aspect of our studies is to identify agents that can harness the negative regulatory ability of mast cells and thereby alter their activation state from a nefarious pro-inflammatory one to that of a beneficial anti-inflammatory one. In 2012, CSL Ltd and our laboratory, together with Professor Gunnar Pejler (Uppsala, Sweden), are investigating the molecular basis for the protective effects of mast cells in this setting, their ability to produce the anti-inflammatory cytokine, IL-10, in response to vitamin D3.

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Chronic myeloid leukemia (CML) is characterised by the Philadelphia chromosome which results from a reciprocal translocation between the long arms of chromosome 9 and 22.

This translocation results in a fusion of the BCR and ABL-1 genes, and this gene fusion encodes a constitutively active tyrosine kinase Bcr-Abl which results in excess proliferation and reduced death of white blood cells. If left untreated, the disease progresses from the chronic phase (CP) into blast crisis, which resembles an acute leukaemia and is invariably fatal. The development of first and second generation tyrosine kinase inhibitors (TKIs; imatinib, nilotinib and dasatinib) has revolutionised targeted therapy and markedly improved treatment outcomes for CP-CML patients. However, there are a group of patients who respond poorly, and intolerances, development of TKI resistance and progression to blast crisis remain of major concern. Even in patients who show good clinical responses to first line drugs, the disease is rarely fully eradicated, thus patients currently expect to be on TKI therapy for life.

In order to identify patients who will respond poorly to imatinib, we have developed assays to measure a patient’s sensitivity to the drug (K50 assay) and to measure the activity of the organic cation transporter 1 (OCT-1), which is responsible for active influx of imatinib into cells. We have previously shown that patients with very low OCT-1 activity are at greatest risk of suboptimal response to imatinib. We are currently exploring different biomarkers, at the gene expression, epigenetic regulation and protein level, to aid the easy identification of those poor responders prior to therapy to enable their treatment to be individualised to ensure the best outcome is achieved.

Nilotinib, dasatinib and the third generation TKI ponatinib, which is effective against the T315I BCR-ABL kinase domain mutation that confers resistance to first and second generation TKIs, are studied in our laboratory. In particular, we investigate the differences in cellular transport and efficacy compared to imatinib. These studies led, for example, to the discovery of a novel nilotinib efflux transporter. Another focus of our lab is to recapitulate TKI resistance development in in vitro models and to thereby identify critical resistance mechanisms, such as the emergence of BCR-ABL mutations and other, BCR-ABL-independent, mechanisms that can potentially be targeted with combination therapies. To this end, autophagy and cytokine signalling have been highlighted and targeting the transcription factor STAT5 became, for instance, another promising approach to be assessed.

Key discoveries 2012

A monoclonal antibody against the IL-3 receptor α (CD123) effectively depletes CML progenitor and stem cells

It has been reported that TKI therapy does not effectively target the leukaemic stem and progenitor cell (LSPC), thus a pool of LSPCs remain and have the potential to repopulate blood and marrow with leukaemia cells even after optimal response or in cases of therapy withdrawal. Protection by cytokines, such as IL-3 and GM-CSF, provides a potential mechanism for LSPCs to escape TKI-mediated cell death. In a project undertaken in collaboration with CSL Limited and the group of Angel Lopez we have demonstrated that the expression of the IL-3 receptor α (CD123) is elevated in CML LSPCs compared to normal haematopoietic stem and progenitor cells. These findings are similar to others reported in acute myeloid leukaemia (AML). Exploiting this further, we have utilised the monoclonal antibody CSL362, which blocks IL-3 signalling and directs NK cells to lyse CD123-expressing cells, and demonstrated effective targeting of CML LSPCs. Of clinical importance, CML patients’ own NK cells were able to execute CSL362-mediated LSPC killing in vitro and the combination of nilotinib and CSL362 showed an additive benefit when compared to either agent alone. CSL362 is currently in a clinical trial for the treatment of AML and may hold a potential for CML therapy in the future (ASH abstract 32, 2012).

The non-steroidal anti-inflammatory drugs (NSAIDs) diclofenac and ibuprofen differentially affect imatinib uptake into leukaemic cells

NSAIDs are frequently used by CML patients to manage musculoskeletal complaints. To investigate their impact on OCT-1 activity, we performed a systematic functional analysis of 12 commonly used NSAIDs in CML cell lines and CP-CML patients’ cells. Interestingly, we found that ibuprofen significantly reduced OCT-1 activity and reduced imatinib effectiveness, while diclofenac was found to increase OCT-1 activity and improve imatinib potency in leukaemic cells. These studies demonstrated that patient cells can be pharmacologically manipulated to increase OCT-1 functional activity, and importantly, exploration of the underlying mechanism of action of diclofenac has revealed previously unidentified biological differences between patients with low and high OCT-1 activity. The results of these studies may have a significant impact not only for imatinib treated patients, but also those treated with other TKIs (Br J Cancer 106: 1772-78, 2012).

Inhibition of autophagy enhances TKI-induced cell death in chronic myeloid leukaemia cells

Autophagy is a means by which cells adapt their metabolism to environmental stresses, facilitating survival during unfavourable metabolic circumstances; and has recently attracted interest as a mechanism of resistance to several cancer therapies. Combination of TKI-induced blockades of survival pathways and inhibition of autophagy by chloroquine has previously been shown to restore sensitivity of TKI-resistant CML cells to TKI-induced cell death. We have now confirmed the role of autophagy in CML and have identified the anti-bacterial chloramphenicol as a potent autophagy inhibitor. Chloramphenicol is one of several macrolide antibiotics that has been demonstrated to inhibit cancer cell growth. A recent case report suggested chloramphenicol dramatically reduces BCR-ABL levels in TKI-resistant patients. Our results indicate that chloramphenicol may be equally as effective as chloroquine at inhibiting autophagy and therefore enabling TKI-induced cell death (Leukemia & Lymphoma 103109/10428194-2012.066777, Epub July 6 2012).

Outcomes for the Community

With current approaches, complete responses are infrequently achieved in CP-CML patients and resistance and intolerance remain significant clinical issues. Research in our laboratory addresses the urgent need to better understand the underlying biology of CML, and to explain why some patients respond poorly to TKI therapy. Furthermore, we are ideally placed internationally to evaluate the potential clinical application of novel targeted therapies. Our overarching aim is to improve the outcome and quality of life of patients with CML.
All disease processes in humans have a genetic component. This can be either inherited (familial and germline), or acquired by somatic mutation during cell division. The identification of genes and mutations that cause or predispose families to diseases, or mutations in genes acquired during disease progression are important as diagnostic and prognostic markers, as well as providing direct targets and biological pathways for therapeutic intervention.

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

Identification of the Autoimmune REGulator (AIRE) gene as being responsible for the human monogenic organ-specific autoimmune disease, Autoimmune Polyendocrinopathy Syndrome Type 1 (APS1). Subsequent studies, have revolutionised our knowledge of central tolerance in immunology and autoimmunity. Studies in both humans and mice with mutations in the AIRE gene have firmly established its role as a master regulator of the expression of RNAs encoding proteins normally restricted to specific tissues or cell types. This occurs in thymic medullary epithelial cells (mTECs) where these tissue specific antigens (TSAs) can then be presented to self-reactive T cells which are subsequently eliminated (negative selection). In the absence of Aire, self-reactive T-cells leave the thymus and, if they encounter self-antigen (Ag), T-cell and B-cell activation, auto-antibody (Ab) production and tissue damage follow. Rare cases of genetic diseases including predisposition to leukemias and lymphomas, infection and autoimmunity can provide insights into the initiation and progression of these diseases. With international and national collaborators as well as the South Australian Familial Cancer Service, we collect samples from rare families with predispositions to haematological malignancies (HMs) and attempt to determine which genes are mutated to cause these disease predispositions. These studies are increasingly using the revolutionary ‘next generation sequencing’ technologies that have reduced the price of whole genome sequencing (sequencing a persons entire DNA composition or genome) to only a few thousand dollars. We have introduced these technologies and skills locally to South Australia. Identification of disease genes has immediate and direct implications for affected families and individuals and are beneficial for counselling, family planning and, ultimately, choices of therapy.

Key discoveries 2012

Post-Aire maturation of thymic medullary epithelial cells

Aire regulated expression of TSAs by mature mTECs is an essential mechanism in the induction of central tolerance. Recent data suggest that the survival of mTECs extends beyond the stage of Aire expression to form a post-Aire mTEC population and Hassall’s corpuscles (HCS). The nature and function of these post-Aire mTECs and structures, however, have remained unknown. Here, we characterized in detail the end-stage development of mTECs and HCs in both Aire-sufficient and Aire-deficient mice. Using a transgenic mouse model in which the LacZ reporter gene is under the control of the endogenous Aire promoter, we purified and analyzed the post-Aire mTECs to characterize their function. We showed that the end-stage maturation of mTECs closely resembles that of keratinocytes and that the lack of Aire results in a marked block of mTEC differentiation, which is partially overcome by ligands for RANK and CD40. We also provide evidence that, during mTEC development, Aire is expressed once and only during a limited 1-2 day period. Loss of Aire expression is followed by a quick downregulation of MHC class II and CD80, and of most of the Aire-dependent and Aire-independent TSAs, with the exception of keratinocyte-specific genes. In the final stage of maturation, mTECs lose their nuclei to become HCs and specifically express desmogleins (DGs) 1 and 3, which, via cross-presentation by APCs, may contribute to tolerance against these pemphigus vulgaris-related TSAs (Frontiers in Immunology 3, 2012).

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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 and its role in cancer and ageing, and
2. understanding the regulation of cellular homeostasis by ubiquitination.

Given the essential role of cell death in normal functioning of the human body, deciphering the mechanisms that mediate cell death is essential for understanding disease processes and to design effective treatment strategies for pathologies which arise due to inappropriate cell death. 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 and ageing.

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

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### Key discoveries 2012

The cell death protease, caspase-2, functions in the DNA damage response and is required for genome stability. Caspases are cysteine proteases that function as critical regulators of apoptosis and inflammation. Recently we have found roles for caspase-2 in apoptotic and non-apoptotic signalling pathways including tumour suppression and ageing. We demonstrated that loss of caspase-2 enhances oncogene-induced cell transformation and augments lymphomagenesis in the EμMyc mouse tumour model. In a recent publication we reported that caspase-2-deficient (Casp2−/−) cells exhibit defective DNA damage signalling response and accumulate excessive damage to DNA, including increased DNA breaks and aberrant chromosomal separation (Cell Death Differ 19: 1288-98, 2012). Consistent with these observations, we observed that loss of caspase-2 leads to aneuploidy and genomic instability which likely contributes to the increased tumour potential of Casp2−/− cells. Thus, our work provides evidence that caspase-2 is a regulator of the DNA damage response and is involved in maintaining genome stability.

Caspase-2 deficiency leads to increased oxidative stress and early onset of ageing in mice

In another paper published in Cell Death Differ (19: 1370-80, 2012) we showed that loss of caspase-2 causes early ageing which is due to its involvement in the oxidative stress response pathway. We found that caspase-2 knockout (Casp2−/−) mice have a shorter maxium lifespan, show early hair greying, reduced fat content and increased bone loss compared to wild type (WT) mice, all of which are indicative of early ageing. Aged Casp2−/− mice show enhanced oxidative stress accompanied by reduced activity of antioxidant enzymes and increased DNA damage. Interestingly, in the aged Casp2−/− animals expression of FoxO family members (FoxO1 and FoxO3a) and some of its target genes were significantly reduced. Our work thus demonstrates that increased DNA damage and oxidative stress associated with caspase-2 deficiency are the causal factors leading to early onset of ageing related traits in Casp2−/− animals.
Ceramide, sphingosine and sphingosine-1-phosphate regulate a diverse range of cellular processes by acting as intracellular second messengers, while sphingosine-1-phosphate also acts as a ligand for a family of 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 from us, and others, showing elevated sphingosine kinase in a variety of human cancer cells, and inhibition of tumour growth in vivo of human cancer cells, and inhibition of tumour growth in vivo.

In addition to this role in tumourigenesis, sphingosine kinase and sphingosine-1-phosphate appear central players in many other cellular processes, including: vascular endothelial cell activation, a hallmark of inflammatory diseases; enhancing blood vessel constriction; 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 identifying the mechanisms regulating sphingosine kinase, the (patho-)physiological functions of signal transduction pathways controlled by this enzyme, and in developing small molecule inhibitors as anti-cancer agents.

In particular, we have made several major breakthroughs in understanding how this enzyme is activated, relocated to the plasma membrane, and deactivated, which have provided novel therapeutic targets to control cancer. We have also identified that the substrate of sphingosine kinase, sphingosine, is a key regulator of the pre-survival 14-3-3 proteins. Indeed, our work suggests that inactivation of 14-3-3 by sphingosine is a key control mechanism that if deregulated can enhance tumourigenesis. Thus, this pathway also represents novel therapeutic target that may be exploited to control cancer.

Sphingosine kinase shows considerable promise as a target for anti-cancer therapy in a diverse range of solid tumours and leukaemias. To date, however, no clinically useful sphingosine kinase inhibitors have been developed. Using a structure-based approach we have recently developed novel sphingosine kinase inhibitors that show considerable promise as anti-cancer agents. These inhibitors are highly specific the sphingosine kinases and in pre-clinical studies these agents show efficacy blocking the progression of a number of different human cancers in vivo.

Sphingosine kinase ameliorates insulin resistance

Obesity is associated with the development of insulin resistance and type 2 diabetes, which is a major health concern. In collaborative work with Professor Mark Febbraio (Baker IDI Heart and Diabetes Institute) we have recently identified that sphingosine kinase is an important regulator of insulin action and can reduce the development of obesity-induced insulin resistance (Diabetes 61: 3148-55, 2012). Specifically, we found that increased sphingosine kinase activity in skeletal muscle results in improved insulin sensitivity in mice fed a high fat diet.

Key discoveries 2012

Development of new anti-cancer sphingosine kinase inhibitors

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Our laboratory focuses on multiple myeloma (MM), an incurable haematological malignancy characterised by the clonal proliferation of malignant plasma cells (PC) within the bone marrow (BM).

Multiple myeloma is the second most common haematological malignancy after non-Hodgkin’s Lymphoma, with approximately 1,400 newly diagnosed patients each year in Australia. Despite recent advances in treatment, MM remains almost universally fatal with a five year survival rate of approximately 30%. The main clinical manifestations of MM are the development of osteolytic bone lesions, bone pain, hypercalcemia, renal insufficiency, suppressed immunoglobulin production and increased BM angiogenesis. It is now widely accepted that most, if not all, multiple myeloma is preceded by a pre-malignant MGUS (monoclonal gammapathy of uncertain significance) stage. However, the genetic factors that trigger the progression from asymptomatic MGUS to overt malignant MM remain to be determined.

Our current projects are focused on:
- Identifying key genetic changes that ‘drive’ the progression from asymptomatic MGUS to overt malignant MM.
- Identifying novel BM microenvironmental factors that contribute to MM disease progression.
- Identifying novel signalling pathways with roles in mesenchymal stem cell differentiation which may be manipulated to increase bone formation in MM patients.

**Key discoveries 2012**

Imatinib is a tyrosine kinase inhibitor that has been successfully used to treat Philadelphia chromosome-positive chronic myeloid leukemia (CML) and Kit (+) gastrointestinal stromal tumors. We have previously shown that imatinib therapy is associated with an increase in trabecular bone volume. We performed a prospective analysis of bone indices in imatinib-treated CML patients to determine the mechanism responsible for this altered bone remodelling using serum markers of bone remodelling, dual-energy x-ray absorptiometry analysis of bone mineral density (BMD) and micro-computed tomography analysis on bone tissue biopsy specimens. We showed that the increase in trabecular bone volume and trabecular thickness after imatinib treatment was associated with a significant decrease in osteoclast numbers, accompanied by a significant decrease in serum levels of a marker of osteoclast activity. In contrast, osteoblast numbers were not altered by up to 24 months of imatinib treatment. Notably, we also found that imatinib caused a site-specific decrease in BMD at the femoral neck (J Clin Endocrinol Metab 2012; 97:2494-502).

Further long-term investigations are required to determine the causes and consequences of the site-specific decrease in BMD at the femoral neck.

Chronic low-back pain of discal origin is linked strongly to disc degeneration.

In this study, we examined the capacity of ovine mesenchymal precursor cells (MPCs) to restore the extracellular matrix of degenerate discs in an ovine model. We found that injection of MPCs into degenerate intervertebral discs contributed to the regeneration of a new extracellular matrix and disc restoration (J Neurosurg Spine 2012 Feb; 16(5):479-88).

Elevated N-cadherin expression in MM PC is associated with poor prognosis and can be used as a novel prognostic marker of high-risk myeloma patients. N-cadherin (cadherin 2, type 1, N-cadherin (neuronal); CDN2) is a homotypic adhesion molecule that is upregulated in breast, prostate and bladder cancer. These studies, for the first time, highlight the prognostic significance of upregulated N-cadherin expression in multiple myeloma (MM). The levels of circulating N-cadherin were elevated in a subset of patients with MM (n = 81; mean: 14.50 ng/ml, range: 0.146-78 ng/ml, relative to age-matched controls (n = 27; mean: 2.66 ng/ml, range: 0.05-96 ng/ml). Notably, patients with abnormally high levels of N-cadherin (>6 ng/ml) had decreased progression-free survival (P = 0.036; hazard ratio: 1.94) and overall survival (P = 0.002; hazard ratio: 3.15), when compared with patients with normal N-cadherin levels (<6 ng/ml). Furthermore, multifactorial analyses revealed the combination of N-cadherin levels and International Staging System (ISS) was a more powerful prognostic indicator than using ISS alone. Collectively, our studies demonstrate that circulating N-cadherin levels are a viable prognostic marker for high-risk MM patients (Br J Haematol 2013 Feb 1:10.1111/bjh.12383).

Osteoporosis and low bone mass are associated with increased morbidity and mortality in myeloma patients (Br J Haematol 2012 Jan; 160(1):6-13). In this study, we examined the effect of imatinib on bone health in CML patients with low bone mass (J Clin Endocrinol Metab 2012 Feb; 97(2):503-10). We showed that imatinib caused a site-specific decrease in BMD at the femoral neck (J Clin Endocrinol Metab 2012; 97:2494-502).

Further long-term investigations are required to determine the causes and consequences of the site-specific decrease in BMD at the femoral neck.

**Outcomes for the Community**

One contribution to the community was through the ‘Clinical Practice Guidelines for Myeloma’ (coordinated by Dr Hang Quach and Professor Miles Prince) prepared by the Medical and Scientific Advisory Group of the Australian Myeloma Foundation. These guidelines provide direction to treating physicians (haematologists/oncologists) as to the most effective treatment strategies for MM. These guidelines are freely accessible on the Myeloma Foundation of Australia Inc website: www.myeloma.org.au
Recent advances, including our own, conclusively show that similar molecules are recruited by both systems to coordinate their development. Our laboratory is particularly interested in understanding the signaling pathways controlling neural stem cell development with the aim of identifying molecular defects underlying neurodevelopmental disorders including neuronal tumours, neurocristopathies and neuropsychiatric illness. Together, these disorders affect over 5% of the population and arise from aberrant neuronal development.

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

Understanding development and integration of the neuronal and vascular systems at the molecular level presents a major challenge to developmental biologists. A key signalling molecule in neurodevelopment and schizophrenia
Schizophrenia is a devastating psychiatric disorder affecting ~1% of the population and is one of Australia’s major medical issues. Although recent advances in the aetiology of schizophrenia provide resounding evidence of a neurodevelopmental origin, the vast majority of underlying defects remain unknown. We recently demonstrated that the regulatory protein 14-3-3ζ is essential for neuronal development by interacting with the schizophrenia risk factor, DISC1. Our findings provide the first cause and effect relationship between deficiency of 14-3-3ζ and neurodevelopmental disorders such as schizophrenia (Molecular Psychiatry 17: 45166, 2012).
The microenvironment profoundly influences the tumour phenotype and there is accumulating evidence of its utility as a prognostic tool as well as a therapeutic target.

Our laboratory works to identify the mechanisms by which the cellular and extra-cellular matrix (ECM) components of the tumour microenvironment impact on the initiation and progression of cancers, and conversely how the cancer acts to remodel its microenvironment, resisting the organism’s attempt to normalise it.

The Rho signalling pathway is well-known to promote cell motility by its ability to regulate the contractility of the cellular actomyosin cytoskeleton. Less well-understood is its role in remodelling the normal tissue microenvironment. Our laboratory uses murine models in which the Rho signalling pathway can be conditionally activated, to determine the mechanisms by which this pathway modifies the ECM.

Using one of these models, we have previously demonstrated that activation of the Rho-signalling pathway within the skin causes an increase in the deposition of collagen, a major ECM protein of the dermis.

The resulting increase in the stiffness and density of the ECM, disrupted normal tissue homeostasis, promoted tumourigenesis, increased the number and size of lesions and the rate of conversion to malignant carcinoma in a model of cutaneous papillomagenesis and squamous cell carcinoma (SCC) (Cancer Cell 19: 776-91, 2012).

We are now working on determining how signalling through the Rho pathway effects these changes within the ECM.

The 14-3-3 family of phospho-serine binding proteins have roles in various cellular processes as a result of their ability to function as adaptor proteins or molecular chaperones. They have also been implicated as modulators of the Rho signalling cascade, which contains several proteins that are regulated by serine phosphorylation. Our laboratory uses mice deficient in 14-3-3ζ to determine the role of this protein in regulating Rho signalling, tissue homeostasis, tumourigenesis and tumour progression.

The Rho-signalling pathway regulates the deposition of ECM proteins in human cutaneous SCC

Following on from our work on Rho-mediated elevation of tissue stiffness and density, we have shown that this signalling pathway not only regulates the deposition of collagen within the ECM, but also the production of other key ECM components such as fibronectin and periostin, which have been previously demonstrated to exhibit pro-tumourigenic properties. Furthermore, in collaboration with Dr Jan Ibbetson of SA Pathology and using primary human cutaneous SCC samples, we have established that the Rho signalling pathway is progressively activated during tumour progression within cells of the tumour as well as the cells of the tumour microenvironment such as immune cells and fibroblasts. Activation of the Rho signalling pathway is accompanied by the increased deposition of collagen, fibronectin and periostin within the tumour microenvironment. It therefore appears that the Rho signalling pathway has a key role in establishing a tumour microenvironment that strongly promotes tumour progression.

CXCR2 inhibition suppresses tumourigenesis

CXCR2 is a chemokine receptor that exhibits context-dependent properties in either promoting or inhibiting the development of tumours. In collaboration with colleagues at the Beatson Institute for Cancer Research, the University of Glasgow UK and the Ludwig-Maximilians Universität, Germany, we have shown that expression of CXCR2 on the surface of neutrophils is required for their recruitment to sites of tumourigenesis, where they act as key members of a pro-tumourigenic inflammatory response that is driven by the incipient tumour. Genetic ablation or pharmacological inhibition of CXCR2 suppressed tumour growth in several murine models of skin and intestinal neoplasia (J Clin Invest 122: 3127-44, 2012). This discovery suggests that antagonising CXCR2 may have therapeutic utility in the treatment of intestinal and skin cancers.

Key discoveries 2012

The progression of cancer from benign to metastatic form is directly responsible for the majority of cancer deaths. While the cost to health and wellbeing is immense, the economic cost of cancer equates to around a tenth of our country’s economy. The major outcome from our work is a greater understanding of the mechanisms by which tumours hijack normal physiological processes to facilitate their growth. In identifying these mechanisms, we uncover key signalling nodes within both the tumour and the tumour microenvironment, against which therapeutic agents could be targeted in order to halt tumour progression and minimise the social and economic cost of the disease.
**Vascular Biology and Cell Trafficking Laboratory**

**Dr Claudine Bonder PhD**

**Endothelial cells (ECs) line the lumen of all blood vessels and thus play a pivotal role in maintaining vascular homeostasis. This dynamic interface services an enormous array of functions including the regulation of inflammation, coagulation, arterial tone, permeability, and vessel growth.**

More specifically, leukocyte recruitment to sites of inflammation is tightly regulated by ECs which, when activated, express several types of adhesion molecules. Controlling these adhesion molecules is critical to combating diseases such as allergy, cancer and heart disease.

Endothelial progenitor cells (EPCs) directly contribute to blood vessel formation (vasculogenesis) in physiological ‘repair’ processes of wound healing and fetal development as well as the pathological settings of cardiovascular disease, cancer, diabetes, arthritis and ischemia/reperfusion injury.

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

**Key discoveries 2012**

**Identification of a new target to treat allergic inflammation**

Rapid recruitment of neutrophils to a site of inflammation is associated with allergic diseases, such as asthma and anaphylaxis. Although anti-histamines and steroids are the mainstay of treatment for symptomatic relief, their effectiveness is variably, thus, a better understanding of acute allergic reactions is required. We have examined the role of sphingosine kinase (SK) mediated P-selectin expression on ECs for the rapid recruitment of neutrophils. SK is a highly conserved lipid kinase that catalyses the phosphorylation of sphingosine to form sphingosine-1-phosphate. Two isoforms of SK exist, SK-1 and SK-2, they are ubiquitously expressed but stored at varying levels in different cell types.

In collaboration with Associate Professor Stuart Plisson, we recently identified that (i) histamine-induced P-selectin expression on human umbilical vein ECs is SK-1 dependent and (ii) histamine-induced neutrophil rolling along the vasculature in vitro and in vivo is SK-1 dependent. Of great interest is that administration of FTY720 (approved pro-drug for treatment of multiple sclerosis) attenuates histamine-induced neutrophil recruitment in vivo (Am J Pathol 180, 1740-50, 2012).

**Defining a new EPC signature**

Current protocols for endothelial progenitor cell (EPC) identification employ combinations of progenitor markers (CD133 and CD34) and the EC marker vascular endothelial cell growth factor receptor 2 (VEGFR2). Using this protocol, EPCs have been isolated from diverse tissues, including bone marrow, umbilical cord blood (UCB) and peripheral blood. However, it is not currently known what proportion of the CD34+CD133+VEGFR2 EPCs in each tissue are in fact bona fide endothelial progenitors with one or some of CD94, CD133 and VEGFR2 described in haematopoietic, fibroblast and cancer cell populations. We recently identified a new population of immature, non-adherent EPCs (naEPCs) (PLoS ONE 7: e46906, 2012). These cells are distinct from ‘currently used’ EPCs by their non-adherence and immature phenotype which will support vascular repair and development across vascular lineages and thus vascular beds. Moreover, naEPCs likely represent the ‘true’ circulating EPCs which constantly survey the vasculature, ready to respond to vascular injury for repair with novel biomarkers (Patent application PCT/AU2011/001415). Our new protocols provide novel expansion methods to generate ~10^9 naEPCs in a serum free medium which provides better therapeutic opportunities for vascular repair.

**Blood vessels are critical for pancreatic islet function**

Pancreatic islet transplantation is an emerging cure for Type 1 Diabetes but success is limited by death of insulin producing beta cells post-transplantation. Vascularized endothelial progenitor cells (EPCs) have the potential to improve islet engraftment, and may also improve islet graft function. In collaboration with Dr Claire Jessup and Associate Professor Toby Coates we have combined EPC and islets into functional mosaic clusters in vitro and assessed the interactions between islets and EPC in vitro and in vivo in a diabetic mouse model of islet transplantation. To date we have shown that mosaic islet clusters can form successfully, using both rat and mouse cells and using confocal microscopy we have demonstrated distribution of EPC throughout rat mosaic islet clusters and glucose stimulation index function was superior to clusters comprised of islet cells only (Islets 3: 1-7, 2011). In 2012 we demonstrated that co-transplantation of islets and EPCs into diabetic mice significantly increased the cure rate when compared to islets alone.

**Outcomes for the Community**

With a focus on immune dysfunction and disease we study the intricate network of blood vessels that carry white blood cells throughout our body. Blood vessels contribute to life threatening diseases but are also essential for tissue regeneration and organ transplantation. Our work may provide new opportunities to, on the one hand, augment blood vessel development in patients with cardiovascular disease and on the other hand, ablate blood vessel development in cancer patients.
Over the last 10 years numerous technological developments have greatly accelerated our understanding of genetics and genomics of both inherited diseases and cancer. New approaches to diagnostics and therapeutics, such as automation and substantive automation, and have been outsourced outside the State, or indeed outside Australia, in terms of both lab space and bring a number of key technologies to the Centre for Cancer Biology and the South Australian research community including NGS from Illumina, Ion Torrent and Roche; microarrays from Affymetrix and Illumina; as well as Fluidigm equipment for the study of single cells. We have substantive automation, and have been first in Australia for several of these technologies, such as automation of epigenomics.

For example, cancers have, traditionally, been classified and subsequently treated based on where they occur, for example lung cancer, and their pathology, such as non-small cell lung cancer. Increasingly however, cancers are being classified and treated based not only on their location, but on their genomics. Recent advances in the power of NGS technologies, together with the discovery of genetic lesions in particular cancers, and the ability to specifically target those mutations with specialised drugs, forms the basis of personalised medicine which will become the standard of patient care in the near future.

Funding has been used to refit new lab space and bring a number of key technologies to the Centre for Cancer Biology. We are now major participants in cutting edge international studies in the causes and treatment of cancer and genetic diseases with in-house capacity and training. Up until now, we have outsourced many of these studies using these technologies, such as automation of epigenomics.

For example, through the ACRF Cancer Genomics Facility, it is now possible to sequence an individual’s genome for a few thousand dollars, and equally important the protein coding genes that form the basis of personalised medicine can now be sequenced for hundreds of dollars in just a few days. This can be of importance in diagnosis and choice of therapy for both cancer and genetic diseases.

Importantly, in collaboration with eResearch SA, South Australia’s high performance computing node, we have started to build our in-house capability to analyse and interpret the vast amounts of data generated by these new technologies. This includes not only “super”-computer infrastructure, but also bioinformaticians, people skilled in analysing and interpreting this data. The prominence and promise of studies using these technologies is shown in high profile international publications, which are changing cutting edge clinical practice for both inherited genetic diseases including cancer predisposition, and many forms of ‘sporadic’ cancer.

Outcomes for the Community

We are now major participants in cutting edge international studies in the causes of cancer and genetic diseases with in-house capacity and training. Up until now, many of these studies, with the vast amounts of data that these technologies generate, have been outsourced outside the State, or indeed outside Australia, in terms of both laboratory manipulations and data analyses.

We continue to develop in-house genetics, genomics and bioinformatics capacity, which helps local researchers and clinicians understand both the promise and demands in applying these new technologies to answer fundamental biological questions and specific clinical problems. We continue to develop in-house genetics, genomics and bioinformatics capacity, which helps local researchers and clinicians understand both the promise and demands in applying these new technologies to answer fundamental biological questions and specific clinical problems. We are working closely with researchers and clinicians in basic science at the Centre for Cancer Biology, clinical translational research (for example, genetic diagnoses and molecular oncology, Centre for Cancer Biology and SA Pathology) as well as working towards implementation of our new technologies into standard health care via the Centre for Cancer Biology, SA Pathology and SA Health.

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**Financial Highlights**

| Research Income 2012 | 11,818,528 |
| Biotechnology Awards | 1,988,186 |
| South Australian Competitive Grants | 778,850 |
| Philanthropic Support | 1,226,804 |
| ACRF Cancer Genome Facility | 2,100,000 |

| Total | 17,912,368 |

All amounts shown are in Australian currency.

**Publications continued**

![Image of a page from a publication]
<table>
<thead>
<tr>
<th>Investigator</th>
<th>Title</th>
<th>Granting Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews P, Ramshaw H, Chromer S, Negrotti P</td>
<td>A newly identified role for 14-3-3ζeta protein in thrombosis and platelet procoagulant activity</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>Bonder C, Lopez A</td>
<td>A new target to combat breast cancer</td>
<td>Cancer Council South Australia</td>
</tr>
<tr>
<td>Bransford S, Hughes T, Scott H, Schreiber A</td>
<td>Identification of molecular signatures at diagnosis of chronic myeloid leukaemia by an examination of the entire expressed leukaemic transcriptome to distinguish poor risk patients</td>
<td>Health Services Charitable Gifts Board The Ray and Shirl Norman Cancer Research Trust</td>
</tr>
<tr>
<td>Bransford S</td>
<td>Evaluation of a major BCR-ABL miRNA assay for patients with CML for consistent interpretation of individual patient response to TKI therapy</td>
<td>Chisinau Pharmaceuticals</td>
</tr>
<tr>
<td>Byrne S, Halliday G, Grimbalestian M</td>
<td>How does sunlight protect from autoimmunity?</td>
<td>Multiple Scleroses Research Australia</td>
</tr>
<tr>
<td>Cari J, Pitson SM</td>
<td>Roles and regulation of sphenoido-kisine 1 during dengue virus infection</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>Corn S</td>
<td>Florey Fellowship</td>
<td>Royal Adelaide Hospital</td>
</tr>
<tr>
<td>D’Andrea RJ</td>
<td>Molecular characterisation of Diamond Blackfan Anaemia</td>
<td>The role of caspase-mediated tumor suppressor pathways and their role in regulating resistance to chemotherapy</td>
</tr>
<tr>
<td>D’Andrea RJ, Gonda T, Brown AL, Lewis ID</td>
<td>Identification and characterisation of novel FLT3-ITD co-operating mutations in adult and childhood acute myeloid leukaemia</td>
<td>National Health and Medical Research Council</td>
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<td>D’Andrea RJ, To LB</td>
<td>Dissociating the blood cell defect in Diamond Blackfan Anaemia</td>
<td>Captain Courageous Foundation, University of Melbourne</td>
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<td>Ebert L, Brown A, Bonder C</td>
<td>A new molecule involved in the development of blood vessels within tumours</td>
<td>Cancer Council South Australia</td>
</tr>
<tr>
<td>Dostyn L, Kumar S</td>
<td>Deciphering the mechanisms of a caspase mediated tumour suppressor pathway</td>
<td>Association for International Cancer Research</td>
</tr>
<tr>
<td>Grimbalestian M, Samuel M, Dzidzernat T</td>
<td>Mast cells are key negative regulators of skin tumourigenesis</td>
<td>Cancer Council South Australia</td>
</tr>
<tr>
<td>Grimbalestian M</td>
<td>Commercial in Confidence funding</td>
<td>CSL Ltd</td>
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<tr>
<td>Gronthos S, Zannatino A</td>
<td>Mesenchymal Stem Cell maintenance and recruitment during skeletal repair and bone disease are dependent on Ezh2 expression</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>Harvey N, Scott H</td>
<td>Defining the role of GATA2 in lymphatic vascular development as a means to understanding how GATA2 mutations predispose to human lymphoedema</td>
<td>Cancer Council South Australia</td>
</tr>
<tr>
<td>HWiase D, Hahn C, To LB, Bundy P, Scott H, Malo J</td>
<td>Mutation detection in MDS patients using mass spectrometry: Predicting responses to therapy and long term outcome</td>
<td>Royal Adelaide Hospital Contributing Haematologists’ Committee</td>
</tr>
<tr>
<td>Hughes T</td>
<td>Practitioner Fellowship</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>Jessup C, Coates P, Bonder C</td>
<td>The importance of cell-cell interactions in juvenile (Type 1) diabetes</td>
<td>Channel 7 Children’s Research Foundation</td>
</tr>
<tr>
<td>Jessup C, Paliw H, Keating D, Bonder C</td>
<td>The role of the calcium regulator RCAN1 in pancreatic islet function</td>
<td>Diabetes Australia Research Trust</td>
</tr>
<tr>
<td>Kumar S</td>
<td>Autophagy and growth signalling in developmentally programmed cell death</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>Kumar S, Dostyn L</td>
<td>Deciphering the function of caspase-2 in DNA damage response and tumour suppression</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>Lewis ID, D’Andrea RJ</td>
<td>Investigation of dysregulated HGF-MET signalling in AML</td>
<td>Royal Adelaide Hospital Contributing Haematologists’ Committee</td>
</tr>
<tr>
<td>Lewis ID, D’Andrea RJ, Brown AL</td>
<td>Gene expression consequences of altered KLF5 activity in poor prognosis</td>
<td>Royal Adelaide Hospital Contributing Haematologists’ Committee</td>
</tr>
</tbody>
</table>

Investigator | Title | Granting Body |
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<thead>
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<tr>
<td>Li J, Liu L, Niu J, Goodall GJ</td>
<td>Developing novel data mining methods to reveal complex group relationships from heterogeneous data</td>
<td>Australian Research Council</td>
</tr>
<tr>
<td>Lloyd A, Dona G, George T, Board M</td>
<td>Program Grant: Hepatitis C infection: epidemiology, pathogenesis and treatment</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>McRae S, Foster D</td>
<td>Pharmacokinetic based dosing of patients with severe haemophilia A</td>
<td>ACHD Clinical Excellence Fund</td>
</tr>
<tr>
<td>McRae S, Ross D, Rodgers S, Dale B</td>
<td>Laboratory assessment of thrombotic risk in myeloproliferative neoplasms</td>
<td>Royal Adelaide Hospital Contributing Haematologists’ Committee</td>
</tr>
<tr>
<td>Muto Jr, Whitelaw M, Hughes TP</td>
<td>Transcriptional and post-transcriptional regulation of the BCR-ABL gene in chronic myeloid leukaemia</td>
<td>Cancer Council South Australia</td>
</tr>
<tr>
<td>Muto Jr, Hughes TP, Johnson BV</td>
<td>Transcriptional regulation of the BCR-ABL Oncogene</td>
<td>Royal Adelaide Hospital Contributing Haematologists’ Committee</td>
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<tr>
<td>Neil J</td>
<td>Veronika Sacco Postdoctoral Clinical Cancer Research Fellowship</td>
<td>University of Adelaide Rady Foundation</td>
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<tr>
<td>Parker W</td>
<td>Postdoctoral Fellowship</td>
<td>Leukaemia Foundation of Australia / Cure Cancer Australia Foundation</td>
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<tr>
<td>Pitman MR</td>
<td>Royal Adelaide Hospital Research Foundation Fellowship</td>
<td>Royal Adelaide Hospital Research Foundation</td>
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<tr>
<td>Pitson SM</td>
<td>Senior Research Fellowship</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>Ramshaw H, Ebert P</td>
<td>Does CD123 provide a biological advantage to Leukaemia stem cells?</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>Ramshaw H</td>
<td>Senior Research Fellowship</td>
<td>Peter Nelson Leukaemia Research Fund</td>
</tr>
<tr>
<td>Reynolds P, Curnel D, Bonder C</td>
<td>Development of novel gene and cell therapies for pulmonary hypertension</td>
<td>Heart Foundation</td>
</tr>
<tr>
<td>Samuel M</td>
<td>Future Fellowship</td>
<td>Australian Research Council</td>
</tr>
<tr>
<td>Samuel M, Lopez A, Grimbalestian M, Ramshaw H</td>
<td>Skin tumourigenesis and tumour progression: A new function for 14-3-3ζeta?</td>
<td>Cancer Council of South Australia</td>
</tr>
<tr>
<td>Schwarz Q</td>
<td>Defining the role of NAD34 in neural crest cell development</td>
<td>National Health &amp; Medical Research Council</td>
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<tr>
<td>Steiberg G, Bliss T, Grimbalestian M</td>
<td>NH 1 TR12 Grant Meningeal mast cells: key effectors of stroke pathology</td>
<td>National Institutes of Health, USA</td>
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<tr>
<td>Vandyke K</td>
<td>Mary Overtone Fellowship</td>
<td>Royal Adelaide Research Foundation</td>
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<tr>
<td>White D, Mulligan C, Hughes T, Sutton R</td>
<td>Screening for recently defined genetic lesions in poor risk adult and childhood ALL, and development of targeted treatment approaches to target causative pathways</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>White D, Mulligan C</td>
<td>Childhood Ph-like ALL: Improving diagnostic screening and therapeutic rationale</td>
<td>Leukaemia Foundation</td>
</tr>
<tr>
<td>White D, Mulligan C, Hughes T</td>
<td>Investigating the prevalence of druggable novel gene fusions, detectable by phospho-flow analysis in high risk adult B-ALL</td>
<td>Australian Leukaemia and Lymphoma Group</td>
</tr>
<tr>
<td>White D, Mulligan C, Hughes T</td>
<td>Assessing the cause and drug susceptibility of adult high-risk ALL</td>
<td>Cancer Council of South Australia</td>
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<tr>
<td>Yong A, Hughes T</td>
<td>Characterisation of immune responses in CML patients on riboflavin and interferon alpha</td>
<td>Leukaemia Foundation</td>
</tr>
</tbody>
</table>
Seminar Program

Assoc Prof Richard Lake
Tumour Immunology Group Research
University of Western Australia, Perth
Chemokinesis for macrophages: from mouse to man 8/03/12

Dr Dagmar Wilhelm
Institute for Molecular Bioscience
University of Queensland, Brisbane
Towards a new understanding of the reproductive system, a tale of miRNAs and ovaries 15/03/12

Dr Daniela Stock
Laboratory Head, Structural and Computational Biology Division, Victor Chang Cardiac Research Institute, Sydney
Structure and dynamics of molecular rotary motors 22/03/12

Prof Michael Good (AO)
Head, Laboratory for Vaccines for the Developing World Australia Fellow, Institute for Glycomics
Griffith University, Griffith, Queensland
A novel strategy to develop a malaria vaccine 29/03/12

Prof Shudong Wang
Professor in Medicinal Chemistry, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide
Discovery and early clinical development of cell-cycle kinase inhibitors as anti-cancer agents 05/04/12

Prof David Vaux (FAA)
Head, Cell Signalling and Cell Death Division, Assistant Director, Walter and Eliza Hall Institute, Melbourne
Inhibitors of apoptosis proteins (IAPs) and a deal with the inhibitors as anti-cancer agents 05/04/12

Prof Peter Leadman
Head, Laboratory for Cancer Medicine
Deputy Director, WA Institute for Medical Research, Perth
miRNAs and cancer: insights and challenges 05/07/12

MR Joel Geoghegan
Deputy Director, WA Institute for Medical Research, Perth
Overview of the new ACRF SA Cancer Genome Facility: from bench to bedside, and back again 03/12/12

Assoc Prof Paul Beresford
Senior Research Fellow, Brain Tumour Laboratory
University of Queensland, Brisbane
Paraspeckles: Dynamic nuclear bodies formed by key long noncoding RNA-protein interactions 06/09/12

Assoc Prof Nick Topham
NHMRC Australia Fellow; Director, UNSW Centre for Vascular Research
Growth regulatory networks in vascular pathobiology 08/11/12

Dr Levon Khachigian
NHMRC Australia Fellow; Director, UNSW Centre for Vascular Research
Growth regulatory networks in vascular pathobiology 20/11/12

Dr Paul Timpson
Head, Invasion and Metastasis Group
Garvan Institute and KCONNECT Centre, Sydney
Imaging the molecular dynamics of cancer cell behaviour in the tumour using fluorescent biosensors 03/12/12

Dr Samantha Stitichfield
PostDoc, University of California, San Francisco, USA
Implications for Migration and Metastasis: The microtubule +TIP CLASP mediates localized exocytosis to control extracellular matrix degradation and focal adhesion turnover 06/12/12

Assoc Prof Martin Lavin
Acting Director, Queensland Institute of Medical Research
Brisbane
Dual role for sestrin, defective in ataxia oculomotor apraxia type 2, in protecting the genome 24/06/12

Assoc Prof John Pimanda
Prince of Wales Clinical School
University of New South Wales, Sydney
Embryonic haematopoietic stem cell enhancers are active in leukemic cells and predict clinical outcome 31/03/12

Assoc Prof Carol Wicking
Molecular Genetics and Development, Institute of Molecular Bioscience, University of Queensland, Brisbane
Using mouse models to understand human ophthalmia 07/06/12

Prof Arthur Chippindale
Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences and Dept of Pharmacology
Monash University, Melbourne
Allostytic and biased ligand drug discovery at G protein-coupled receptors 21/06/12

Assoc Prof Susan Brantford
Head, Leukaemia Unit, Genetics and Molecular Pathology Centre for Cancer Biology, Adelaide
Biomarkers of response and drug resistance in chronic myeloid leukaemia: from single mutant miRNAs and proliferation rate, to clonal diversity 28/06/12

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## Invited Presentations 2012

### Acute Leukaemia Laboratory

**Prof Richard D'Andrea**
- **Session Chair**
- Australian Epilineage Epigenetics 2012 Conference
  - Adelaide, Australia, May
- Co-Chair
  - Organising and Scientific Committees
  - New Directions in Leukaemia Conference (NDL2012)
  - Suriname Coast, Australia, March

**Haematopoiesis Session, Australasian Society for Stem Cell Research, 5th Annual Meeting (ASSCR)**
- Adelaide, Australia, November

**Assoc Prof Ian Lewis**
- Co-Chair
  - The Cellular Therapies Working Committee, Center for International Blood and Marrow Transplant Research (CIBMTR)
  - San Diego USA February
- Invited Speaker
  - 5th Asia-Pacific Histocompatibility and Immunogenetics Association Meeting
  - Adelaide, Australia, November

**Dr Sarah Bray**
- Invited Speaker
  - 12th Diamond Blackfan Anaemia International Consensus Conference (DIBA ICC)
  - New York, USA, March

**Dr Michelle Perugini**
- Invited Speaker
  - Centre for Personalized Cancer Medicine Annual Symposium
  - University of Adelaide, Adelaide, Australia, September

### Cell Signalling Laboratory

**Dr Yosim Khow-Goodall**
- Invited Speaker
  - Ganin Signalling Meeting
  - Sydney, Australia, October

**Hunter Cellular Biology Conference**
- Pokolbin, Australia, March

**Phosphatases in Human Diseases (Satellite to Lorne Protein)**
- Pokolbin, Australia, March

### Gastroenterology Research Laboratory

**Assoc Prof Andrew Ruszkiewicz**
- Invited Speaker
  - 11th National Cancer Conference
  - Bangkok, Thailand, March

**International Scientific and Business Meeting of Australian Society of Cytopathology**
- Adelaide, Australia, October

**Australian Gastroenterology Week 2012**
- Adelaide, Australia, October

**Gene Regulation Laboratory**

**Prof Greg Goodall**
- Invited Speaker
  - International Society of Nephrology Forefronts Symposium
  - Melbourne, Australia, October

**Peter MacCallum Cancer Centre**
- Melbourne, Australia, October

**ComBio 2012**
- Adelaide, Australia, September

**Japanese Cancer Association, Sapporo, Japan, September**
- University of Adelaide School of Molecular and Biomedical Science Research Symposium, Adelaide, Australia, July

**Munroch Dunn’s Research Institute**
- Melbourne, Australia, April

**NYU Langone Medical Center**
- New York, USA, March

### Haematology Clinical Research Laboratory

**Professor Luen Bik To**
- Invited Speaker
  - 8th Australian Health and Medical Research Congress
  - Adelaide, Australia, November

**Haematology Education Session for Adelaide Northern Division of General Practice**
- Adelaide, Australia, September

**2012 HSANZ Queensland State Meeting**
- Brisbane, Australia, March

**Ms Elizabeth Duncan**
- Invited Speaker
  - Australian Society for Thrombosis and Haemostasis
  - Melbourne, Australia, October

**Dr Simon McRae**
- Invited Speaker
  - Australian Society for Thrombosis and Haemostasis
  - Melbourne, Australia, October

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**Gastroenterology Research Laboratory**

**Assoc Prof Andrew Ruszkiewicz**
- Invited Speaker
  - 11th National Cancer Conference
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**Peter MacCallum Cancer Centre**
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**ComBio 2012**
- Adelaide, Australia, September

**Japanese Cancer Association, Sapporo, Japan, September**
- University of Adelaide School of Molecular and Biomedical Science Research Symposium, Adelaide, Australia, July

**Munroch Dunn’s Research Institute**
- Melbourne, Australia, April

**NYU Langone Medical Center**
- New York, USA, March

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- Adelaide, Australia, September

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  - Australian Society for Thrombosis and Haemostasis
  - Melbourne, Australia, October

**Dr Simon McRae**
- Invited Speaker
  - Australian Society for Thrombosis and Haemostasis
  - Melbourne, Australia, October

**Second ASIAN Federation of Haematology Scientific Congress, Singapore, September**
- HAA 2012 Meeting, Melbourne, Australia, October

**Session Chair**
- Master Class: Haemophilia Management, HAA 2012
- Melbourne, Australia, October

**Symposium: Haemophilia Update, HAA 2012**
- Melbourne, Australia, October

## Leukaemia Biology Group

**Prof Junia V. Malo**
- Keynote Speaker
  - Journal Clubs at the Royal North Shore Hospital, Westmead Hospital and Royal Prince Alfred Hospital
  - Sydney, Australia, November

**Nikitis (Novartis) Investigator Meeting**
- Bordeaux, France, October

**Leukaemia new frontiers in therapeutic options**
- BMS Educational Symposium, Melbourne, Australia, October

**The microRNA 2012 International Symposium**
- São Paulo, Brazil, March

**Invited Speaker**
- 54th Annual Meeting of the American Society of Hematology
  - Atlanta, USA, December

**Novartis Industry Workshop on Chronic Myeloid Leukaemia at the 54th Annual Meeting of the American Society of Hematology**
- Atlanta, USA, December

**CML Opinion Leader Training Programme (COLT)**
- Adelaide, Australia, October

**44th Advances in Haematology Course, London, UK, October**
- Clinical Oncology Grand Rounds, Fred Hutchinson Cancer Research Center, Seattle, USA, September

**Highlights of ASH (American Society of Hematology)**
- In Latin America, Foz do Iguaçu, Brazil, May

**4th Novartis R&D Symposium, Melbourne, Australia, May**

**Novartis Symposium, São Paulo, Balital Hozonte and Río de Janeiro, Brazil, March**

**Plenary Speaker**
- The 14th European Society of Haematology International CML Conference, Baltimore, USA, September

**The Muter Medical Research Institute (MMRI)**
- Stem Cell Symposium, Brisbane, Australia, May

**Chairperson, Invited Speaker and Inaugural Lecturer**
- The Haematology Multidisciplinary Conference
  - Hospital Saint-Antoine, Paris, France, September

### Leukaemia Unit, Genetics and Molecular Pathology

**Assoc Prof Susan Branford**
- Invited Speaker and/or Session Chair
  - The American Society of Hematology, ASH CML Education Session-Monitoring after successful therapy
  - Atlanta, Georgia, USA, December

**Medical and scientific meetings, Meet the Expert sessions**
- Shanghai and Beijing, China, November

**European School of Haematology 14th International Conference on CML**
- Biology and Therapy, Baltimore, USA, September

**Asian Pacific Summit on CML, Kuala Lumpur, Malaysia, July**

**Egyptian Stem Cell Transplantation and Hematological Disease Association Conference (ESHA) and CML Experts meeting**
- Cairo, Egypt, May

**Haematology Conference and Haematopathology Workshop**
- Ampang Hospital, Kuala Lumpur, Malaysia, March

**European School of Oncology meeting:**
- Lymphomas and Leukaemias 2012, including Meet the Expert session
- Mumbai, India, January

### Lymphatic Development Laboratory

**Assoc Prof Natasha Harvey**
- Invited Speaker and/or Session Chair
  - 42nd Annual Meeting of the Australasian Society for Immunology
  - Melbourne, Australia, December

**Inaugural Meeting of the Australian Network of Cardiac and Vascular Developmental Biologists**
- Sydney, Australia, December

**Australian Health and Medical Research Congress**
- Adelaide, Australia, November

**ComBio 2012**
- Adelaide, Australia, September

**Suzhou International Symposium on Basic and Translational Vascular Research, Suzhou, China, May**

**Gordon Research Conference: Molecular Mechanisms in Lymphatic Function and Disease**
- Ventura, California, USA, March

**Centenary Institute Combi: ‘Biology and Diseases of the Endothelium’ Sydney, Australia, February**
- Invited seminars

**Brasilia Developmental Biology Seminar Series**
- Institute for Molecular Biosciences
  - Brasilia, Australia, November

**Australian Regenerative Medicine Institute Seminar Series**
- Melbourne, Australia, September

**UCLA, Department of Molecular, Cell and Developmental Biology**
- Special Seminar, Los Angeles, USA, March

**Heart Research Institute Seminar Series**
- Sydney, Australia, February
Mast Cell Laboratory
Assoc Prof Michele Grimbaldesont
Invited Speaker and/or Session Chair
Australian Society for Immunology, 43rd Annual Meeting Melbourne, Australia, December
6th AHMIRC Congress, Molecular and Experimental Pathology Society of Australia, Adelaide, Australia, November
Malaghan Institute, Wellington, New Zealand, November
Collegeium Internationale Allergologicum 20th Symposium Jeju Island, South Korea, October
Genentech Ltd, California, USA, October
ComBio 2012, Adelaide, Australia, September
Australasian Society for Immunology, SA/NT 8th Adelaide Immunology Retreat, Australia, September
NSW Immunology Retreat, Sydney, Australia, August
University of Sydney Dermatology, Sydney, Australia, August
University of Queensland Diamantina Institute Brisbane, Australia, August
Australian Society for Medical Research SA Conference Adelaide, Australia, June
3rd Co-Joint Meeting Australian Society for Dermatology and The Australasian Wound and Tissue Repair Society Sydney, Australia, May
BioC12 Ltd, Melbourne, Australia, May
THING: Tasmanian Haematology, Immunology, Necrosis Group Meeting, Hobart, Australia, April

Melissa White Memorial Laboratory
Professor Timothy Hughes
Invited Speaker
Brazilian Haematology Society, Sao Paulo, Brazil, November
Hematologic Malignancies 2012, Houston, USA, October
BMS Satellite Meeting, Haematology Society of Australia and New Zealand, Melbourne, Australia, October
Novartis Symposium / European Haematology Association, Amsterdam, Holland, June
CML GOLS 2012, Munich, Germany, March
New Directions in Leukaemia Research conference (NDLR) Sunshine Coast, Australia, March
Conference Organiser
ESH-ICML International Conference, Chronic Myeloid Leukaemia: Biology and Therapy, Baltimore, USA, September
New Directions in Leukaemia Research conference (NDLR) Sunshine Coast, Australia, March

Associate Professor Deborah White
Invited Speaker
Lunchtime Research Seminar Duke NUS University Singapore, November
Breakfast Research meeting, Peter MacCallum Cancer Research Institute, Melbourne, Australia, November
Lunchtime Research Meeting, Royal Melbourne Hospital Melbourne, Australia, November
Special Breakfast Seminar on ALL subtypes Austin Hospital, Melbourne, Australia, November
Special Lunchtime Seminar on ALL subtypes Alfred Hospital, Melbourne, Australia, November
Lunchtime Meeting, Gold Coast Hospital Haematology Journal Club, Gold Coast, Australia, October
Research Spotlight Dinner Meeting, Royal Brisbane Hospital Brisbane, Australia, October
Lunchtime Research Forum, Princess Alexandra Hospital Brisbane, Australia, October
CML: ESH-ICML International Conference, Chronic Myeloid Leukaemia: Biology and Therapy, Baltimore, USA, September
New Directions in Leukaemia Research conference (NDLR) Sunshine Coast, Australia, March
CML: Molecular Workshop Dhar, India, February
CML: Predictive Markers and Translation, Jaipur, India, February
Organising Committee Member
New Directions in Leukaemia Research conference (NDLR) Sunshine Coast, Australia, March

Molecular Pathology Research Laboratory
Professor Hamish Scott
Invited Speaker and/or Session Chair
PeterMac Institute Seminar, Melbourne, Australia, November
National Association of Research Fellows Symposium, 6th Australian Health and Medical Research Congress Adelaide, Australia, November
HSSA SA Branch, Annual Meeting Adelaide, Australia, October
ComBio 2012, Adelaide, Australia, September
Haematology Society of Australia and New Zealand (SA Branch) Blood Club, Adelaide, Australia, June
Australian Institute of Medical Scientists Cairns, Australia, June
Australian Institute of Medical Scientists Barossa Valley, Australia, April
New Directions in Leukaemia Research conference (NDLR) Sunshine Coast, Australia, March
Lorne Genome 2012, Lorne, Australia, February

Molecular Regulation Laboratory
Prof Sharad Kumar
Invited Speaker and/or Session Chair
Institute of Molecular Cell Biology, Singapore, November
NARF Symposium, The Australian Health and Medical Research Congress, Adelaide, Australia, November
Biscortor, Innsbruck Medical University Innsbruck, Austria, September
20th European Cell Death Organisation (ECCDo) Meeting on Apoptosis, Rome, Italy, September
Lowy Cancer Research Centre Seminar Series, Children’s Cancer Institute Australia for Medical Research Sydney, Australia, August
University of Rome Tor Vergata, Rome, Italy, July
Gordon Research Conference on Cell Death, Lucca, Italy, July
2012 Hunter Cell Biology Meeting, Pokolbin, Australia, March
Deputy Program Chair, Invited Chair for a Plenary Session and Nominated Speaker ComBio 2012, Adelaide, Australia, September

Dr Loretta Dorothy
Invited Speaker
ComBio 2012, Adelaide, Australia, September

Dr Donna Denton
Invited Speaker
ComBio 2012, Adelaide, Australia, September

Dr Loretta Dorothy
Invited Speaker
ComBio 2012, Adelaide, Australia, September

Molecular Signalling Laboratory
Assoc Prof Stuart Pitson
Invited Speaker
6th Ganun Meeting, Sydney, Australia, October
Baker ID Heart and Diabetes Institute Melbourne, Australia, August
3rd Australasian Wound and Tissue Repair Society Meeting Sydney, Australia, May
Conference Convener
ComBio 2012 Conference, Adelaide, Australia, September

Myeloma Research Laboratory
Professor Andrew Zannettino
Invited Speaker
ComBio 2012 Conference, Adelaide, Australia, September
AHMIRC 2012, Adelaide, Australia, November
SA Multiple Myeloma Interest Group Adelaide, Australia, September
St Vincent Research Institute Seminar Series Melbourne, Australia, June
Public Lecture
Leukaemia Foundation Patient Information Day AHMIRC 2012, Adelaide, November

Neurovascular Research Laboratory
Dr Quentin Schwarz
Invited Speaker and/or Session Chair and/or Panel Member
Australian Society for Stem Cell Research Junior Investigator Workshop, AHMIRC Congress Adelaide, Australia, November
4th Cell and Developmental Biology Meeting Brisbane, Australia, October
Human Genetics Society of Australasia Annual Symposium Adelaide, Australia, October
ComBio 2012 Conference, Adelaide, Australia, September
2nd ANZSCDB Cell and Developmental Biology Meeting University of Adelaide, Australia, September
Department of Biochemistry, University of Adelaide, Australia, June
Department of Psychiatry, University of Adelaide, Australia, May
12th Hunter Cell Biology Meeting, Hunter Valley, Australia, March

Tumour Microenvironment Laboratory
Dr Michael Samuel
Invited Speaker
ANZSCDB, Adelaide Cell & Developmental Biology Symposium Adelaide, Australia, November
Australian Health and Medical Research Congress Adelaide, Australia, November
ANZSCDB, Brisbane Cell and Developmental Biology Symposium Brisbane, Australia, October
Center for Bioengineering and Tissue Regeneration, UCSF San Francisco, USA, October
ComBio 2012, Adelaide, Australia, September
Australian Society for Medical Research Annual Scientific Meeting Adelaide, Australia, June
King’s College London, London, UK, May

Vascular Biology and Cell Trafficking Laboratory
Dr Claudine Bonder
Invited Presentations
Women’s and Children’s Hospital, Delivery Suite Midwifery Group Adelaide, Australia, October
Australian Vascular Biology Society, Gold Coast, Australia, September
South Australian Cardiovascular Research Forum Adelaide, Australia, September
Adelaide Midwifery Meeting Group Adelaide, Australia, July
Organising Committee
Australian Society for Stem Cell Research Adelaide, Australia, October

58 Centre for Cancer Biology Annual Report 2012

59 Invited Presentations 2012 continued
Awards 2012

Acute Leukaemia Laboratory
Shahrin NH, Brown AL, Dialek S and D’Andrea RJ
ASH Abstract Achievement Award
Blood (ASH Annual Meeting Abstracts), Nov 2012; 120: 2313

Cell Signalling Lab
Ms Leila Belle
PhD Thesis Research Excellence Award
Sponsor: Australian Society for Biochemistry and Molecular Biology

Cytokine Receptor Laboratory
Dr Hoyley Ramshaw
Senior Research Fellowship
Peter Johnson Leukaemia Research Fund
Ms Nicole Christie
Best PhD Presentation
Adelaide Immunology Retreat (AIR) 2012
Overall Best Poster at ASHI, Melbourne 2012

Gene Regulation Laboratory
Dr Simon Conn
Florey Fellowship, Royal Adelaide Hospital
Mr Yat Yuen Lim
Dean’s Commendation for Doctoral Thesis Excellence

Mast Cell Laboratory
Assoc Prof Grimaldueston
Collegium Internationale Allergologicum Alain de Weck Award
Dr Dave Yip
ASMR Early Career Research Award
Ms Natasha Kolesnikoff
MPhar Best Poster Award, 6th NHMRC, Adelaide, SA
Mr Hung Taing
Student Best Poster Award, ComBio, Adelaide, SA

Lymphatic Development Lab
Ms Kelly Betterman
PhD Thesis Research Excellence Award
Sponsor: Australasian Society for Immunology

Molecular Pathology Laboratory
Dr Chris Hahn
Best Primary Research Publication
2012 Centre for Cancer Biology Research Prize
Sponsor: Mitbion Biotech
Mr King-Hwa (Michael) Ling
PHD Thesis Research Excellence Award
Sponsor: Australian Society for Biochemistry and Molecular Biology

Molecular Signalling Laboratory
Ms Tamara Leclercq
Best Student Primary Research Publication
2012 Centre for Cancer Biology Research Prize
Sponsor: Qiagen
Assoc Prof Stuart Pitson
NHMRC Senior Research Fellowship
Dr Melissa Pitman
Royal Adelaide Hospital Research Foundation Fellowship

Molecular Regulation Laboratory
Prof Sharad Kumar
Finalist, GSK Award for Research Excellence, 2012
Finalist, South Australian Scientist of the Year, 2012
Ms Jackie Wong
Best Poster Presentation, Faculty of Health Sciences 2012
Postgraduate Research Conference, Adelaide

Myeloma Research Laboratory
Dr Kate Vandyke
Mary Overton Fellowship
Royal Adelaide Hospital Research Foundation
PhD Thesis Research Excellence Award
Sponsor: Life Technologies
Dr Jacqueline Neil
Veronika Sacco Postdoctoral
Clinical Cancer Research Fellowship
University of Adelaide Florey Foundation
Dr Sally Martin
Early Career Investigator Award
2012 Centre for Cancer Biology Prize
Sponsor: Qiagen

Vascular Biology and Cell Trafficking Laboratory
Ms Wai Sun
Australian Health and Medical Congress
‘Best of the Best’ Poster Prize
Faculty of Health Sciences
The University of Adelaide Florey Foundation
Mr Nikhil Thyagarajan
Florey Medical Research Foundation Honours Scholarship

Ms Jackie Wong accepting Mr Michael Ling’s PhD Thesis Research Excellence Award from Dr Keith Shearwin, state representative for ASBMB, sponsors of the award.
Students who completed their degrees during 2012
- Mr Yat Yuen Lim (PhD)
- Mr Daniel Thomson (PhD)
- Ms Victoria Arnet (PhD)

Cell Signalling Laboratory

Professor Hamish Scott

Dr Jinghua Feng
Dr Lucia Gaglardi
Dr Christopher Hahn
Dr Manuela Klingse-Hoffmann
Ms Milena Babic
Dr Christopher Hahn
Dr Lucia Gaglardi
Dr Christopher Hahn
Dr Manuela Klingse-Hoffmann
Ms Milena Babic
Dr Michael Samuel
Dr Melissa Pitman
Dr Melissa Pitman
Dr Briony Gliddon

Molecular Pathology Research Laboratory

Professor Sharad Kumar
Dr May Aung-Hut
Dr Natasha Boase
Dr Hazel Dalton
Dr Donna Denton
Dr Loretta Dorstyn
Dr May Aung-Hut
Dr Natasha Boase
Dr Hazel Dalton
Dr Donna Denton
Dr Loretta Dorstyn

Molecular Regulation Laboratory

Dr James Richardson (PhD)
Ms Chea Man Chong (Hons)
Ms Mary Matthews (PhD)
Ms Natasha Boase
Dr Hazel Dalton
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The RAH Research Fund Team raise funds for the Centre for Cancer Biology
Top: Mark Goldsmith, Fundraising Manager | Maria Flamminio | Matt Jackson
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