As I reflect on the future of health care for the State, I greatly appreciate how well SA Pathology and the CCB fit with the wider SA research community. SA Pathology strongly supports the Morision Report with its motto of ‘Better health through research’ as this could not epitomise better what we value in SA Pathology as part of our comprehensive commitment to research, teaching and education for the benefit of our patients and our population.

Not only do we contribute to the SA research community, but we also form part of a wider group of national and international scientific and clinical collaborations. This makes us a key partner in health care research and has helped establish SA Pathology as one of the leading cancer research centres in Australia.

Since its establishment in 2009 as the South Australian hub of cancer research excellence, the CCB has steadily grown in size and success. New key staff have been recruited, new technologies brought in and new facilities have been established. This recurrent 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, 2013 has been 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 awards and donations for much needed state-of-the-art equipment. The prestigious NHMRC grants for instance, ensure our researchers continue to be competitive which facilitates the translation of discoveries into better cancer treatments and outcomes.

I have been in charge of SA Pathology for two years now and I am delighted with the research partnerships and alliances the CCB and other SA Pathology researchers have formed with our universities and the South Australian Health and Medical Research Institute (SAHMRI) which will provide even richer sharing of ideas and infrastructure. In particular the insipient alliance between SA Pathology and the University of South Australia over the CCB promises to strengthen and facilitate the CCB growth into the future. Off course the close association of our clinical 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 essential integration of the CCB work with our own clinicians and clinicians at the Royal Adelaide Hospital provides reciprocal benefits to research and the clinical care of our patients.

This close association between diagnostic and research activities continues to be boosted with the growing reputation and success of the ACRF Cancer Genomics Facility, creating wonderful integrated research and teamwork. Together, this integrated approach is helping further advance the personalised cancer care provided by SA Pathology, as well as boosting cancer, genomics and bioinformatics research for the CCB, for the benefit of 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 facilitates 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 greatly appreciate how well SA Pathology and the CCB fit with the wider SA research community. SA Pathology strongly supports the Morision Report with its motto of ‘Better health through research’ as this could not epitomise better what we value in SA Pathology as part of our comprehensive commitment to research, teaching and education for the benefit of our patients and our population.
We are delighted to present the 2013 Annual Report of the Centre for Cancer Biology. As you will see below, the CCB has had a highly successful year as measured by publications, peer reviewed grant funds awarded and new advances in cancer diagnostics and treatments. But what has really stood out this year is the alliance being forged between the Department of Health (through SA Pathology) and the University of South Australia to strengthen the CCB in the long term. This new alliance is the product of the realisation that additional resources were needed to grow the CCB and is designed to bolster existing resources to enhance the human potential of the CCB and support cancer research excellence.

Fresh support is being invested in the CCB and new research fellowships are being created to enhance critical mass and bring new cancer expertise into the CCB. We are delighted to note that as part of this overall endeavour, a new facility to accommodate the CCB will be built. This has been possible thanks to funding by the University of South Australia and matching funds provided by the Federal Government to provide the CCB with a flagship building that will ensure its future growth. At a ceremony in June 2013, Prime Minister Julia Gillard announced $40 million federal funds towards this endeavour. The University has recognised the opportunity to create a flagship building and has added significant new funding so that the building can accommodate major complementary facilities. The new building will be erected on the west end side of North Terrace in what is rapidly being known as the SA Health Precinct. The design of the building has been in earnest and we will be updating the community of its progress and no doubt asking for help as we seek to maximise this opportunity. These are truly exciting times for cancer research in South Australia and we would like to thank all those involved in taking the CCB into this new and promising phase.

In 2013, the CCB has continued to make inroads into discovering the causes of certain cancers and through new research and the rapidly expanding ACRF Genomics Facility, has made significant advances in personalised medicine. In terms of discovery, in 2013 we reported in the Proceedings of the National Academy of Sciences how caspase-2, a gene thought to be involved in cell death, suppresses lymphomas; in a paper published in Nature Communications, that a gene often mutated in multiple cancer types controls cell death; and in two papers in Oncogene we reported the discovery of genes involved in tumour initiation and metastasis. Our translational efforts to bring our discoveries closer to patients have been boosted by further involvement of the pharmaceutical industry. The recent agreement between CSL and Janssen on CSL 362 will now enable this candidate drug, based on our antibody 703 against acute myeloid leukaemia, to be tested in patients worldwide. This example of personalised medicine is rapidly being followed by new tests and analyses being developed with our ACRF Genomics Facility. The application of genomics to cancer patients in the setting of the CCB-embedded in the health system promises to revolutionise how we diagnose and treat individual cancer patients. SA Pathology and the CCB have changed the standard way we treat many tumours. Instead of testing for one mutation at a time, we now test for almost 200 mutations in five genes: each one of these gives the clinician treatment options. This is resulting in more patients being enrolled in clinical trials.

In 2013, we published 141 scientific articles encompassing studies on various solid and blood cancers. Our work continues to be well received as indicated by frequent invitations that our Faculty and other staff receive from international cancer institutes and major international scientific meetings. Our younger members are thriving and it is pleasing to see the growing number of graduate students seeking to enrol in Honours and PhD programs at the CCB.

We are pleased to report that in 2013 we continued to receive new peer reviewed funding and fellowships from local, national and international sources. Importantly, many of our new investigators received research grants as well as the more established ones. In the latest round of the highly competitive NHMRC Project Grants, CCB researchers Sharad Kumar, Natasha Harvey, Greg Goodall, Quentin Schwartz, Andrew Zannatino, Tim Hughes, Michael Baird, Richard D’Andria and Michelle Gribbleskson were successful, bringing in over $6 million of research funds. The CCB was also successful in winning a prestigious Program Grant. The Program Grant, led by Professors Angel Lopez, Michael Parkinson (St Vincent’s Institute of Medical Research) and Timothy Hughes, was awarded $6.7 million over five years to investigate the causes of and seek better treatments in leukaemia.

We take much pleasure in reporting that Co-Director Professor Sharad Kumar was recognised for his scientific contributions through the ASBM Lennerng Medal, the FACBMB Research Excellence Award and by being elected a Fellow of the Australian Academy of Science, one of the highest honours bestowed for scientific work in Australia. Associate Professor Natasha Harvey received a prestigious Future Fellowship from the Australian Research Council. Drs Claire Wilson and Craig Wellington-Biedoe received NHMRC Early Career Fellowships to work with Professor Kumar and Professor Pitson respectively.

In 2013 we welcomed as a new member to the CCB Faculty, Associate Professor Ian Lewis. Ian already has established collaborations with CCB scientists and the strong translational impact of his work in leukaemia and bone marrow transplantation is already improving the lives of many cancer patients.

On 20 June 2013, the CCB held its Annual General Meeting, Professor Doug Hilton, Director of the Walter and Eliza Hall Institute, Melbourne, was the invited keynote speaker. He emphasised the importance of resilience and dedication in medical research and noted how the CCB fulfils the mission of the first two pillars of the National Health and Medical research Council, namely achieving transformative discoveries and implementing their translation into better health care. We were referred to as “one of the greatest, if not the greatest, research institutes in the world.”

In 2013 we received $40 million in new funding for our work from the CCB. We look forward to continuing this good work.

As Hanson founders and beneficiaries, we appreciate the continuous hard work by Mark and his team in raising valuable funds for the work of the CCB. We look forward to continuing our close association well into the future.

Professors Angel Lopez and Sharad Kumar
Co-Directors, Centre for Cancer Biology
On the 21 – 23 November 2013 we hosted the 6th Barossa Meeting on the theme of Cell Signalling in the Omics Era. As with previous instalments in this biennial series, the 2013 Barossa Meeting had a strong focus on cutting-edge discoveries in cell signaling and how this knowledge can be exploited to improve human health.

The meeting hosted an array of high profile international speakers including Thomas Brabletz, Arul Chinnaiyan, Vishva Dixit, Ulf Eriksson, Richard Flavell, Wanjin Hong, Richard Moriggl, Luke O’Neill, Nigel Pyne, Veronica Sexl and James Wells. A further 13 invited interstate speakers rounded out a stellar program that attracted the maximum capacity of 130 delegates to the meeting.

The meeting was comprised of ten scientific sessions, including those entitled Cancer Genomics and Epigenetics, VEGFs: the Vasculature and Beyond, Cell Signalling Architecture, Mechanisms of Tumour Progression, Metabolism and Disease, Molecular Therapeutics, Cell Signalling Modules, and Novel Therapeutics. Approaches to meet the challenge of analysing large scale ‘omic’ data sets to answer both specific and global biological questions was a major theme throughout the meeting. This was no better exemplified by the work of Professor James Wells (University of California at San Francisco) who described cutting-edge tools towards understanding apoptosis via global identification of caspase substrates.

In addition to highlighting the latest trends in cell signalling in disease, the Barossa meetings also provide a vehicle for the presentation of the Clifford Prize for Cancer Research. The 2013 recipient was Professor Arul Chinnaiyan of the University of Michigan for his outstanding work in understanding the genetic lesions that contribute to cancer development and progression. The Prize, presented by Ms Jenny Richter, Deputy Chief Executive for System Performance of SA Health, comprised a perpetual trophy crafted by South Australian glass artist Nick Mount, and a magnum of Grange Hermitage donated by Penfolds. With this award Professor Chinnaiyan joins an illustrious list of past winners that include Axel Ullrich (Munich), Tony Hunter (San Diego), John Dick (Toronto) and Vishva Dixit (San Francisco).

As always the 2013 Barossa Meeting provided an intense three and a half days of quality science, complemented by equally impressive food and wine. The gastronomic highlight of the meeting was the food of Elli Beer at the Clifford Prize Dinner held at The Farm, Barossa Function Centre. Delegates at this function were also treated to an impressive list of carefully selected, high quality wines, introduced by wine expert John Leydon.

The Barossa meetings continue to provide outstanding opportunities for students, early career and more established researchers to mix with world class scientists in a convivial, but scientifically rigorous atmosphere conducive to the development of collaborations. As always, the meeting also showcased the quality of South Australian science and continues to develop as one of the premier biomedical research meetings on the scientific calendar.

Professor Stuart Pitson
Convenor, 6th Barossa Meeting
Acute Leukaemia Laboratory
Professor Richard D’Andrea PhD
Associate Professor Ian Lewis MBBS PhD FRACP FRCPA

Acute Myeloid Leukaemia (AML) accounts for 20% of leukaemia in children and is the most common form of acute leukaemia in adults. AML results from the accumulation of immature myeloid cells in the bone marrow and peripheral blood, and is heterogeneous in nature, with many different subtypes classified according to molecular aberrations.

Overall survival for adult AML is still only 30-40% with median overall survival for some high-risk patient groups as low as 10 months. The molecular basis for many subtypes is still largely unclear. With new therapies becoming available there is a clear need to improve patient stratification in order to select the best available treatment for each patient. A better understanding of AML biology is also important to develop new treatments that can be targeted to the specific patient groups that are associated with poor outcomes on standard therapy.

A major focus is understanding the mechanisms underlying normal blood cell development, and the changes associated with haematological malignancy, in particular AML, and pre-leukaemic diseases including Myeloproliferative neoplasms and bone marrow failure syndromes. A significant research focus of our laboratory is the investigation of receptor signalling mechanisms that control stem and progenitor cell responses to a number of key growth factors, and which are commonly up-regulated or mutated in AML. Additionally we have an interest in the genetic changes that lead to altered metabolism in cancerous cells, and the identification and testing of novel therapeutics that target these changes. We also use genetic and epigenetic approaches to identify new genes and mutations that contribute to myeloid disease.

During 2013, the research activities of the Acute Leukaemia Laboratory focused on:

- Promoter methylation status of the GADD45A gene — we showed that this can be used as a prognostic marker in identifying a subset of AML patients who experience a poor outcome from standard therapy.
- Identification of novel mutations in families of genes using high-throughput sequencing for 100 AML samples. Work is ongoing to determine frequency and overlap of mutations in these genes with common AML mutations, and to correlate these mutations with gene expression signatures, altered properties of AML cells, and clinical outcomes.
- Identification of novel pathways that may be targeted in disease cells, and preliminary investigations of selective inhibitors of these pathways using cell line models and primary disease material. This line of research has the potential to identify effective targeted treatments to improve patient outcomes.

Key discoveries 2013

Role of KLF5 and Methylation in AML
We have used a mouse gene-ablation model of KLF5 to show that this transcription factor plays an important role in differentiation of myeloid cells. We have also demonstrated that hyper-methylation of KLF5 contributes to reduced KLF5 expression in AML (Diakiw et al, 2013). Patient survival analyses showed that methylation of intron 1 of KLF5 is associated with poor prognosis (particularly for the ‘intermediate risk’ patient group).

Prognostic Significance of GADD45A promoter hyper-methylation in AML
In 2013 we reported that GADD45A is silenced by methylation in approximately 40% of AML patients. We tested the clinical significance of GADD45A promoter hyper-methylation in a large AML patient cohort (167 AML patients). 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. We also showed that GADD45A methylation is associated with a DNA hypermethylation profile, and with selected mutations in a number of key genes that are frequently mutated in AML. These findings suggest a treatment strategy for these patients with current and emerging hypomethylation agents.

Hyper-methylation of KLF5 intron 1 in AML patients and its correlation with poor overall survival, particularly in the intermediate risk group

Outcomes for the Community
Our research has provided new insights into the biology of AML and important leads for improving treatment of patients with myeloid malignancies. The identification of prognostic markers that may allow identification of subsets of AML patients that will benefit from targeted hypomethylation therapy has potential to improve patient outcomes. The identification of novel pathways that can be targeted with inhibitors to reduce death of diseased cells in AML is also important and we will directly test these approaches using animal models.
Outcomes for the Community

Solid tumours make up the majority of human cancers whereby the progression to metastasis is the main cause of morbidity and mortality in these patients. Currently, there is little effective treatment for metastatic diseases. Our studies aim to increase knowledge of the molecules driving metastasis using multiple strategies so that we may identify and open up avenues for new therapeutics to be developed.

Key discoveries 2013

This year we published works showing that the miR-200 family of microRNAs are critical regulators of cell invasion involved in colon cancer (Paterson et al) and in breast cancer we also identified a key target of miR-200 not associated with its role in regulating epithelial-mesenchymal transition that regulates metastasis in vivo (Li et al).

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

Our primary research interest is to understand how a cancer cell progresses from a benign state, with good prognosis, to a malignant state resulting in metastatic disease. In solid cancers, which constitute 80% of human cancers, the vast majority of deaths are due to metastasis.

The two main areas of research are:

Regulation of protein trafficking by tyrosine phosphorylation

Cells express a range of surface receptors and secrete a range of cytokines and growth factors that influence their growth and the activities of neighbouring cells. However, the spectrum of secreted proteins and cell surface receptors are often vastly altered in cancer cells relative to their cell of origin. These vast changes to the secretome and plasma membrane proteome of cancer cells which can make them grow better, more metastatic or chemoresistant are seemingly coordinated but how this occurs is not understood. We are interested in elucidating the signal transduction pathways that regulate trafficking of receptors and secreted proteins and how these are dysregulated in cancer cells to promote growth and metastasis.

Molecular regulation of cell invasion

The ability of cancer cells to invade their surrounding tissue is critical for their spread to secondary organs. We are identifying molecules critical for assembly and regulation of the invasive machinery in breast cancer and in neuroblastoma, how they act to promote invasion and how they are regulated.
Cytokine Receptor Laboratory

Professor Angel Lopez MMBS PhD FRCPA

Cytokine receptors are important membrane proteins that transduce signals from the immediate environment to elicit a cellular response. As cytokines are released in the extracellular space, cytokine receptors on the cell surface recognize them, initiating a process which ultimately determines whether cells will divide, differentiate or perform other specific functions.

This is a tightly controlled process which, when dysregulated, leads to diseases such as chronic inflammation and cancer. The focus of this laboratory is to understand how a discrete subset of cytokine receptors, termed the βc cytokines, function in health and disease. In particular, our work is relevant in diseases such as leukaemia which exhibit abnormalities in βc cytokine receptor expression, and in asthma where excessive βc cytokine receptor stimulation of myeloid cells in the lung causes recurrent damage.

A major aspect of our work is to understand how βc cytokines recognize their receptors and initiate cellular activities. To facilitate these studies, we have an ongoing need to develop effective methods for the large-scale production of the protein components (PLoS ONE 8, 2013). In collaboration with Prof Parker’s group at St Vincent’s Institute of Medical Research in Melbourne, we are determining the 3-D structure of βc cytokine receptor expression, and in asthma where excessive βc cytokine receptor stimulation of myeloid cells in the lung causes recurrent damage.

As cytokine receptors are activated on the cell surface they trigger a variety of biochemical responses within the cell. We are characterizing these in collaboration with Prof Pittson’s and Dr Guthridge’s laboratories and finding that cytokine receptors themselves can be phosphorylated and activated by the lipid kinase PI-3 kinase leading to extended cell survival with clear implications in leukaemia (PLoS Biology 11, 2013).

As part of this signallingosome, the 14-3-3 adaptor proteins are emerging as key regulatory molecules. We are finding that their exquisite modulation using compounds that alter the 14-3-3 dimer interface have profound consequences on whether cells will live or die.

Interestingly, this 14-3-3 family of proteins so critical in myeloid cell function appear to be important in some brain functions and are linked to dopamine transport activities (Transl Psychiatry 3:e327, 2013).

The influence of βc cytokines in human disease is being pursued in a variety of settings. In allergic inflammation models, we are finding in collaboration with Associate Professor Grimbaldeston and with CSL Limited that βc cytokines are powerful activators of mast cell function and that the pro-inflammatory activity of most cells can be tamed with new compounds that we are developing. In autoimmune diseases, we have found in collaboration with Professor J Schrader (Vancouver) and Professor J-Hamilton (University of Melbourne) that autoantibodies against GM-CSF are pathogenic (PNAS 110, 2013). In several experimental cancer models, we have succeeded in controlling tumour growth with new compounds that inhibit 14-3-3 function. Lastly, in collaboration with Professor T Hughes and CSL Limited, we found that certain human myeloid leukaemias can be controlled in vitro by appropriately targeting CD123 (Br J Haematol 161, 2013). As we understand more and more the mechanism of action of βc cytokines, new opportunities arise to better control some forms of cancer and other diseases.

Structure of the human IL-3 receptor

In collaboration with Professor Parker (St Vincent’s Institute of Medical Research) and CSL Limited, we have solved the structure of the human IL-3 receptor in complex with the Fab fragment of the blocking antibody 7G3/CSL362. Crystal structures of the IL-3 receptor showed the N-terminal domain existing in an “open” and a “closed” state, probably a reflection of the mobility of this domain. In turn, this suggests a dynamic process whereby the “closed” receptor leads to optimal engagement of the βc subunit allowing sustained receptor activation and cellular signalling.

Anti-leukaemic activity of the anti-CD123 antibody CSL362

In collaboration with CSL Limited, we have found that the antibody CSL362, optimized for antibody-dependent cell-mediated cytotoxicity, is a strong enabler of NK cell killing of acute myeloid leukaemia cells in vitro and in vivo animal models. We have also extended these observations to chronic myeloid leukaemia in collaboration with Professor T Hughes, Professor D White and CSL Limited in which leukaemia stem-like cells over-express CD123 and are susceptible to CSL362-mediated NK cell killing.

Key discoveries 2013

- Structure of the human IL-3 receptor
- Anti-leukaemic activity of the anti-CD123 antibody CSL362

Outcomes for the Community

We have continued to uncover the molecular basis of βc receptor activation. This understanding is essential for generating breakthroughs that can then be exploited to devise new therapeutics. We are delighted that after many years of work on the human IL-3 receptor, the antibody CSL362 against this receptor is currently in clinical trials in the USA and Australia for the treatment of acute myeloid leukaemia.
Our studies aim to advance the knowledge of biology of bowel cancer and its precursor lesions including conventional adenomas and serrated polyps.

Until recently, the serrated polyps were regarded as innocuous, non-neoplastic lesions with no malignant potential. We are particularly interested in characterization of colorectal cancers bearing somatic BRAF V600E mutation as these tumours are particularly aggressive and do not respond to conventional chemotherapy treatment.

We have recently demonstrated elevation of Claudin1 expression in colorectal serrated polyps with BRAF V600E mutation. This finding significantly widens the serrated polyp spectrum and provide additional support for a close relationship between BRAF mutated hyperplastic polyp and sessile serrated adenoma which may, in fact, represent a continuous spectrum of the same neoplastic process.

We are also involved in discovery and validation of biomarkers of colorectal neoplastic lesions and actively working on the development of accurate non-invasive blood based test for detection of colorectal cancer and its precursors.

Our research work on the serrated pathway and biomarkers of colorectal cancer is conducted in close collaboration with researchers from CSIRO, gastroenterologists and colorectal surgeons.

Our interest in familial colorectal cancer including Hereditary non-Polyposis Colorectal Cancer (HNPCC, Lynch syndrome) resulted in several publications including international multicenter collaborative studies evaluating practicality of various approaches in clinical practice. Our laboratory (NATA accredited) was one of the first in Australia to offer testing for mismatch repair genes immunohistochemistry in a diagnostic setting.

Our laboratory staff are responsible for operations of the Colorectal Cancer Tissue Bank which holds samples of colorectal cancers and other gastrointestinal tumours, colorectal polyps, 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 laboratories of the Centre for Cancer Biology.

Mismatch repair genes immunohistochemistry is used to screen for hereditary colorectal cancer (Lynch syndrome, HNPCC). Loss of nuclear protein expression indicates inactivated gene prioritising gene mutation analysis. This case demonstrates concomitant loss of MSH2 and MSH6 proteins (B and D respectively) in the cancer tissue and preserved expression of MLH1 and PMS2 proteins (A and C respectively). Subsequent mutation study revealed a germ line mutation in the MSH2 gene.

Using Next Generation Sequencing we have identified a group of genes which are frequently mutated in sessile serrated adenomas and serrated pathway colorectal cancers including a particularly aggressive form of this disease characterised by BRAF V600E mutation and intact mismatch repair system.

After successfully adopting a novel technique of detection of cell-free circulating tumour DNA in patients with colorectal cancer we are evaluating this method as a potential tool for detection of early recurrence of cancer and response to chemotherapy. This non-invasive method allows detecting tumour specific somatic mutations in patient’s bloodstream potentially eliminating the need for repeated tumour biopsies.

Key discoveries 2013

Outcomes for the Community

Our studies aim to advance the knowledge of biology of bowel cancer and its precursor lesions including conventional adenomas and serrated polyps. This is a necessary step to improve early detection and treatment options of the disease which is the second most common cause of cancer related death in Australia, killing 4000 patients each year.
Several years ago in collaboration with the Khew-Goodall lab, we made the fortunate discovery of a microRNA family that has remarkably potent effect on controlling epithelial to mesenchymal transition (EMT), a process now recognised to be crucial for solid cancers such as breast, colon and prostate cancer to metastasise and thereby be lethal.

Gene Regulation Laboratory
Professor Greg Goodall PhD

Since our report on this in 2008 (Gregory et al, Nature Cell Biol, now cited over 1500 times) we have been investigating how this family of microRNAs (called miR-200) has its inhibitory effects on cancer metastasis and how the microRNAs themselves are regulated. We have developed methods to detect where the microRNAs are located in tumours, allowing us to confirm the role that miR-200 has in colon cancer invasion; we have used laboratory models of breast cancer to identify the pathways through which miR-200 has its effects; and we have studied the molecular mechanisms that act on the miR-200 gene to determine its activity.

Identification of an enhancer that controls miR-200b-200a-429 gene expression in breast cancer cells
To better understand how expression of the miR-200 family of microRNAs is regulated, we analyzed the miR-200 gene region for epigenetic modifications that are likely to influence activity of the miR-200 gene in breast cancers. We discovered a region of the gene that has the epigenetic modifications typical of a regulatory region that enhances gene activity. We constructed chimeric reporter genes incorporating this region and found it could increase gene activity 27-fold in breast epithelial cells. Furthermore, we found that a region of this activity enhancer was itself active at producing RNA, although ectopic over-expression of this enhancer RNA did not affect the miR-200b-200a-429 gene activity. While additional investigations of the miR-200b enhancer RNA function will be necessary, it is possible that it may be involved in interactions with the the miR-200b-200a-429 gene that control its activity. (Attama et al, Plos One, 2013)

Epigenetic modulation of the miR-200 family is associated with transition to a breast cancer stem cell-like state. Because breast cancer stem cells resemble cells that have undergone epithelial-mesenchymal transition, and the miR-200 family is a key regulator of EMT, we investigated whether miR-200 has a role in controlling the transition between cancer stem cell-like and non-stem-cell-like states. We found immortalized human mammary epithelial (HMLE) cells can undergo spontaneous conversion from a non-stem to a stem-like phenotype and this conversion was accompanied by the loss of miR-200 expression. Stem-like cells isolated from metastatic breast cancers also displayed loss of miR-200 indicating similar molecular changes may occur during breast cancer progression. The phenotypic change observed in HMLE cells was directly controlled by miR-200 because restoration of its expression decreased stem-like properties while promoting a transition to an epithelial phenotype. Investigation of the mechanisms controlling miR-200 expression revealed both DNA methylation and histone modifications were significantly altered in the stem-like and non-stem phenotypes. In particular, in the stem-like phenotype, the miR-200b-200a-429 cluster was silenced primarily through polycomb group-mediated histone modifications whereas the miR-200c-141 cluster was repressed by DNA methylation. These results indicate that the miR-200 family plays a crucial role in the transition between stem-like and non-stem phenotypes and that distinct epigenetic-based mechanisms regulate each miR-200 gene in this process. Therapy targeted against miR-200 family members and epigenetic modifications might therefore be applicable to breast cancer. (Jim et al, J Cell Sci, 2013).

Outcomes for the Community
Our discoveries indicate potential avenues towards development of drugs that block cancer metastasis. They have influenced many labs around the world to take up investigation of the role of miR-200 in cancer metastasis, with our publications receiving 1260 citations in 2013.
Haematology Clinical Research Unit

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

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

Outcomes for the Community

The Haematology Clinical Research Unit has a core translational focus of improving the treatment of patients with malignant and non-malignant diseases of the blood. This is achieved through collaborations with fundamental research groups, involvement in clinical trials utilizing novel agents and provision of key infrastructure to facilitate these activities. A key outcome for 2013 is the establishment of the South Australian Cancer Research Biobank which is now processing and banking leukaemia samples from patients across major hospitals in Adelaide.

Clinical Trials 2013

1. Therapeutic infusion of most closely HLA-matched third party donor-derived virus-specific cytotoxic T lymphocytes in patients with active viral reactivation post-allogeneic stem cell transplantation. FuACT
   Principal Investigator: Dr Agnes Yong
   2. A Phase 1, Randomised, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Istasalab (GS-1101) in Combination with Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas. GS-US-313-0124
   Principal Investigator: Dr Pratyusha Giri

3. A Phase 3, Randomised, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Istasalab (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas. GS-US-313-0125
   Principal Investigator: Dr Pratyusha Giri

4. A Phase 3, Multicentre, Randomised, Double-Blind Study to Compare the Efficacy and Safety of Oral Azacitidine Plus Best Supportive Care versus Placebo plus Best Supportive Care in Subjects with Red Blood Cell Transfusion-dependent Anaemia and Thrombocytopenia Due to PSS Lower Risk Myelodysplastic Syndromes. AA-ZDS-003
   Principal Investigator: Dr Devendra Hiarase

5. A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Protective Efficacy and Safety of a Therapeutic Vaccine, AS1013, in Cytomegalovirus (CMV)-Seropositive Recipients Undergoing Allogeneic Haematopoietic Cell Transplant (HCT)
   Principal Researcher: Associate Professor Ian Lewis

6. A phase II multi-centre, open label, randomized study to assess safety and efficacy of two different schedules of oral LDE225 in adult patients with relapsed/refractory or untreated elderly patients with acute leukaemia. LDE225X2203
   Principal Investigator: Associate Professor Ian Lewis

7. An Open-label, Single-arm, Multicenter Phase 2 Study of the Bruton’s Tyrosine Kinase Inhibitor PCI-32765 (B rated) in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma with 17p Deletion. PCYGC-1117-CA
   Principal Investigator: Professor Bik To

8. A Randomized, Open-label Phase 3 Study of Carfilzomib, Mantelpalin, and Prednison versus Bortezomib, Melfalan, and Prednison in Transplant-Indegeous Patients with Newly Diagnosed Multiple Myeloma. 2012-035
   Principal Investigator: Dr Noemi Horvath

9. A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton’s Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (B rated), in Combination with Bendamustine and Rituximab (BR) in Subjects With Newly Diagnosed Mantle Cell Lymphoma. PCI-32765MCL3002 (SHINE)
   Principal Investigator: Dr Pratyusha Giri

10. A Phase II, single arm, open label study of treatment-free remission in Chronic Myeloid Leukaemia (CML) chronic phase (CP) patients after achieving sustained MR4.5 on nilotinib. CAMRF017A2408
    Principal Investigator: Professor Timothy Hughes

11. A Phase 3, randomised, double-blind, placebo-controlled study to compare the efficacy and safety of oral azacitidine plus best supportive care as maintenance therapy in subjects with Acute Myeloid Leukemia in complete remission. CC-486-AML-001
    Principal Investigator: Associate Professor Ian Lewis

12. An open-label, multicentre, single-arm, phase 2 study of PCI-32765 (B rated) in subjects with refractory follicular lymphoma. PCI-32765FL2002 (DAMN)
    Principal Investigator: Dr Pratyusha Giri

    Principal Investigator: Professor Tim Hughes

    Principal Investigator: Dr Pratyusha Giri

15. A prospective randomised Phase II study of single agent pomalidomide maintenance versus combination pomalidomide and low dose dexamethasone maintenance following induction with the combination of pomalidomide and low dose dexamethasone in patients with relapsed and refractory myeloma previously treated with Lenalidomide. ALLG MM14
    Principal Investigator: Dr Noemi Horvath

    Principal Investigator: Dr Pratyusha Giri

17. A pilot study exploring the impact of nursing case management and comprehensive genatic assessment on patients with MDS.
    Principal Investigator: Dr Simon McRae

18. A Phase 3 Randomised, Double-blind, Multicentre Study Comparing Oral MLN9708 plus Lenalidomide and Dexamethasone versus Placebo plus Lenalidomide and Dexamethasone in Adult Patients with Relapsed and/or Refractory Multiple Myeloma. 120010
    Principal Investigator: Dr Noemi Horvath
Control of the innate immune response

The early cellular innate response to a viral infection involves various signalling cascades that culminate in the production of hundreds of interferon-stimulated genes (ISGs), most with unknown function. Work in our laboratory looks at defining which ISGs are important anti-viral effectors, and delineating their function. We have previously demonstrated the ISG viperin to be anti-viral against HCV, HIV and Dengue virus. Recent data from our laboratory has been able to show that viperin is also able to modulate a number of innate immune signalling cascades, as well as impact the bacterial Recyclo. This is the first time that an interferon stimulated gene has been shown to limit such a wide variety of pathogens, including both DNA and RNA-viruses, as well as bacteria, and also play a role in control of cellular innate signalling in response to pathogens, making viperin one of the most potent ISGs described to date. We have recently developed a knockout murine model of viperin to continue examining its role in early innate immunity.

HCV genotype 6 replication and antivirals

The hepatitis C virus (HCV) is classified into six genotypes according to the specific sequence of the virus. Genotype-6 HCV is particularly common in the Asia-Pacific region, especially in Thailand and Egypt. However, as the majority of hepatitis C infections globally are classified as genotype-1 or -2, genotype-6 hepatitis C virus is a neglected area of research. For example, the new direct acting antivirals (DAAs) targeting the HCV NS3 serine protease are only licensed to treat patients with genotype-1 infection. A major reason for this is the lack of models to study genotype-6 HCV replication in the laboratory. We developed a new model for genotype-6 HCV that allows us to study the effect of DAAs specifically targeting the HCV NS3 protease. We have used this model to investigate the effectiveness of a currently available NS3 specific DAA (boceprevir) and found that it is able to inhibit HCV replication with similar efficacy to that of HCV genotype 1. These studies are significant in that they suggest that the HCV NS3 inhibitor, boceprevir can significantly impact genotype 6 HCV replication, which will form the basis for clinical trials in regions where HCV genotype 6 is endemic.

Dynamic imaging of HCV replication complexes:

Like all positive strand RNA viruses, HCV infection induces cytoplasmic membrane rearrangements that support and compartmentalize the replication of its genome. Using a combination of fluorescent labelling approaches (tetracysteine tags, fluorescent proteins and SNAP tags) we have developed techniques to image the localization and dynamics of HCV proteins NS5A and core, HCV RNA and relevant host cell factors in living virus-producing cells. We have demonstrated that the traffic of NS5A positive cytoplasmic structures throughout the cytoplasm depends on an intact microtubule network and the dynein motor protein complex. Furthermore we have demonstrated that both relatively static and highly motile NS5A structures are enriched with fluoroceantly labelled HCV RNA and the host cell factors VAP-A and Rab5A. Finally we have visualised the association of NS5A positive Rac1s with core-coated lipid droplets in the context of a productive infection and demonstrated the interaction of these proteins by proximity ligation assays. Through the use of pharmacological inhibitors of cellular pathways and viral protein function we are now in a position to further dissect aspects the HCV life cycle in real-time.

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 with the new HCV DAAs will inform therapeutic strategy in particular with HCV genotype 6 that predominates in Asia.

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 (DAA) 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 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. Through these approaches we hope to add to our understanding of how HCV causes disease and identify novel therapeutic targets. Specific areas of research include:

- Investigating the interferon stimulated gene response (ISG) in HCV infection and the identification and characterization of novel antiviral ISGs. We are specifically interested in ISG control of the positive RNA strand flavivirus family.
- Understanding the dynamics of viral replication at the cellular level using a live cell imaging approach to study HCV replication in real time. We are also interested in visualising HCV RNA in real time and have engineered HCV genomes containing the bacteriophage MS2 detection system that allows us to track RNA in living cells.
- Exosomes are small membrane vesicles that contain cellular RNA and protein and represent a novel mechanism of cellular communication. We are interested in how viral infection may change the composition of exosomes that may in turn impact pathogenesis.

Key discoveries 2013

Hepatitis C Virus Laboratory

Associate Professor Michael R Beard

Hepatitis C Virus Laboratory

Guillaume Fiches | Nicholas Eyre | Karla Helbig | Amanda Aloia

Erin McCartney | Onruedee Khantisitthiporn | Sumudu Narayana | Viet Hoang

Live cell imaging of the hepatitis C virus NS5A and core proteins during a productive infection

HCV core protein (tetracysteine-tagged and labeled with ReAsH; red) predominantly localized to cytoplasmic lipid droplets (LDs), while mature NS5A (tetracysteine-tagged; green) were irreversibly compartmentalized to core capped LDs.

PhD

Hepatitis C Virus Laboratory 21

Centre for Cancer Biology  Annual Report 2013
The early molecular response to drug therapy can identify patients who may be able to stop taking their medication. Tyrosine kinase inhibitor drugs have made a remarkable difference to survival for patients with CML. Most patients can now enjoy a normal life expectancy as long as they continue to take their medication regularly. This year the results of an Australian study that commenced in 2004 was published that investigated the possibility of stopping medication without relapse. Patients were carefully selected and had received therapy for at least 3 years and had a very good response during that time. Their leukaemia was not detected using sensitive techniques. About 40% of the patients who enrolled in the study did not relapse. Those who did relapse were very quickly and safely rescued by restarting their medication. The study demonstrated that it is safe to stop therapy under very controlled conditions for some carefully selected patients.

Another study of more than 400 patients identified the factors that predict which patients may eventually be able to undertake a trial of stopping therapy. We found that very few patients actually achieve the criteria for stopping. Females and those patients who had a very rapid initial response to therapy are more likely to be able to stop. The outcome from this study is that more patients may be able to reach the criteria for stopping if they are treated with a more potent kinase inhibitor. This will benefit patients who currently face the prospect of lifelong therapy with ongoing side effects.

The rate of leukaemic cell death may be an important factor for response. Those with a very rapid initial response have been identified as having the best long-term prospects, whereas those with a slow response may need a change of therapy to avoid disease progression and death. Optimisation of therapy is frequently needed for the best outcomes.

Biological factors, such as a patient’s inherited genetic makeup, may play a role in the dynamics of leukaemic cell death (apoptosis) and hence affect an individual’s response to therapy. We are investigating genes involved in the apoptotic process to determine if inherited factors modulate leukaemic cell death (apoptosis) and hence affect an individual’s response to therapy. We are also investigating genes involved in the monitoring of treatment response and the early prediction of drug resistance. Biological factors, such as a patient’s inherited genetic makeup, may play a role in the dynamics of leukaemic cell death (apoptosis) and hence affect an individual’s response to therapy. We are investigating genes involved in the apoptotic process to determine if inherited factors modulate treatment response. Our aim is to identify biomarkers at the time of diagnosis that will predict response and to guide the most appropriate type of drug the patient should receive. We are also using new technology to search all genes for acquired, harmful mutations that may be present at the time of diagnosis of disease. This may lead to rapid disease progression. This only occurs in a few patients but can lead to devastating consequences. Our research continues to offer guidance to haematologists in terms of appropriate monitoring of treatment response and the early prediction of drug resistance.

Outcomes for the Community

Our research has benefited some patients with CML by identifying the factors that may lead to a trial of drug cessation. Although side effects in some patients may be minor, they can impact the long-term quality of life. Stopping therapy successfully means that patients may be able to lead a normal life. Additionally, the cost saving of drug therapy for the community is substantial and millions of dollars could be saved annually.

Key discoveries 2013

Drug resistance causing BCR-ABL1 mutations can remain dormant for many years and lead to drug resistance with a change of therapy. Some patients develop resistance to kinase inhibitor therapy. The main mechanism is a mutation within the gene that causes CML, BCR-ABL1. These mutations interfere with drug binding, but for most mutations a change of therapy restores sensitivity. The new therapy needs to be carefully selected to ensure that the mutation does not cause resistance to the new drug as well. By carefully monitoring patients with mutations over many years who had changed therapy, we found that some sensitive mutations are not eradicated by the new drug, but remain dormant and undetectable. These patients should not receive another therapy change if their historical mutation causes resistance to the next drug. In these cases, the dormant mutation can rapidly grow, cause resistance again and lead to a very poor outcome. Our study demonstrated for clinicians the importance of knowing the patient mutation history and considering the history when making therapeutic decisions.
Lymphatic Development Laboratory

Associate Professor Natasha Harvey PhD

Lymphatic vessels are a key component of the cardiovascular system. These specialised vessels maintain fluid homeostasis, absorb fats from the digestive tract and are an important highway for immune cell traffic. Defects in the growth and development of lymphatic vessels underlie human disorders including primary lymphoedema, lymphangiectasia, and lymphangioma.

Cancer cells exploit the lymphatic vasculature as a route for metastasis and in some cases, promote the growth of new lymphatic vessels within the tumour environment as a means to gain entry to this vascular highway and thereby spread throughout the body. The focus of our laboratory is to understand how the lymphatic vascular network is constructed during development.

We are interested in identifying and characterising genes that are important for lymphatic vessel growth, patterning and maturation. Once we understand how lymphatic vessel growth and development is normally controlled, we will gain new insight into how this process 'goes wrong' in human disease and moreover, will be afforded the opportunity to rationally design novel therapeutics able to block or promote lymphatic vessel growth and/or function and thereby treat human lymphatic vascular disorders.

Outcomes for the Community

Lymphatic vessels are of major importance to cancer patients. Cancer cells exploit lymphatic vessels as a ‘highway’ for metastasis and can enter pre-existing lymphatic vessels, or promote the growth of new lymphatic vessels in order to gain access to the lymphatic vascular network. Lymphatic vessel damage following lymph node resection results in secondary lymphoedema, a disabling condition for a substantial proportion of cancer patients. There are currently no effective, curative treatments for lymphoedema.

By understanding the signals that control the growth and development of lymphatic vessels, we hope to design new therapeutics that either block, or promote lymphatic vessel growth. Blocking agents should prove valuable for the inhibition of tumour metastasis, while growth promoting agents could provide novel therapeutics for the treatment of secondary lymphoedema.

Key discoveries 2013

Defining the role that GATA2 plays in lymphatic vessel development

In collaboration with Professor Hamish Scott’s team at the Centre for Cancer Biology, we recently discovered that heritable mutations in the transcription factor GATA2 predispose carriers to lymphoedema and myelodysplasia syndrome (MDS)-acute myeloid leukaemia (AML) (Kazenwadel et al, Blood, 2012). This discovery revealed a key role for GATA2 in lymphatic vessel growth, maturation and/or function. We have subsequently shown that GATA2 is present at high levels in lymphatic vessel valvules and that GATA2 regulates the expression of genes required for valve development. Our current work aims to define precisely how GATA2 regulates the development of lymphatic vessel valves, in order to understand how GATA2 mutations result in lymphoedema. Ultimately, we aim to identify new therapeutic targets to which effective therapeutics for the treatment of lymphoedema could be designed.

Precise control of retinoic acid levels is important for development of the lymphatic vasculature

During lymphatic vascular development in the mammalian embryo, a subset of endothelial cells in the cardinal veins is programmed to adopt a lymphatic endothelial fate once they ‘switch on’ the transcription factor Prox1. However, very little is known about how the size of this progenitor pool is programmed. In collaboration with Dr Mathias Francois at the Institute for Molecular Bioscience, Brisbane, we have shown that genetic modulation of retinoic acid levels has a dramatic impact on lymphatic endothelial progenitor cell specification and lymphatic vascular development (Bowles et al, Dev Biol, 2013). Increased levels of retinoic acid resulted in many more lymphatic endothelial progenitor cells present within the cardinal veins and accordingly, in greatly enlarged lymphatic vessels. Conversely, reduced levels of retinoic acid resulted in smaller lymphatic vascular structures. This work revealed that precise regulation of retinoic acid levels is important for normal development of the lymphatic vasculature.

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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, point 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.

Vitamin D3 metabolites repress IgE-mediated mast cell activation

Mast cells have long been recognized as active participants of the allergic response at specific sites. Whether in the skin or the lung, the binding and cross-linking of IgE on the surface of mast cells stimulates the release of inflammatory mediators that exacerbate the allergic response. Our new findings demonstrate that the pro-inflammatory properties of MCs in certain IgE-dependent immune settings can be reduced upon vitamin D3 metabolite administration. Utilizing the powerful tool of mast cell-deficient c-kit mutant mice, that can be successfully repaired of their mast cell deficiency by selective engraftment of bone marrow-derived cultured mast cells, we observed that topical cutaneous application of biologically active (1a,25(OH)2D3) or inactive (25OHD3) 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 (Journal Allergy Clinical Immunology, in press).

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 collaboration with Dr Michael Samuel (CCB), Dr Thomas Gobberdort (University of Melbourne) and Professor Gunnar Pejler (Uppsala, Sweden), we are investigating the important question of whether mast cell function at the peri-lesional interface provides a permittive tumourigenic environment or guards against rapid neoplastic progression during skin carcinogenesis. At the molecular level we have identified that at certain stages of UVB-induced neoplastic progression, mast cells protect against detrimental inflammation and tissue changes by secreting IL-10 and the chymotrypsin-like protease, mast cell protease 4.

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 my laboratory, together with Professor Angel Lopez (CCB), formed a partnership 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 (Commercial in Confidence) with such efficacy in vitro and we are now investigating them for their therapeutic potential utilizing humanised mouse models of nasal polyp growth, and thereby establishing proof of principle prior to engagement in Phase I clinical trials.
The primary focus of this laboratory is translational research into Chronic Myeloid Leukaemia (CML), characterised by the constitutively active tyrosine kinase Bcr-Abl, and more recently also Acute Lymphoblastic Leukaemia (ALL).

While the majority of patients with these malignancies respond well to current therapies, there is no real cure and a significant proportion of patients are likely to develop resistance to these therapies leading to relapse and/or persistent disease.

Research in The Melissa White Memorial Laboratory strives to understand the underlying biological principles of resistance to therapy, to evaluate the usefulness and clinical relevance of novel targeted therapies and to develop tests to identify poor responders at diagnosis, so that therapy can be altered accordingly.

Chronic myeloid leukaemia (CML) is characterised by the Philadelphia chromosome that results from a reciprocal translocation between the long arms of chromosome 9 and 22. This translocation results in a fusion of the BCR and ABL1 genes, and this fusion gene 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 leukemia and is invariably fatal. The development of first, second and third generation tyrosine kinase inhibitors (TKIs: imatinib, nilotinib, dasatinib and most recently ponatinib) has revolutionised targeted therapy and markedly improved treatment outcomes for CP-CML patients.

Despite the remarkable efficacy of tyrosine kinase inhibitors (TKIs) in eliminating differentiated chronic myeloid leukaemia (CML) cells, recent evidence suggests that leukemic stem and progenitor cells (LSPCs) persist long-term, which may be partly due to cytokine-mediated resistance. We evaluated the expression of the IL-3 receptor α subunit (CD123), an established marker of acute myeloid leukaemia (AML) stem cells, on CML LSPCs and the potential of targeting those cells with the humanised anti-CD123 monoclonal antibody CSL362. Compared to normal donors CD123 expression was higher in CD34+/CD38+ cells of both chronic phase and blast crisis CML patients, with levels increasing upon disease progression. CSL362 effectively targeted CML LSPCs by selective antibody-dependent cell-mediated cytotoxicity (ADCC)-facilitated lysis of CD123+ cells and reduced leukemic engraftment in mice. Importantly, not only health donor allogeneic natural killer (NK) cells were able to mount an effective CSL362-mediated ADCC response, but also CML patients’ autologous NK cells.

Most patients with chronic myeloid leukemia (CML) treated with imatinib will relapse if treatment is withdrawn. We conducted a prospective clinical trial of imatinib withdrawal in 40 chronic-phase CML patients who had sustained undetectable minimal residual disease (UMRD) by conventional quantitative polymerase chain reaction (PCR) on imatinib for at least two years. Patients stopped imatinib and were monitored frequently for molecular relapse. At 24 months, the actuarial estimate of stable treatment-free remission was 47.1%. Most relapses occurred within four months of stopping imatinib, and no relapses beyond 27 months were seen.

In the 21 patients treated with interferon before imatinib, a shorter duration of interferon treatment before imatinib was significantly associated with relapse risk, as was slower achievement of UMRD after switching to imatinib. Highly sensitive patient-specific BCR-ABL DNA PCR showed persistence of the original CML clone in all patients with stable UMRD, even several years after imatinib withdrawal. No patients with molecular relapse after discontinuation have progressed or developed BCR-ABL mutations (median follow-up, 42 months). All patients who relapsed remained sensitive to imatinib re-treatment. These results confirm the safety and efficacy of a trial of imatinib withdrawal in stable UMRD with frequent, sensitive molecular monitoring and early issuance of molecular relapse. (Blood. 2015; 122(4): 515-522)

Monoclonal antibody targeting of IL-3 receptor α with CSL362 effectively depletes CML progenitor and stem cells. Despite the remarkable efficacy of tyrosine kinase inhibitors (TKIs) in eliminating differentiated chronic myeloid leukemia (CML) cells, recent evidence suggests that leukemic stem and progenitor cells (LSPCs) persist long-term, which may be partly due to cytokine-mediated resistance. We evaluated the expression of the IL-3 receptor α subunit (CD123), an established marker of acute myeloid leukemia (AML) stem cells, on CML LSPCs and the potential of targeting those cells with the humanized anti-CD123 monoclonal antibody CSL362. Compared to normal donors CD123 expression was higher in CD34+/CD38+ cells of both chronic phase and blast crisis CML patients, with levels increasing upon disease progression. CSL362 effectively targeted CML LSPCs by selective antibody-dependent cell-mediated cytotoxicity (ADCC)-facilitated lysis of CD123+ cells and reduced leukemic engraftment in mice. Importantly, not only health donor allogeneic natural killer (NK) cells were able to mount an effective CSL362-mediated ADCC response, but also CML patients’ autologous NK cells. In addition, CSL362 also neutralized IL-3-mediated rescue of TKI-induced cell death. Notably, combination of TKI and CSL362 induced ADCC caused even greater reduction of CML progenitors and further augmented their preferential elimination over normal hematopoietic stem and progenitor cells. Thus, our data supports the further evaluation of CSL362 therapy in CML.
Molecular Pathology Research Laboratory

Professor Hamish S Scott | Bergithe Oftedal | Young Lee | Lucia Gagliardi | Chan-Eng Chong

Many 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 can either 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 to treat and monitor these diseases. Our “model” diseases are typically blood cell diseases such as leukemias, lymphomas and autoimmunity (e.g. arthritis). These diseases are mechanistically linked, being caused by excessive clonal expansion of a specific blood cell type, and often occur together. We also work on rare, or orphan, diseases with unmet clinical need, such as genetic diagnoses for family planning.

Recent discoveries include our genetic studies of Familial Bilateral Macronodular Adrenal Hyperplasia (BMAH), which is a rare cause of Cushing’s syndrome, a disease characterised by the excessive effects of long-term cortisol excess. These include: insulin resistance and diabetes, hypertension, visceral obesity, osteoporosis and fragile fractures and a predisposition to venous thromboembolism. Early diagnosis is paramount in reducing disease morbidity. Whilst previously considered to occur sporadically, we and others have reported on families affected by BMAH. The onset of Cushing’s in BMAH is typically insidious, making early diagnosis difficult and until recently, potentially affected individuals from BMAH kindreds could only be identified by repeated clinical, biochemical and radiological screening. We undertook genetic studies to identify the inherited basis of familial BMAH in three kindreds in which we previously phenotyped. Whole exome capture and sequencing of two affected individuals from each of three BMAH kindreds identified a single gene (ARMC5) harbouring novel variants in all exome samples. Others have reported ARMC5 mutations occurring in approximately 65% of patients with “sporadic” forms of BMAH.

BMAH-01

BMAH-02

BMAH-03

Segregation analysis of the ARMC5 variant in kindreds BMAH-01, BMAH-02 and BMAH-03

Within kindreds, the variant segregated with the disease phenotype as defined by a diagnosis of Cushing’s syndrome or the presence of adrenal nodules. In BMAH-03: B-1: One of four offspring carried the variant B-3 and B-4. One offspring from each individual was tested and negative for the variant B-5. Two offspring were tested and negative for the variant SNV – single nucleotide variant.

Indicates individuals who were exome sequenced

Indicates the variant

Indicates the number of offspring – gender not specified

Outcomes for the Community

Our discoveries imply that what were previously regarded as predominantly sporadic diseases can in fact be due to germline mutations in many affected patients. Furthermore, the discovery of the germline basis of BMAH has enabled the development of a diagnostic genetic test at SA Pathology for ARMC5 mutations. This will be of benefit to BMAH families because genetic testing will identify mutation carriers, who would benefit from periodic clinical screening and testing, whilst sparing those who do not carry the mutation from unnecessary investigations.

Key discoveries 2013

Familial PAX5 mutations confer susceptibility to pre-B cell acute lymphoblastic leukemia

Somatic alterations of the lymphoid transcription factor gene PAX5 (also known as BSAP) are a hallmark of B cell precursor acute lymphoblastic leukemia (B-ALL), but inherited mutations of PAX5 have not previously been described. Here we report a new heterogeneous germline variant c.547G>A (p.Gly183Ser), affecting the octapeptide domain of PAX5 that was found to segregate with disease in two unrelated kindreds with autosomal dominant B-ALL. Leukemic cells from all affected individuals in both families exhibited 9p deletion, with loss of heterozygosity and retention of the mutant PAX5 allele at 9p13. Two additional sporadic ALL cases with 9p loss harbored somatic PAX5 substitutions affecting Gly183. Functional and gene expression analysis of the PAX5 mutation demonstrated that it had significantly reduced transcriptional activity. These data extend the role of PAX5 alterations in the pathogenesis of pre-B cell ALL and implicate PAX5 in a new syndrome of susceptibility to pre-B cell neoplasia.

Genetic studies of Familial Bilateral Macronodular Adrenal Hyperplasia

Bilateral macronodular adrenal hyperplasia (BMAH) is a rare cause of Cushing’s syndrome, a disease characterised by the excessive effects of long-term cortisol excess. These include: insulin resistance and diabetes, hypertension, visceral obesity, osteoporosis and fragile fractures and a predisposition to venous thromboembolism. Early diagnosis is paramount in reducing disease morbidity. Whilst previously considered to occur sporadically, we and others have reported on families affected by BMAH. The onset of Cushing’s in BMAH is typically insidious, making early diagnosis difficult and until recently, potentially affected individuals from BMAH kindreds could only be identified by repeated clinical, biochemical and radiological screening. We undertook genetic studies to identify the inherited basis of familial BMAH in three kindreds in which we previously phenotyped. Whole exome capture and sequencing of two affected individuals from each of three BMAH kindreds identified a single gene (ARMC5) harbouring novel variants in all exome samples. Others have reported ARMC5 mutations occurring in approximately 65% of patients with “sporadic” forms of BMAH.

Aire dependent Thymic Deletion and Regulatory T Cells Prevent Anti-myeloperoxidase Glomerulonephritis (GN)

Loss of tolerance to neutrophil myeloperoxidase (MPO) underlies the development of ANCA-associated vasculitis and GN, but the mechanisms underlying this loss of tolerance are poorly understood. Here, we assessed the role of the thymus in deletion of autoreactive anti-MPO T cells and the importance of peripheral regulatory T cells in maintaining tolerance to MPO and protecting from GN. Thymic expression of MPO mRNA predominantly localized to medullary thymic epithelial cells. To assess the role of MPO in forming the T cell repertoire and the role of the autoimmune regulator Aire in thymic MPO expression, we compared the effects of immunizing Mpo2/2 mice, Aire-/- mice, and control littermates with MPO. Immunized Mpo2/2 and Aire-/- mice developed significantly more proinflammatory cytokine-producing anti-MPO T cells and higher ANCA titers than control mice. When we triggered GN with a subnephritogenic dose of anti-glomerular basement membrane antibody, Aire-/- mice had more severe renal disease than Aire+/- mice, consistent with a role for Aire-dependent central deletion in establishing tolerance to MPO. Furthermore, depleting peripheral regulatory T cells in wild-type mice also led to more anti-MPO T cells, higher ANCA titers, and more severe GN after immunization with MPO. Taken together, these results suggest that Aire-dependent central deletion and regulatory T cell-mediated peripheral tolerance both play major roles in establishing and maintaining tolerance to MPO, thereby protecting against the development of anti-MPO GN.
Our broad research focus is on cellular and molecular basis 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 (2) understanding the regulation of cellular homeostasis by ubiquitination.

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

Ubiquitination (attachment of ubiquitin to a target protein) is a common type of protein modification that is involved in the regulation of protein stability, degradation, localization 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. 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 disease.

Outcomes for the Community
Our research will provide a better understanding of disease mechanisms and the functioning of the human body. For example, we have identified Nedd4-2 as a regulator of ion channels in the central nervous system, which are involved in pain and epilepsy. We are also deciphering the mechanism of key genes involved in cell death, ageing and tumour progression, including Caspase-2 and UTX. These findings provide the potential to discover new disease markers and novel therapeutic targets.
Key discoveries 2013

Sphingosine kinase contributes to cancer progression through transferrin receptor 1

Sphingosine kinase shows considerable promise as a target for anti-cancer therapy in a diverse range of solid tumours and leukemias. To date, however, the mechanisms whereby sphingosine kinase enhances cancer progression have been not well understood. Using a gene expression array approach, we have demonstrated a novel mechanism whereby sphingosine kinase regulates cell survival, proliferation and neoplastic transformation through enhancing expression of transferrin receptor 1. Importantly, these findings, published in Oncogene, identify a novel means of targeting the oncogenic signalling of sphingosine kinase via blocking transferrin receptor 1 function.

Dengue virus inhibition of sphingosine kinase contributes to pathogenesis

In collaborative work with Dr Jillian Carr of Flinders University published in the Journal of General Virology, we have shown that dengue virus infection results in a significant reduction in cellular sphingosine kinase activity, which contributes to elevated virus-induced cell death and pathogenesis associated with this infection. We have also determined the mechanism whereby dengue virus reduces sphingosine kinase activity by showing that the viral RNA hijacks host cell eEF1A, a direct activator of sphingosine kinase, and thereby blocks its stimulatory effects on this enzyme. Importantly, this provides valuable information in understanding of the pathogenesis of this mosquito-borne virus that may enable future therapeutics to be developed to combat this disease.

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 by genetic or chemical suppression of sphingosine kinase.

In addition to this role in tumourigenesis, sphingosine kinase and sphingosine 1-phosphate appear central players in many other cellular processes, including regulation of leukocyte migration, enhancing blood vessel formation, and enhancing constriction of airway smooth muscle cells. Thus, sphingosine kinase is also a potential target for therapeutic intervention in inflammation, atherosclerosis, hypertension and asthma.

Recent work in the Molecular Signalling Laboratory has concentrated on identifying the mechanisms regulating sphingosine kinase, the cellular functions controlled by this enzyme, and in developing small molecule inhibitors as 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 and other diseases. We have also identified that the substrate of sphingosine kinase, sphingosine, is a key regulator of the pro-survival 14-3-3 proteins. Indeed, our work suggests that inactivation of 14-3-3 by sphingosine is a key control mechanism that if deregulated can enhance tumourigenesis. Thus, this pathway also represents a novel therapeutic target that may be exploited to control cancer.

Outcomes for the Community

Cancer continues to have a major human and economic impact on the community, with new therapeutic options desperately needed to combat this disease. Our research has not only helped to determine the molecular basis for the progression and chemotherapeutic resistance of some cancers, but also identified new targets for therapeutic intervention in the treatment of these cancers.
Key discoveries 2013

Demonstrated that N-cadherin protein and gene expression is abnormally increased in trephine biopsies and plasma cells from myeloma patients, when compared with those of normal donors.

In addition, we demonstrated for the first time that the levels of circulating N-cadherin were elevated in a subset of patients with myeloma, relative to age-matched controls. Notably, we demonstrated that patients with abnormally high levels of N-cadherin had decreased progression-free survival and overall survival when compared with patients with normal N-cadherin levels. Furthermore, multivariate analyses revealed that 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 myeloma patients.

Increase in trabecular bone volume and trabecular thickness after imatinib treatment is associated with a significant decrease in osteoclast numbers, accompanied by a significant decrease in serum levels of a marker of osteoclast activity.

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. In the present study, we performed a prospective analysis of bone indices in imatinib-treated CML patients to determine the mechanism responsible for this altered bone remodeling. Our studies show 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. These data suggest that imatinib therapy dysregulates bone remodeling, causing a generalized decrease in osteoclast number and activity that is not counterbalanced by a decrease in osteoblast activity, leading to increased trabecular bone volume. Further long-term investigations are required to determine the causes and consequences of the site-specific decrease in BMD at the femoral neck.

Using flow cytometry, we demonstrated myeloma plasma cell infiltration into the bone marrow leads to an increase in mesenchymal stromal cells and a concomitant decrease in alkaline phosphatase osteoblasts in patients with multiple myeloma. Notably, this increase in mesenchymal stromal cell numbers correlated closely with plasma cell burden at the time of diagnosis. In addition, in comparison with the osteoblast population, the mesenchymal stromal cell population was found to express higher levels of plasma cell- and osteoclast-activating factors, including RANKL and IL-6, providing a mechanism by which an increase in mesenchymal stromal cells may promote and aid the progression of myeloma. Importantly, these findings were faithfully replicated in the C57BL/6J.xID.RJ murine model of myeloma, suggesting that this model may present a unique and clinically relevant system in which to identify and therapeutically modulate the bone microenvironment and, in turn, alter the progression of myeloma disease.

Outcomes for the Community

Contribution to the Australian Myeloma Foundation Medical and Scientific Advisory Group amyloidosis guidelines to assist general practitioners and haematologists-oncologists in the detection and treatment of amyloidosis.

Myeloma Research Laboratory

Professor Andrew Zannettino PhD

The Myeloma Research Laboratory studies the molecular and cellular basis for the development of the bone marrow cancer, multiple myeloma. Myeloma is characterised by the clonal proliferation of malignant plasma cells (an immune cell type that normally protects us against infection).

Myeloma is the second most common blood cancer affecting humans, with over 1,500 Australians diagnosed each year. Despite recent advances in treatment, myeloma remains almost universally fatal with a 10-year survival rate of approximately 17%. The main clinical manifestations of myeloma are the development of osteolytic bone lesions, bone pain, hypercalcaemia, renal insufficiency, suppressed immunoglobulin production and increased BM angiogenesis (blood vessel formation).

It is now widely accepted that most, if not all, cases of myeloma are preceded by a premalignant asymptomatic stage of the disease, known as bone marrow plasma cell disorder (MGUS). The diagnosis of MGUS is made when a patient has an increase in bone marrow plasma cells above specified criteria. The Myeloma Research Laboratory studies the molecular and cellular basis for the progression of myeloma disease.

Current projects are focused on:

- Identification of genetic factors that trigger the progression from asymptomatic MGUS to overt malignant MM.
- Defining the role of the bone microenvironment in disease pathogenesis.
- Determining the affects of myeloma plasma cells on mesenchymal stromal cell (MSC) differentiation.
- Identifying the role of the mTOR pathway in mesenchymal stem cell biology and bone formation.

Bone marrow trephine biopsy from a myeloma patient stained with an antibody to CD138 to highlight the malignant plasma cells.
Understanding development and integration of the neuronal and vascular systems at the molecular level presents a major challenge to developmental biologists. Recent advances, including our own, conclusively show that similar molecules are recruited by both systems to coordinate 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.

Neurovascular Research Laboratory
Dr Quenten Schwarz PhD

Outcomes for the Community
Our findings provide novel insight to the aetiology of a large number of neuronal and craniofacial disorders. Aberrant stem cell functions sit at the centre of many disorders. Our laboratory found that the E3 ubiquitin ligase Nedd4 plays an essential role in promoting the identity and survival of neural crest stem cells. Mice lacking this gene had aberrant neural crest cell death and according defects in the cranial skeleton. Our current work is aimed at understanding the role of this ubiquitin ligase in stem cell maintenance in general.

Found an essential role for the protein 14-3-3ζeta in dopaminergic signalling, the key pathway that is perturbed in mental disorders such as schizophrenia and autism. Together, these neurodevelopmental disorders affect over 5% of the population and represent one of Australia’s major medical issues. We showed that 14-3-3ζeta modulates activity of the dopamine transporter DAT that is a major site of drug therapy. Our current work is unravelling the mechanisms through which 14-3-3ζeta controls DAT function.
The Translational Oncology Laboratory is associated with the Royal Adelaide Hospital Cancer Clinical Trials Unit, which has a tumour subtype focus of melanoma and lung cancer.

Accordingly, melanoma projects include a NHMRC-funded phase 1 clinical trial of autologous chimeric antigen receptor (CAR) gene modified T cells in patients with advanced melanoma. The CAR is directed toward the glycolipid, GD2, which is expressed in most metastatic melanoma samples and which may be associated with a resistant, invasive, mesenchymal phenotype of melanoma. In up to a half of advanced melanoma cases, BRAF inhibitor therapy provides short to medium term tumour control. However, this therapy eventually fails in most cases because of mutational and non-mutational mechanisms.

We are investigating genotype/phenotype correlations of BRAF inhibitor-resistant melanoma in collaboration with Associate Professor. Stuart Pitton, Associate Professor Claudine Borderie, and Dr Lisa Ebert (CCB). The molecular mechanisms of resistance in melanoma cell lines are being studied as well as the role of vasculogenic mimicry in the phenotype of BRAF inhibitor-resistant melanoma cells. The findings are likely to be of direct therapeutic relevance.

First-line therapy for lung cancer typically involves cytotoxic chemotherapy, which is DNA-damaging and causes cancer cell death. We have preclinical proof of concept for a novel method of detecting cancer cell death based on the APOMAB® monoclonal antibody that is specific for a ribonucleoprotein (immuno-PET). In an extension of this project, we shall also investigate the therapeutic potential of APOMAB® antibody-drug conjugates (ADCs). ADCs are an emerging class of cancer drugs, which may be associated with a resistant, invasive, mesenchymal phenotype of melanoma. We are studying the anti-tumour activity of APOMAB® ADCs in pre-clinical lung tumour models and have shown that the activity depends solely on bystander killing effects.

New targeted therapies are shrinking and stabilising cancers of the lung and other organs mainly by blocking kinase-mediated signal transduction. A remaining challenge is how best to translate this therapeutic potential clinically so that more patients can be matched efficiently with the right treatment. Hence, in collaboration with Professor Hamish Scott, Dr Karin Kassahn, and Professor Angel Lopez (CCB and ACRF Genomics Facility, SA Pathology), we are studying the application of various genomic technologies to samples of patient blood and tumour tissue to enable ‘reflex’ tumour genotyping. Of particular interest is detection of activating and primary resistance mutations in the epidermal growth factor receptor gene in non-small cell lung cancer.

Using the long-lived positron emitter, Zirconium-89, APOMAB will be adapted for immuno-PET imaging (immuno-PET). In an extension of this project, we shall also investigate the therapeutic potential of APOMAB® antibody-drug conjugates (ADCs). ADCs are an emerging class of cancer drugs, which include monoclonal antibodies linked to a cytotoxic, cell-killing mechanism. Our work is focused on the development of antibody-drug conjugates for use in lung cancer and other solid tumours.

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Epidermal growth factor receptor (EGFR) targeting via radioimmunotherapy and in conjunction with standard cytotoxic chemotherapy and PARP inhibition resulted in eradication of patient-derived xenografts of triple-negative breast cancer. EGFR binding resulted in non-canonical signalling that interfered with tumour repair of double-strand DNA breaks thus further contributing to tumour cell death and anti-effects in vivo (Al-Ejeh et al, J Nucl Med 2013; highest ranked journal in field of Nuclear Medicine).

BRAF inhibitor therapy using dabrafenib has made a dramatic impact on tumour control in patients with advanced melanoma. However, drug resistance is virtually inevitable and occurs via MEK-dependent and independent mechanisms. This paper shows in comparing genomic analyses of baseline and on-treatment tumour biopsies that deletion or mutation of PTEN, increased copy number of CCND1, and reduced copy number of CDKN2A, were all associated with shorter progression free survival of advanced melanoma patients who are treated with dabrafenib ( Nathansson et al, Cancer Res 2013; ranking 11 out of 196 journals in the category ‘Oncology’).

Key discoveries 2013

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The biophysical and biochemical properties of the tumour microenvironment strongly influence the progression of cancers and determine key elements of the prognosis. Increasingly, normalisation of the microenvironment is an important goal of cancer therapy. Our laboratory works to understand how the microenvironment is remodelled at both the biophysical and biochemical levels during tumour initiation and progression, aiming to identify new targets that would be useful as novel cancer therapies.

The Rho signalling pathway is well-known to promote cell motility by its ability to regulate the synthesis and 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 and the cellular component of the microenvironment. 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). More recently we have established that ROCK, the major effector protein of RhoA/C is highly activated within fibroblasts, macrophages and mast cells populating the tumour microenvironment. We are now working on determining how signalling through the Rho pathway modifies the ECM and the cellular component of the microenvironment. Using one of these models, we have previously demonstrated that activation of the Rho-signalling pathway at this location, provides temporal control on the production and remodelling of the ECM components that make up the new dermal tissue at the site. We have also shown that 14-3-3ζ acts to restrain Rho signalling at this location, preventing temporal control on the production and remodelling of the ECM and through this the speed of re-epithelialisation, enhancing the quality of the resulting healed skin. Slow healing wounds such as those exhibited by diabetics, frequently exhibit high levels of 14-3-3ζ expression. Our observations suggest that the slow wound healing observed may be related to increased inhibition of the Rho signalling pathway in patients.

A skin cell deficient in 14-3-3ζ exhibits enhanced Rho pathway activation as determined by the formation of actin stress fibres (visualised using red fluorescent phalloidin) and the colocalisation of a phosphorylated form of the regulatory myosin light chain (visualised by green immunofluorescence) to the stress fibres.

Regulation of the Rho signalling pathway in wound healing

Using a strain of mice in which 14-3-3ζ expression has been abolished, we have established a novel role for this 14-3-3ζ isoform in the regulation of Rho signalling during wound healing. The Rho signalling pathway is known to be upregulated at wound margins to permit the establishment of an actomyosin ring that facilitates wound closure. We have established for the first time that Rho signalling at wound margins is also crucial for the production and remodelling of the ECM components that make up the new dermal tissue at the site. We have also shown that 14-3-3ζ acts to restrain Rho signalling at this location, providing temporal control on the production and remodelling of the ECM and through this the speed of re-epithelialisation, enhancing the quality of the resulting healed skin. Slow healing wounds such as those exhibited by diabetics, frequently exhibit high levels of 14-3-3ζ expression. Our observations suggest that the slow wound healing observed may be related to increased inhibition of the Rho signalling pathway in patients.

The 14-3-3 family of phospho-serine binding proteins have diverse functions in cellular processes. They have 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. More recently, we have been working on how 14-3-3ζ regulates the Rho signalling pathway during wound healing.

Epithelial tumours and chronic wounds exhibit altered microenvironments associated with aberrant signalling via the Rho pathway. We are working to identify approaches by which normalising this pathway could lead to novel therapeutic approaches to treating both conditions.

Key discoveries 2013

The function of the Rho signalling pathway in the tumour microenvironment

In collaboration with the Mast Cell Laboratory at the Centre for Cancer biology, we have demonstrated in murine models of skin and intestinal cancer, that tumour associated fibroblasts, macrophages and mast cells exhibit increased signalling through the Rho pathway (Ibbetson et al. 2013 and unpublished). Activation of the Rho signalling pathway within these cell types correlates with tumour progression and is not observed in the corresponding normal tissue types. We are currently working on establishing the function of Rho pathway activation in fibroblasts and mast cells within the tumour microenvironment, with the goal of identifying whether normalising Rho signalling within these cell types may be used therapeutically as an approach to targeting the microenvironment.

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With a focus on human disease we study the intricate network of blood vessels that carry white blood cells throughout the body. Blood vessels contribute to life threatening diseases such as cancer and heart disease but are also essential for fighting infection and wound repair.

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, vascular tone, permeability, and vessel growth.

A major focus of our group is to (i) investigate blood vasculature in normal and disease states and (ii) better define blood vessel progenitor cells for clinical application. Our work may provide new opportunities to (i) treat debilitating diseases such as allergy, (ii) assist blood vessel repair in patients with cardiovascular disease and (iii) block blood vessel development in cancer patients. 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.

Outcomes for the Community

With a focus on health and well-being 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 repair. Associate Professor Bonder’s work may provide new opportunities for enhancing blood vessel development following organ transplantation and control their levels of activation during allergic inflammation. A better understanding of blood vessels in disease will provide new treatment options for many debilitating diseases.

Key discoveries 2013

Blood vessels are critical for pancreatic islet function

Pancreatic islet transplantation is an emerging cure for Type 1 Diabetes but success is limited by death of insulin producing beta cells post transplantation. Vasculogenic endothelial progenitor cells (EPCs) have the potential to improve islet engraftment, and may also improve islet graft function. In collaboration with Dr Claire Jessup and Associate Professor Toby Coates we have combined EPCs 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-EPC clusters can form successfully and glucose stimulation index function was superior to clusters comprised of islet cells only (Penko Islets 3:1, 2011). More importantly, in 2013 we demonstrated that co-transplantation of islets and EPCs into diabetic mice significantly increased the cure rate when compared to islets alone (Penko D et al Cell Transplantation, 2013). This work has formed a leading project in the six-year $59M Cell Therapy Manufacturing CRC wherein smart surface biomaterials will be generated to bind both islets and EPCs for therapeutic application.

Identification of a new target to treat allergic inflammation

Rapid recruitment of neutrophils to a site of inflammation is associated with allergic diseases, such as asthma and anaphylaxis. Although anti-histamines and steroids are the mainstay of treatment for symptomatic relief, their effectiveness is varied; thus, a better understanding of acute allergic reactions is required. 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. We recently identified that (i) histamine-induced P-selectin expression on human umbilical vein ECs is SK-dependent and (ii) histamine-induced neutrophil rolling along the vasculature in vitro and in vivo is SK dependent (Sun W et al Am J Pathol, 2012). In 2013 we revealed that administration of Fingolimod (approved pro-drug for treatment of multiple sclerosis) attenuates histamine-induced neutrophil recruitment in multiple animal models of allergic inflammation and have initiated human clinical trials to investigate this additional indication for Fingolimod.

Development of EPCs for therapeutic use:

We recently identified a new population of immature, non-adherent endothelial progenitor cells (naEPCs) (Appleby S et al PLoS ONE 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 ~10^7 naEPCs in a serum free medium which provides better therapeutic opportunities for vascular repair and we have executed in vivo models to validate their application.
Since it’s opening in October 2012 the ACRF Cancer Genomics Facility has become integral to the cutting edge genomics research of CCB researchers.

The facility is the result of a number of generous grants including $3.5 million from the ACRF supported by others from the State Government of South Australia, Therapeutics Innovation Australia (TIA), SuperSceince Fund, MedLab Laboratories, Cancer Council of South Australia, Co-operative Research Centre for Biomarker Translation, The James and Diana Ramsay Foundation and through a partnership of SA Pathology and the University of Adelaide. 2013 saw the installation of another next generation sequencer, an Illumina MiSeq, adding to an already impressive suite of equipment including Ion Proton and Illumina Hiseq sequencers, Fluidigm systems for the analysis of single cells and two microarray platforms. As next generation sequencing technology continues to become more affordable, it’s uptake and translation from research environments to clinical utility has been making real progress. Promising in-house trials of microarrays for cytogenetic testing will see their implementation within SA Pathology in the near future. The facility staff work closely with the Leukaemia Unit and the Molecular Pathology Research Laboratory, respectively.

Bioinformatics
Together with the ACRF Cancer Genomics Facility, the CCB established a dedicated bioinformatics group. Initially, this consisted of a core of three staff funded through the facility to process and analyze the prodigious amounts of data produced by the facility’s sequencers. By the end of 2013 the group has expanded through the addition of another four researchers dedicated, and largely funded through, individual research groups of the CCB as well as the University of Adelaide. During the year the group further hosted two junior staff working together with the Leukaemia Unit and the Molecular Pathology Research Laboratory, respectively.

High end bioinformatics requires state-of-the-art computing infrastructure. The Genomics Facility owns a 48 core/256 RB RAM server and shares access to three more high performance infrastructure. The Genomics Facility owns a 48 core/256 RB RAM server and shares access to three more high performance servers. All are hosted by eResearch SA, who provide supercomputing to South Australia’s research community. The facility is networked to these servers via a fast 1Gbps high-throughput connection facilitated through our partners at the University of Adelaide. A data storage and backup capability of around 25TB on eResearch SA's Dell Compellent system and a metadata capture platform funded through a grant to the Australian National Data Service (ANeDS) has enabled streamlined data-sharing with the Facility’s users, obviating risk of data corruption and loss through exchange of portable hard drives. 2013 also saw a successful application for an initial allocation of 50TB of data storage through the facility’s own Bioinformatics group.

Outcomes for the Community
We continue to work closely with researchers and clinicians in basic science (CCB), clinical translational research (eg genetic diagnoses and molecular oncology, CCB and SA Pathology) as well as working towards implementation of our new technologies into standard health care (CCB, SA Pathology and SA Health).

Next generation sequencing data from two pairs of kindreds diagnosed with a rare form of adrenal Cushing’s syndrome

Two mutations (top right and bottom left) in the gene ARMC5, identical within the kindred but differing between kindreds, were identified via bioinformatic analysis of whole exome data (L. Gagliardi et al. J Clin Endocrinol Metab 2014)
patients in first complete remission have
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<td>Harvey N, Scott H</td>
<td>Defining the role of GATA2 in the construction of lymphatic vessels</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>Haynes D, Cantley M</td>
<td>Targeting histone deacetylases 1 and 5 to reduce inflammation and bone loss in periodontitis</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>Halbg K</td>
<td>Improving treatment outcomes in individuals with chronic HCV and HCV-sassociated diseases</td>
<td>Australian Centre for HIV and Hepatitis Virology</td>
</tr>
<tr>
<td>Halbg K</td>
<td>Early pathogen recognition pathways in the crocodile and the role of viperin in pathogen defence</td>
<td>Charles Darwin University</td>
</tr>
<tr>
<td>Hughes T, White D, Brantford S, Mulgahan C, Yong A</td>
<td>Studies Directed at Maximising Achievement of Treatment Free Remission in CML</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>Jans DA, Bogoyevitch MA, Goodall DJ</td>
<td>Transcription factor nuclear reasidity as a driver of gene expression</td>
<td>Australian Research Council</td>
</tr>
<tr>
<td>Kirk C</td>
<td>Mary Oxton Early Career Fellowship</td>
<td>RAH Research Foundation</td>
</tr>
<tr>
<td>Kumar S</td>
<td>Novel ways of regulating membrane proteins in cell physiology and disease</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>Lewis I, D’Andrea R, Brown A</td>
<td>Identification of mutations in genes encoding mitochondrial complex subunits in AML</td>
<td>RAH Contributing Haematologists’ Committee funding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Title</th>
<th>Granting Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis I, D’Andrea R, Wang S, Brown A</td>
<td>Establishment of xenograft models for the testing of new therapeutics</td>
<td>RAH Contributing Haematologists’ Committee funding</td>
</tr>
<tr>
<td>Lewis I, D’Andrea R, Brown A</td>
<td>Investigation of mutation and altered expression of Fanconi Anaemia genes in Acute Myeloid Leukaemia</td>
<td>RAH Contributing Haematologists’ Committee funding</td>
</tr>
<tr>
<td>Lopez A, Parker M, Hughes T</td>
<td>Ablation Signalling in Leukaemia Program Grant</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>Parker W, Young D</td>
<td>Development of novel methods to examine drug resistance in chronic myeloid leukaemia</td>
<td>Leukaemia Foundation of Australia</td>
</tr>
<tr>
<td>Pitson SM</td>
<td>Characterising a highly oncogenic variant of sphingosine kinase 1</td>
<td>Cancer Council SA/SAHMRI Beat Cancer Project Grant</td>
</tr>
<tr>
<td>Pitson SM</td>
<td>Targeting sphingosine kinase 1 degradation to enhance cancer chemotherapeutic sensitivity</td>
<td>Royal Adelaide Hospital</td>
</tr>
<tr>
<td>Powell JA</td>
<td>Sphingosine kinase 1 as a therapeutic target in acute myeloid leukaemia</td>
<td>Royal Adelaide Hospital</td>
</tr>
<tr>
<td>Pucorni J</td>
<td>Travel Grant</td>
<td>Cancer Council</td>
</tr>
<tr>
<td>Pucorni J</td>
<td>Travel Grant</td>
<td>Discipline of Medicine, University of Adelaide</td>
</tr>
<tr>
<td>Schwarz Q</td>
<td>Analysing the role of VEGF in craniofacial development</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>To LB, Hughes T, Lopez A, Zannettino A, Scott F, D’Andrea R, Kusin B, Lewis I, Cambaret T, White D</td>
<td>South Australian Blood Cancer Tumour Bank</td>
<td>SA Cancer Research Collaborative (Blast Cancer) and Medvet</td>
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<tr>
<td>Wallington-Beddoe CT</td>
<td>Early Career Fellowship</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>White D</td>
<td>Innovative Cancer Imaging and Therapeutics Facility</td>
<td>Australian Cancer Research Foundation</td>
</tr>
<tr>
<td>Wilson C</td>
<td>Early Career Fellowship</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>Woodcock J, Lopez A, Hughes T</td>
<td>Targeting dimeric 14-3-3 protein as therapy for Ph+ leukaemia</td>
<td>Royal Adelaide Hospital</td>
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<tr>
<td>Yang D, Parker W, Ross D, Hughes T, Brantford S</td>
<td>The use of digital PCR to increase sensitivity of MRD detection in Ph+ leukaemia</td>
<td>Contributing Haematologists’ Committee, RAH</td>
</tr>
<tr>
<td>Zannettino A, Gronthos S, Fitter S</td>
<td>Characterisation of the molecular target of the monoclonal antibody STRAD-1, in mesenchymal stem cell mediated tissue repair and immune modulation</td>
<td>Adelaide Research Innovation Commercialization Grant</td>
</tr>
<tr>
<td>Zannettino A, Morgan G, Mulgahan C, To LB</td>
<td>Understanding clonal evolution in multiple myeloma</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>Zannettino A, Morgan G, Mulgahan C, To LB</td>
<td>Molecular determination of the evolution of myeloma</td>
<td>Ray, and Shel Norman Trust</td>
</tr>
<tr>
<td>Zannettino A, Burton L, To LB</td>
<td>Does modifying the bone marrow stromal environment alter the disease course of multiple myeloma?</td>
<td>Cancer Council</td>
</tr>
<tr>
<td>Zannettino A, LB To</td>
<td>Is elevated N-cadherin a prognostic indicator in multiple myeloma patients?</td>
<td>Cancer Australia Leukaemia Foundation</td>
</tr>
</tbody>
</table>
Dr Kieran Harvey
Group Leader, Cell Growth and Proliferation, Peter MacCallum Cancer Centre, Melbourne
Organ size control and the Hippo pathway 07/03/13

Prof David Treantick
Head of Genome Biology Dept, John Curtin School of Medical Research, Australian National University, Canberra
Linking chromatin structure with cell fate 14/03/13

Associate Professor Claudine Bonder
Head, Vascular Biology and Cell Trafficking Laboratory, Centre for Cancer Biology, Adelaide
Control the vasculature, for good or for evil 04/04/13

Dr Antje Blumenthal
Balan Research Fellow, Epithelial Cancer Division, University of Qld, Diamantina Institute, Brisbane

Dr Pritinder Kaur
Institute for Molecular Bioscience, University of Qld, Brisbane
SOXF transcription factors: from developmental biology to drug discovery 06/06/13

Dr Mathias Francois
Balzan Research Fellow, Epithelial Cancer Division, University of Qld, Diamantina Institute, Brisbane

Dr Alice Pébay
Senior Research Fellow, Neuroregeneration Research Unit, Centre for Eye Research Australia, Department of Ophthalmology, University of Melbourne
Modulation of neural stem/progenitor cell biology by Lysophosphatidic acid. Potential implication for neurotrauma 23/05/13

Dr Peter Czabotar
Laboratory Head, Structural Biology Division, Walter and Eliza Hall Institute, Melbourne
Crystal structures of Bax and Eliza Hall Institute, Melbourne

16/05/13

Dr Jeff Babon
Laboratory Head, Structural Biology Division, Walter and Eliza Hall Institute, Melbourne
Control of Cytokine Signalling 18/04/13

Prof Charles Mackay
Centre for Immunology and Inflammation, Monash University Clayton, Vic
Do Diet and the gut microbiota as a basis for western lifestyle inflammatory diseases 02/05/13

Assoc Prof Matthias Ernst
Laboratory Head, Cell Signalling and Cell Death, Walter and Eliza Hall Institute, Melbourne
Therapeutically exploiting Statll signalling in gastrointestinal tumourigenesis 09/05/13

Prof Paul Thomas
Pfizer Australia Research Fellow, School of Molecular and Biomedical Science, University of Adelaide elucidating mechanisms of brain and gonad disorders using Sox3 transgenic mice 16/05/13

Dr Peter Czabotar
Structural Biology Division, Walter and Eliza Hall Institute, Melbourne
Crystal structures of Bax and Eliza Hall Institute, Melbourne

20/06/13

Dr Douglas Fairlie
Laboratory Head, Structural Biology Division, Walter and Eliza Hall Institute, Melbourne
Apoptosis regulation and therapeutic targeting 04/07/13

Assoc Prof Geraldine O’Neill
Group Leader, Children’s Cancer Research Unit, Children’s Hospital at Westmead, Sydney
Intracellular decoration: Tropomyosin in actin dynamics and cell migration 11/07/13

Prof Paul Glasson
Head, Dept of Biochemistry and Molecular Biology, University of Melbourne, Biok1, Institute, Melbourne
Membrane transport and recycling of internalised membrane proteins: relevance to development, disease and therapeutics 18/07/13

Dr Andrew Webb
Division of Systems Biology and Personalised Medicine, Walter and Eliza Hall Institute, Melbourne
Quantitative proteomic techniques in biological and medical research 24/07/13

Prof John O’Leary
Chair of Pathology, Trinity College Dublin, Ireland
New insights into the cancer metastatic cascade 24/07/13

Prof Richard Simpson
La Trobe Institute for Molecular Science (LIMS), La Trobe University, Melbourne
Exosomes: proteome insights and diagnostic potential 25/07/13

Dr Sark Tey
Bons Marrow Transplantation Laboratory, Queensland Institute of Medical Research, Brisbane
Cellular therapy for graft-versus-host disease 01/08/13

Assoc Prof David Tarlinton
Division of Immunology, Walter and Eliza Hall Institute, Melbourne
Plasma cells from beginning to end 08/08/13

Dr Kaylene Simpson
Head, Victorian Centre for Functional Genomics, Peter MacCallum Cancer Centre, Melbourne
Functional genomics strategies for gene discovery 15/08/13

Assoc Prof Joan Heath
Division of Chemical Biology, Walter and Eliza Hall Institute, Melbourne
Zebrafish mutants provide insights into mRNA splicing, autophagy and colon cancer 22/08/13

Assoc Prof Leanne Dibbens
Head, Epilepsy Research Program, School of Pharmacy and Medical Sciences, University of South Australia
New Genes and Pathways in Epilepsy and the Co-morbidities including Intellectual Disability and Psychiatric Features 29/08/13

Dr Linda Wakim
Postdoctoral Fellow, Microbiology and Immunology, University of Melbourne
IFITM3 – rendering tissue resident memory T cells resistant to virus infection 05/09/13

Assoc Prof Simone Schoenwaelder
Australian Centre for Blood Diseases, and Department of Clinical Haematology, Monash University
F4-3-3eta regulation of the styling platelet 09/09/13

Dr Elizabeth Forbes-Blom
Senior Research Fellow, Allergic and Parasitic Diseases Laboratory, Malaghan Institute, New Zealand
IL-25 regulates intestinal/homeostasis 12/09/13

Prof Stephen Clarke
Director of Translational Research, Royal North Shore Hospital, University of Sydney
The impact of cancer-associated inflammation on outcomes of cancer treatment 19/09/13

Prof Allison Cowin
Centre for Regenerative Medicine, Masxon Institute, Adelaide
Cancer: the wound that never heals? Similarities between the role of the cytoskeletal protein Fil in wound repair and cancer 26/09/13

Prof Mark Febbraio
Head, Cellular and Molecular Metabolism Laboratory, Baker ID Heart and Diabetes Institute, Melbourne
Targeting ghrelin to prevent inflammation and promote insulin action 03/10/13

Prof Alpha Yap
Head, Division of Molecular Cell Biology, Institute for Molecular Bioscience, University of Qld, Brisbane
Tension in the minority: the junctional cytoskeleton and oncogenic extrusion 10/10/13

Prof Heddy Zola
SA Pathology, Core Facilities and Central Research Services Feedback 17/10/13

Dr James Wells
Epilephal Cancer Group, University of Qld Diamantina Institute, Brisbane
Activating T-cells in the skin to treat skin cancer 24/10/13

Dr Lisa Ebert
Division of Molecular Medicine, Walter and Eliza Hall Institute of Medical Research, Melbourne
Haematopoiesis during embryonic development 14/11/13

Barossa Meeting 20–21 November 2013

Assoc Prof Rohan Toadale
Laboratory Head, Molecular Cell Biology Division, Institute for Molecular Bioscience, University of Qld, Brisbane
The Role of Retromer Mediated Sorting of Cargo in Parkinson’s Disease and Insulin-Stimulated Trafficking in Adipocytes 28/11/13
Invited Presentations

Acute Leukaemia Laboratory
Professor Richard D'Andrea
Invited Speaker
Invited Presentations 59
Invited Session Chair: Acute Leukaemia Laboratory
Professor Richard D'Andrea
Invited Speaker
6th Barosa Science Amongst the Vines Scientific Meeting: Cell Signalling in the Omics era Adelaide, Australia. November
Lowy Cancer Symposium. Discovering Cancer Therapeutics. Sydney, Australia. May
Associate Professor Ian Lewis
Invited Speaker
19th Annual Meeting of the International Society of Cellular Therapy. Auckland, New Zealand. April
10th Malaysian National Haematology Scientific Meeting. Penang, Malaysia. April
Dr Anna Brown
Invited Speaker
Blood and Bone Symposium: 11th One-Day Symposium of the Human Genetics Society of Australia - South Australian Branch. Adelaide, Australia. September
Cell Signalling Laboratory
Associate Professor Yeasmin Khaw-Goodall
Invited Speaker/Chair/Co-Chair
19th Annual Meeting of the International Society of Cellular Therapy. Auckland, New Zealand. April
Invited Session Chair and Plenary Speaker
Professor Ben Goodall
Invited Speaker
6th Barosa Science Amongst the Vines Scientific Meeting: Cell Signalling in the Omics era Adelaide, Australia. November
Dr Tim Hennessey
Invited Speaker
Invited Session Chair
8th Australasian Conference on Viral Hepatitis C Virus and Related Viruses. Melbourne, Australia. October
Dr Nick Eyre
Invited Speaker
Invited Session Chair
Lowy Cancer Symposium. Discovering Cancer Therapeutics. Sydney, Australia. May
Heart and Vascular Biology Australia. September
Leukaemia Unit, Genetics and Molecular Pathology
Associate Professor Susan Cranford
Session Chair and Abstract Reviewer
Central European Society of Haematology. Conference. New Orleans, USA. December
Leukaemia Unit, Genetics and Molecular Pathology
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Heart and Vascular Biology Australia. September
Leukaemia Unit, Genetics and Molecular Pathology
Associate Professor Susan Cranford
Session Chair and Abstract Reviewer
Central European Society of Haematology. Conference. New Orleans, USA. December
Heart and Vascular Biology Australia. September
Haematology Clinical Research Laboratory
Professor Luan Bik To
Invited Speaker
‘Art of Haematology’ Meeting. Kuala Lumpur, Malaysia. November
Associate Professor Ian Lewis
Invited Speaker
10th Malaysian National Haematology Scientific Meeting. Penang, Malaysia. April
Dr Simon McRae
Invited Speaker
H4A Meeting. Gold Coast, Australia. October
East Asia Haematology Forum. Seoul, Korea South, July
Cytokine Receptor Laboratory
Professor Angel Lopez
Invited Speaker
Inaugural Meeting of the International Cytokine and Interleukin Society (ICIS). San Francisco, USA. September
International Cell Death Society Meeting. Faenza, Italy. June
Lowy Cancer Research Centre Seminar Series. Sydney, Australia. September
Invited Speaker
15th International Congress of Immunology. Milan, Italy. August
38th Lorne Conference on Protein Structure and Function. Lorne, Australia. February
Co-Convenor
6th Barosa Science Amongst the Vines Scientific Meeting: Cell Signalling in the Omics era Adelaide, Australia. November
Invited Speaker
Genes Regulation Laboratory
Professor Greg Goodall
Selected Speaker
6th International EMT Meeting. Adelaide, Australia. June
Invited Speaker
Inaugural Meeting of the International Cytokine and Interleukin Society (ICIS). San Francisco, USA. September
Invited Speaker
International Cell Death Society Meeting. Faenza, Italy. June
Invited Speaker
38th Lorne Conference on Protein Structure and Function. Lorne, Australia. February
Hepatitis C Virus Research Laboratory
Associate Professor Richard Board
Convenor
20th International Symposium on Hepatitis C Virus and Related Viruses. Melbourne, Australia. October
Invited Speaker
8th Australasian Conference on Viral Hepatitis. Auckland, NZ. September
Keynote Presentation
Royal Golden Jubilee (RGLJ) Research Congress. Thailand. April
Dr Karl Helbig
Invited Session Chair
20th International Symposium on Hepatitis C Virus and Related Viruses. Melbourne, Australia. October
Organising Committee
Australian Centre for HIV and Hepatitis Research Workshop 2013. Melbourne, Australia. October
Dr Nick Eyre
Invited Speaker
20th International Symposium on Hepatitis C Virus and Related Viruses. Melbourne, Australia. October
Dr Amanda Aoki
Seminar Chair
Australian Centre for HIV and Hepatitis Research Workshop 2013. Melbourne, Australia. October
Leukaemia Unit, Genetics and Molecular Pathology
Professor Susan Cranford
Session Chair and Abstract Reviewer
American Society of Hematology. Conference. New Orleans, USA. December
Session Chair
European School of Haematology. 10th International Conference on OML, Biology, and Therapy. Estoril, Portugal. September
Invited speaker
1st Indian Cancer Congress, Monitoring OML Therapy. Delhi, India. November 2013
Haematology Lead Meetings. Sydney, Melbourne, Port, Adelaide, Darwin, Liverpool May, July, August, October
Seminar in Best Practices in Molecular Monitoring of OML. Kota Bahru, Malaysia. September
2nd Haematology Updates 2013. The goal of OML therapy in 2013 and Beyond. Kuala Lumpur, Malaysia. September
Journal Club Meetings
Peter MacCallum Cancer Centre, Royal Melbourne Hospital and Austin Hospital. Melbourne, Australia. September
GET Haematology Weekend meeting, Future directions in molecular monitoring. Sydney, Australia. June
Australian Leukaemia and Lymphoma Group (ALLG) Haematology Educational Day for Medical Officers and research nurses. Adelaide, Australia. May
Singapore Society of Haematology Annual Scientific Meeting. Singapore. April
Integrated Clinical Oncology Network. Lecture and post lecture discussion. Brisbane, Australia. April
OML, China Taiwan/India. The Goal of OML Therapy and the Importance of Achieving Early Response in OML. India and Taiwan. March
International update on OML. K’s Medical University. Lucknow, India. March
Global Opinion Leaders Summit (GOLS) 2013. Helsinki, Finland. February
Lymphoid Development Laboratory
Associate Professor Natasha Harvey
Invited Speaker and/or Session Chair
2nd Meeting of the Australian Network of Cardiac and Vascular Developmental Biologists. Gold Coast, Australia. October
ComBio 2013. Perth, Australia. September
Flinders University, Adelaide, Australia. May
3rd Vincent’s Institute of Medical Research. Melbourne, Australia. August
Co-Convenor
Australian Vascular Biology Society - Australia Zealand Monoclonal Spleen Society Joint Meeting. Barrosa Valley, Australia. September
3rd Adelaide Cell and Developmental Biology Meeting. Adelaide, Australia. November
Mast Cell Laboratory
Associate Professor Michele Grimboldi
Invited Speaker and Symposium Chair
6th Asia and Ocean Asia Congress on Photobiology. Sydney, Australia. November
Invited Speaker for Journal Clubs
Royal North Shore Hospital, Westmead Hospital, Royal Prince Alfred Hospital, Millennium Research Institute, and Centenary Institute. Sydney, Australia
Keynote Speaker
Australian Society of Clinical Immunology: SA Branch. Adelaide, Australia. June
Invited Speaker
Bio21 and CSIRO Ltd Speaker Program. Melbourne, Australia. February
Melissa White Memorial Laboratory
Professor Timothy Hughes
Chair and Invited Speaker
ASHCML Education Talk. New Orleans, USA. December
Co-Chair and Invited Speaker
ESHICML CML Meeting. Estoril, Portugal, September
CML, Global Opinion Leaders Summit (GOLS). Helsinki, Finland. March
Plenary Speaker and Organiser
Society of Haematological Oncology (SHO) Meeting Houston, USA. September
Invited Speaker
The Haematology Annual Meeting. Gold Coast, Australia. October
AP Summit, Japan. July
1st Arab World Congress on Public Health. Dubai. April
Professor Deborah White
Invited Speaker
CML Monitoring Advisory Board. Adelaide, Australia. December
2013 Haematology: New Frontiers in Therapeutic Options. Gold Coast, Australia. October
iCMLf Meeting, Portugal. September
Walter and Eliza Hall Institute Translational Research Symposium. Melbourne, Australia. July
Invited Speaker for Journal Clubs
Royal North Shore Hospital, Westmead Hospital, Royal Prince Alfred Hospital, Millennium Research Institute, and Centenary Institute. Sydney, Australia
Molecular Pathology Research Laboratory
Professor Hamish Scott
Keynote Speaker
HOGA SA Branch. 2013 Annual Meeting. Adelaide, Australia. October
Invited Speaker / Conference Committee / Session Chair
Conference Committee
The 5th National Epigenetics Meeting. Shoul Day, Australia. November
Molecular Regulation Laboratory
Professor Sharned Kumar
Invited Speaker
Institute of Molecular and Cellular Biology. A* Star. Singapore. December
Bio21, University of Melbourne. Melbourne, Australia. October
University of Rome Tor Vergata. Rome, Italy. October
Monash Institute of Medical Research. Clayton, Australia. September
International Cell Death Society Meeting. Malaga, Spain. June
Institute of Biochemistry II, Goethe University School of Medicine. Frankfurt, Germany. June
University of Technology Sydney. Sydney, Australia. July
Cold Spring Harbor Asia Conference. Suzhou, China. April
2013 Hunter Call Biology Meeting. Pokolbin, Australia. March
EMBO Workshop. Obergurg, Austria. January
New Fellow’s Talk
Science at the Shine Dome, Australian Academy of Science, Canberra, Australia. May
Invited Symposium Chair, Chair of a Plenary Session
ComBio 2013. Perth, Australia. September
Plenary Lecture
23rd Federation of Asian and Oceanian Biochemists and Molecular Biologists (FACMBI) Conference. Singapore. December
Dr Domina Denton
Invited speaker
2013 Hunter Call Biology Meeting. Pokolbin, Australia. March
Mr Joey Puccini
Invited Speaker
Cell Growth and Proliferation Gordon Ralseis Seminar. Vermont, USA. June

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Molecular Signalling Laboratory

Professor Stuart Pitman
Co-Convenor
6th Barossa Science Amongst the Vines Scientific Meeting: Cell Signalling in the Omics era Adelaide, Australia. November
Invited Speaker
Monash Institute of Pharmaceutical Sciences, Melbourne, Australia. November
Dr Melissa Pitman
Invited Speaker
Adelaide Protein Group Early Career Researcher Awards, Adelaide, Australia. October

Dr Jason Powell
Invited Speaker
6th Barossa Science Amongst the Vines Scientific Meeting: Cell Signalling in the Omics era Adelaide, Australia. November
Invited Speaker

Myeloma Research Laboratory

Professor Andrew Zannettino
Invited Speaker
School of Aeronautics, Mechanical and Mechatronic Engineering, University of Sydney, Sydney, Australia. October
ANZBMS Annual Scientific Meeting, Melbourne, Australia. September

Neurovascular Research Laboratory

Dr Quenten Schwarz
Invited Speaker
EMBL Australia, Monash University, Melbourne, Australia. December
CSCHR Seminar and Networking Forum, Robinson Centre, University of Adelaide, Adelaide, Australia. December
Department of Medicine, Melbourne University, Melbourne, Australia. December
6th Barossa Science Amongst the Vines Scientific Meeting: Cell Signalling in the Omics era Adelaide, Australia. November
SAAHMP Mind and Brain Mini Symposium, The Science Exchange, Adelaide, Australia. November
2nd Meeting of the Australian Network of Cardiac and Vascular Gold Coast, Australia. November
2nd Translational Psychiatry Symposium, Adelaide, Australia. October
Neural Crest in Stem Cells, Development and Disease Meeting, Weizman Institute, Rehovot, Israel. October

Vascular Biology and Cell Trafficking Laboratory

Associate Professor Claudine Bonder
Co-Chair
Barossa Cell Signalling Meeting, Adelaide, Australia. November
Australian Vascular Biology Society, Adelaide, Australia. September
Australian Society for Medical Research, Adelaide, Australia. June
Invited Speaker
Centre for Stem Cell Research, University of Adelaide, Adelaide, Australia. December
6th Barossa Science Amongst the Vines Scientific Meeting: Cell Signalling in the Omics era Adelaide, Australia. November
Queen Elizabeth Hospital, Cardiology Seminar Series, Adelaide, Australia. October
Flinders University, Neuroscience Seminar Series, Adelaide, Australia. September
Dr Lisa Ebert
Invited Speaker
Melbourne Immunotherapy Group Symposium, Melbourne, Australia. October
Australian Society for Immunology (ASI) Adelaide Immunology Retreat, Murray Bridge, Australia. August

Translational Oncology Laboratory

Professor Michael P Brown
Co-Chair
6th Barossa Science Amongst the Vines Scientific Meeting: Cell Signalling in the Omics era Adelaide SA. November
Invited Speaker
International Society for Cell Therapy Annual Scientific Meeting. Auckland, New Zealand. April
Novelita Melanoma Investigator Forum 2013, Singapore. May
Dr Alex Staudacher
Invited Speaker
European Association of Nuclear Medicine 2013 Congress. Lyon, France. October

Tumour Microenvironment Laboratory

Dr Michael Samuel
Selected Speaker
Beatson International Cancer Conference: Targeting the Tumour Stroma. Glasgow, UK. July
Invited Speaker
6th Barossa Science Amongst the Vines Scientific Meeting: Cell Signalling in the Omics era Adelaide, Australia. November
University of Adelaide Biochemistry Research Reports. Adelaide, Australia. May
6th Imaging Workshop, 13th Hunter Meeting, Hunter Valley, Australia. March
Keynote Speaker
University of Adelaide Postgraduate Research Symposium, Adelaide, Australia. July
Conference Organiser/Session Chair
6th Barossa Science Amongst the Vines Scientific Meeting: Cell Signalling in the Omics era Adelaide, Australia. November

Acute Leukaemia Laboratory

Dr Sarah Bray
European Hematology Association Travel Grant

Cytokine Receptor Laboratory

Ms Nicole Christie
Beat PhD Presentation at the Australian Society of Medical Research Annual Scientific Meeting 2013
Runner-up Best Poster for the University of South Australia Division of Health Sciences Research Policy Committee Poster Competition 2013

Haematology Clinical Research Laboratory

Mr Rick Tocicetti and Ms Mererilee Clarke (BloodMove)
SA Health Award
Excellence in Non-clinical Services
Australian College of Health Services Management 2013 Excellence and Innovation Award

Hepatitis C Virus Research Laboratory

Dr Guillaume Fiches
HCV2013 International Symposium on Hepatitis C Virus and Related Viruses Travel Award (Melbourne)

Leukaemia Unit, Genetics and Molecular Pathology

Associate Professor Susan Brainford
Australian Society of Medical Research SA Leading Lights Award 2013
Centre for Cancer Biology Best Primary Research Publication for 2012

Dr Wendy Parker
South Australian Young Woman of the Year Award 2013 from the South Australian Women of Year Reunion Group
Simpson Prize, Best Published Paper (Early Career)

Lymphatic Development Laboratory

Associate Professor Natasha Harvey
ARC Future Fellowship
ANZSCDB Young Investigator Award

Dr Garagevits Secker
Best Postdoctoral Oral Presentation, 3rd Adelaide Cell and Developmental Biology Meeting

Mast Cell Laboratory

Mr Nicholas Hauschild
Beat Presentation by a Research Assistant, Australian Society for Immunology SANT State Branch Adelaide Immunology Retreat

Ms Alicia Chenoweth
Best Presentation by an Honours Student, Australian Society for Immunology SANT State Branch Adelaide Immunology Retreat
First Class Honours Degree

Ms Viera Stanekova
High Achiever Vacation Research Scholarship, University of South Australia
Chancellor’s Letter of Commendation, University of South Australia
University of South Australia University of South Australia Medal 2013

Melissa White Memorial Laboratory

Ms Lisa Schafarnek
American Hematology Society Abstract Excellence Award, American Society of Hematology Annual Conferences, New Orleans, USA
Flinders Medical Research Poster Presentation Prize (F1S conference), Faculty of Health Sciences Postgraduate Research Conference, National Wine Centre, Adelaide, SA
Finalist/Runner-up Medical Staff Society Prize, Royal Adelaide Hospital Medical Staff Society, Adelaide, SA
Faculty Finalist 3 minute thesis competition, School of Medicine, University of Adelaide, Adelaide, SA

Mr Dale Watkins
SAAHMP Beat Poster Prize, University of Adelaide Faculty of Health Sciences Postgraduate Research Conference, Adelaide, SA

Ms Lisa Schafer
SA Health Award:
Haematology Clinical Research Department of Medicine, University of South Australia Scholarship, University of South Australia
High Achiever Vacation Research Scholarship, University of South Australia
Mr Guillaume Fiches
HCV2013 International Symposium on Hepatitis C Virus and Related Viruses Travel Award (Melbourne)

Mr Pranay Goel
Poster Prize, ANZSCDB, Adelaide 2013 Federation of Asian and Oceanian Biochemistry and Molecular Biology (FASBO) 2013 Lemberg Medal, the highest honour bestowed by the European Association of Nuclear Medicine and Molecular Imaging (EANM) Award for Research Excellence, the highest honour bestowed by the EANM

Dr Tessa Gargett
PHD (University of Adelaide)

Dr Alexander Stuecher
2013 EANM Eckard and Siegler Abstract Award, Lyon, France

Ms Kate Parham
SAAHMP Beat Poster Prize, University of Adelaide Faculty of Health Sciences Postgraduate Research Conference, Adelaide, SA

Dr Melissa Pitman
Runner-up, Adelaide Protein Group Early Career Researcher Awards, Adelaide, SA

Ms Heidi Naubauer
University of Adelaide School of Molecular and Biomedical Sciences Beat Poster Award, Adelaide, SA
Barossa 2013: Cell Signalling in the Omics Era meeting Student Poster Award, Barossa Valley, SA

Myeloma Research Laboratory

Dr Melissa Cantley
NHMRC Peter Doherty Early Career Fellowship
Selected to attend the Nobel Laureates meeting in June 2014

Neurovascular Research Laboratory

Dr Sophie Wilsnak
Beat Presentation, 3rd ANZSCDB State Meeting, Adelaide, SA

Ms Eiman Saleh
Beat Presentation, Adelaide Protein Group Meeting 2013, Adelaide, SA
Poster Award Combined 2013

Ms Viera Stanekova
Runner-up Best Poster Robinson Stem Cell Centre Annual Retreat

Translational Oncology Laboratory

Dr Tessa Gargett
PHD (University of Adelaide)

Dr Alexander Stuecher
2013 EANM Eckard and Siegler Abstract Award, Lyon, France

Ms Kate Parham
SAAHMP Beat Poster Prize, University of Adelaide Faculty of Health Sciences Postgraduate Research Conference, Adelaide, SA

Ms Lisa Schafer
SA Health Award:
Haematology Clinical Research Department of Medicine, University of South Australia Scholarship, University of South Australia
High Achiever Vacation Research Scholarship, University of South Australia
Mr Guillaume Fiches
HCV2013 International Symposium on Hepatitis C Virus and Related Viruses Travel Award (Melbourne)

Mr Pranay Goel
Poster Prize, ANZSCDB, Adelaide 2013 Federation of Asian and Oceanian Biochemistry and Molecular Biology (FASBO) 2013 Lemberg Medal, the highest honour bestowed by the European Association of Nuclear Medicine and Molecular Imaging (EANM) Award for Research Excellence, the highest honour bestowed by the EANM

Dr Tessa Gargett
PHD (University of Adelaide)

Dr Alexander Stuecher
2013 EANM Eckard and Siegler Abstract Award, Lyon, France

Vascular Biology and Cell Trafficking Laboratory

Associate Professor Claudine Bonder
ASMF Leading Light Award

Molecular Signalling Laboratory

Professor Sharad Kumar
Elected a Fellow of the Australian Academy of Science 2013
Lambeth Medal, the highest honour bestowed by the Australian Society for Biochemistry and Molecular Biology (ASHMB)

2013 Federation of Asian and Oceanian Biochemists and Molecular Biologists (FASBO) Award for Research Excellence, the highest honour bestowed by the FASBO

Dr Claire Wilson
NHMRC Early Career Research Fellowship

Mr Pranay Goel
Student Poster Prize, ANZSCDB, Adelaide

Mr Joe Youssef
Student Oral Presentation, ANZSCDB, Adelaide
Research Staff and Students

Acute Leukaemia Laboratory
Professor Richard D’Andrea
Associate Professor Ian Lewis
Dr Sarah Bray
Dr Anna Brown
Dr Mark Howie
Dr Michelle Pangui
Dr Saunya Samarawara
Mr Grant Engler
Ms Diana Iarossi
Mr Nick Lui
Ms Amilia Wai

Students
Nisha Rung (PhD)
Tanita Sadas (PhD)
Nur Huzin (Sahrun (PhD)
Kwok Zai Yu Maung (PhD)
Mohammad Basad (PhD)
Puspita Sudhi Walanthera (Masters of Biotechnology)
Yu Fang (Hons)

Students who completed their degrees during 2013
Yu Fang (Hons)
Tanita Sadas (PhD)
Puspita Sudhi Walanthera (Masters of Biotechnology)

Cell Signalling Laboratory
Associate Professor Yaosim Khan-Goold
Dr Lela Belle
Dr Xiaochun Li
Ms Freya Galhering

Students
Mr James Paltridge (PhD)
Ms Elizabeth Duncan (PhD)
Mr Rick Tocchetti
Ms Judy Stevens
Ms Susan Rodgers
Ms Judy Stevens
Mr Rick Tochetti
Mr Michael Yo

Students
Ms Elizabeth Duncan (PhD)

Gastroenterology
Research Laboratory
Associate Professor Andrew Ruszkiewicz
Dr Mario Caruso
Dr Jing Song Chen
Dr Melissa Thompson
Ms Teresa Tan

Gene Regulation Laboratory
Professor Greg Goodall
Dr Joanna Attonna
Dr Cameron Brackin
Dr Simon Corn
Dr Philip Gregory
Dr Kimi Homma
Dr Katherine Pilman
Dr Marika Salamindis
Dr Anna Tsikin
Mr Matthew Anderson
Mr Andrew Bart
Ms Saruya Roslan
Ms Rosemary Stallc

Haematology Clinical Research Laboratory
Professor L BK To
Dr}

Ms Kariaila Minka
Ms Zoe Donaldson
Ms Chai Field
Ms Guang Li (Masters)
Ms Kathleen Davey (Hons)

Leukaemia Unit, Genetics and Molecular Pathology
Associate Professor Susan Brantford
Dr Justina Marum
Dr Wendy Parker
Dr Layna Purins
Dr Doris Slang
Dr Paul Wang
Dr Nicholas Channon
Ms Zoe Donaldson
Ms Chai Field
Ms Jasmira Georgievski
Ms Mary Looong
Dr Stuart Phillips
Ms Nicola Roberts
Mr Brad Sullivan
Ms heavenly young (PhD)
Ms Chislina ivanson (Masters)

Lymphatic Development Laboratory
Associate Professor Natasha Harvey
Dr Kyle Paterson
Dr Genoveva Secker
Dr Declan O’Donnell
Dr Sebastian Tabony
Ms Jan Kaziendar

Mas Cell Laboratory
Associate Professor Michelle Grimbleston
Dr Natasha Kokoshnik
Dr Kevi Ho Yip
Ms Nicholas Hasun
Ms Svetlana Vassilieva

Students
Mr Han Yuan (Undergraduate)

Molecular Regulation Laboratory
Professor Shashidhar Kumar
Dr May Ang-Hiu
Dr Natasha Soase
Dr Donna Danton
Dr Lonita Doherty
Dr Natalie Foot
Dr Kimberly Mackenzie
Dr Jannett Manning
Dr Ian Nicholas
Dr Sonia Shahi
Dr Claire Wilson
Ms Ayisha Colaco
Ms Shannon Nicholas
Mr Andrej Nikolic

Students
Ms Swati Dawar (PhD)
Mr Prainy Goel (PhD)
Mr Lukas Painter (PhD)
Mr Joey Puccini (PhD)
Ms Tianqi (Cindy) Xu (PhD)

Molecular Signalling Laboratory
Professor Stuart Pitson
Dr Briny Qiang
Dr Melissa Pitman
Dr Jason Powell
Dr Craig Wellington-Beddoes
Dr Joanna Woodcock
Ms Kristy Alexander
Mr Carl Cooleen
Ms Lorena Davies
Ms Julia Dobbs

Translational Oncology Laboratory
Professor Michael P Brown
Dr Timo Smita
Dr Alexander Stachaur
Ms Rosa Katalanesa

Students
Ms Prithibha Sachi
Hons, co-supervised with Dr Lisa Ebert

Tumour Microenvironment Laboratory
Dr Michael Samuel
Dr Tony Poissant

Ms Jasmin Klaar

Gene Regulation Laboratory
Professor Andrew Zannettino
Dr Stanley Chaung
Dr Duncan Hewett
Dr Stephen Pittard
Dr Sally Martin
Dr Jacqueline Noll
Dr Kate Vandevi
Dr Melissa Cartney

PhD Students
Ms Krystyna Mroz
Ms Mary Matthews
Mr Arild Dutta
Ms Chia Min Chong
Ms Natalia Martin

Technical/Research Assistants
Ms Emma Thompson
Ms Kali Perham (PhD)
Ms Wai Yan Sun (PhD)
Ms Prithibha Sacari (Hons)

ACRF Cancer Genomics Facility
Professor Hamish Scott

Facility Manager: Dr Joel Geoghegan
Bioinformatics: Dr Andreas Schreiber
Dr Mark van der Hoek
Ms Roseale Kanyon
Ms Ming Li

Mr David Lawrence
Dr Angela Nol

Mr Jinghua (Frank) Fang

Dr Katherine Pitman
Mr Paul Wang
Mr John Toubia

Biocomputational
Bioinformatics: Dr Andreas Schreiber
Dr Mark van der Hoek
Ms Roseale Kanyon
Ms Ming Li

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