QUEENSLAND PREMIER'S AWARDS FOR HEALTH AND MEDICAL RESEARCH

Organised by the ASMR Qld Branch Committee and Queensland Health

Finalists for 2005

Post-graduate Student Award

Grant A. Challen
Institute for Molecular Bioscience, University of Queensland

Jennifer A. Kricker
Tissue BioRegeneration and Integration Program
School of Life Sciences
Queensland University of Technology

Daniel Lee Timms
The Prince Charles Hospital

Post-doctoral Award

Becky L. Conway-Campbell
Institute for Molecular Bioscience, University of Queensland

Maša Čemažar
Institute for Molecular Bioscience, University of Queensland

Chung Fai Wong
Epithelial Pathobiology Group, Cancer Biology Programme
Centre for Immunology and Cancer Research
University of Queensland
Princess Alexandra Hospital

Senior Post-Doctoral Award

Daniel F. Wallace
Queensland Institute of Medical Research

Katherine T. Andrews
Queensland Institute of Medical Research

Dagmar Wilhelm
Institute for Molecular Bioscience, University of Queensland

Grant A. Challen

In Search of Kidney Stem Cells

Institute for Molecular Bioscience, University of Queensland

In Australia, there are over 60,000 cases of advanced chronic renal disease (CRD) with about 7000 patients receiving dialysis at a cost of AUS$360 million per annum. The current treatment options are dialysis, which is expensive and has considerable morbidity, and transplantation which is limited by the number of donor organs available for transplant. An alternative treatment strategy currently being explored is the potential for stem cell therapy in renal failure patients. The main goal of this study is to identify and isolate potential stem cell populations from embryonic and adult mouse kidneys. Two approaches have been undertaken to facilitate this; (1) determining the molecular phenotype of the renal progenitor population via microarray gene expression profiling and (2) the characterisation of purified potential stem cell populations from embryonic and adult mouse kidneys.

(1) By analysing the genetic profile of the earliest cells in development that become committed to forming the kidney by microarray, it is anticipated that genes strongly expressed by these cells might be used to identify any resident stem cells in the adult kidney. Cell surface markers of renal progenitor cells are now being used to isolate cells with similar characteristics from adult kidneys by fluorescence-activated cell sorting (FACS).

(2) I have isolated potential stem cells from adult mouse kidneys based on properties that identify stem cells in other organs. I have purified these cells and analysed their stem cell capacity in numerous ways such as microinjection into embryonic kidneys and injection into mice with a chemically induced model of kidney disease. These models are now being employed to test the ability of various kidney cell populations to act as renal stem cells.

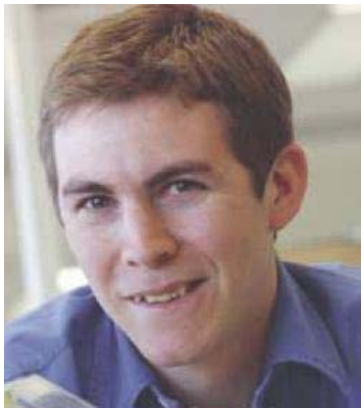
This work forms part of the renal regeneration consortium (RRC), a collaboration of Australian researchers with the long-term goal of developing cellular therapies for the treatment of kidney disease.

Jennifer Ann Kricker

Functional Analysis of the Impact of Glycosylation and Heparin-Binding Regions of IGFBPs on the Interaction of IGF-I with Vitronectin

Tissue BioRegeneration and Integration Program
School of Life Sciences
Queensland University of Technology

Breast cancer is the most commonly diagnosed form of cancer in Australian women, accounting for 26% of diagnosed cancers and 21% of cancer deaths among women. One in eleven women will develop breast cancer before the age of 75. There is currently no means of preventing breast cancer, however the focus of research has largely been on treatments and understanding the mechanisms behind its formation and spread. In 2001, the government estimated the annual total expenditure within the health system at $241 million. Early diagnosis is crucial for patient survival as the primary cause of death is the establishment and metastasis of the cancer from the breast to other sites within the body. This project has investigated the role of a group of proteins that are present within normal as well as metastatic breast tissue. Exposure of cells to these proteins in complex together, namely insulin-like growth factors (IGFs), IGF-binding proteins and vitronectin, act to increase cell growth and cell movement. This protein complex is a key requirement for effective wound healing. However, the interaction of IGFs with vitronectin via IGF-binding proteins is also found in breast cancer, whereby the body fails to recognise that the complex stimulates the migration of unhealthy cells which may lead to metastasis. Both the IGFs and vitronectin independently bind to cell surfaces and have been shown to cooperate to increase both cell growth and migration. Through understanding the interaction and the regions of the proteins involved as well as the effects of modifications such as glycosylation (addition of carbohydrate), the complex provides a potential target for therapeutics to disrupt the source of stimulated and unwanted cell migration. Clearly, this research is fundamental to understanding a mechanism behind breast cancer metastasis. Any intervention that lowers the cost of effective treatments would have a significant impact on the health care expenditure.



Daniel Lee Timms

A Medical Device to Give Cardiac Patients a Change of Heart

The Prince Charles Hospital

A new generation artificial heart under development at QUT and TPCH could ease the worldwide donor heart crisis, and extend the lifetime of cardiac patients by over 10 years.

Heart disease is the developed world's biggest killer, and the shortage of donor hearts has accelerated the development of mechanical alternatives.

Scientists, engineers and clinicians have tried to replicate the human heart for over 50 years. Although a number of pulsating devices have been developed, and in some cases worked briefly, they have invariably failed to match the success of heart transplantation.

In an attempt to produce a suitable alternative, current research is focused on devices that do not replace the heart; but rather work along side it to assist its function. Many of these current devices help the failing left ventricle; however some patients require the additional implantation of a second device to assist a failing right ventricle. This increases implantation time and associated risk, and because of the size of the current devices, reduces the access of smaller patients to this vital technology.

The research conducted at QUT and TPCH focused on developing a single rotary type bi-ventricular assist device (Bi-VAD) that has the capability to assist both ventricles of a failing heart simultaneously. This device employs both magnetic and hydrodynamic suspension techniques to float the rotating impeller, a technique that reduces blood damage and component wear, two of the major problems encountered with current generation devices.

Successful development of this innovative Bi-VAD will provide an alternative to heart transplantation, potentially saving thousands of lives each year. No longer would heart transplant candidates need to wait for the untimely death of a donor to provide a suitable heart. Instead, this new generation device would be available immediately, and be almost universally compatible with all patients. It has the potential to dramatically increase a patient’s expected lifetime, and to deliver them a higher quality of life.

Becky L. Conway-Campbell

Nuclear Localization of the Growth Hormone Receptor is Associated with Dysregulated Cell Cycle Progression and Tumorigenesis *In Vivo*

Institute for Molecular Bioscience, University of Queensland

Growth hormone (GH) is the major regulator of post-natal growth. Disease conditions include GH excess (acromegaly or gigantism) and GH deficiency (dwarfism). In addition to GH's most obvious effect on long bone growth, GH is known to have a number of beneficial metabolic effects including decreased fat deposition, increased lean muscle mass, anti-aging properties, immune and reproductive function. However the subject of debate recently has the disturbing occurrence of side effects associated with GH excess and GH treatment. One particular concern is that GH excess patients are predisposed to a variety of cancers, with colorectal, breast, and haematological malignancies being reported most frequently. Furthermore, a significant risk of metaplasia with long term GH treatment has been reported, and epidemiologic studies have indicated an increased risk from colon cancer with elevated plasma GH. Therefore our research is focussing on determining which signalling pathways are involved in this uncontrolled proliferative effect of GH, versus its beneficial metabolic effects. We have found that in normal proliferating cells, the GH receptor (GHR) is transiently nuclear localized at the beginning of the growth phase of the cell. However in cases of proliferative disorders, we find that there is an aberrant increase in nuclear GHR present. We have reconstituted this finding in a cell model, by targeting the GHR to the nucleus of a pre-leukemia cell line. We find that the increased nuclear localization is sufficient to render the cells factor independent, and to upregulate a number of genes associated with high proliferative status and tumorigenicity. When the nuclear-targeted GHR expressing cells were injected into immunocompromised mice, large aggressive metastatic tumours formed at every site of injection. In contrast, no tumours arose from cells expressing normal wild type GHR. Our research indicates that it is the deregulated nuclear localization of the GHR, rather than normal GH signalling per se that is associated with its cancer progressing properties. Therefore, strategies aimed at blocking GHR nuclear localization may provide potentially useful cancer therapeutics.

Maša Čemažar

Novel cyclic peptides for the treatment of multiple sclerosis

Institute for Molecular Bioscience, University of Queensland

Multiple sclerosis (MS) is a debilitating disease of the central nervous system that affects more than two million people worldwide, including about 25000 Australians. There is no curative treatment for this disease, in which the protective cover of the nerve fibres is damaged, causing a disruption in nerve transmission.

Fragments of proteins from the protective cover have been identified that might be able to significantly slow, if not halt, the progression of the disease. However, the direct use of peptides as therapeutics is limited by their intrinsic instability. In this study this limitation is overcome by placing the bioactive peptide into a stable molecular framework. The novel frameworks used here are the cyclotides, recently discovered natural plant peptides with a cyclic backbone that have a superb intrinsic stability.

To engineer lead molecules for the treatment of MS, we incorporated fragments of proteins from the nerve protective cover onto the cyclic framework of the model cyclotide kalata B1. The novel cyclic peptides were assessed for their structural similarities to the native framework by means of nuclear magnetic resonance spectroscopy. A structure of a representative peptide was determined and it shows remarkable resemblance to the native framework, which confirms the suitability of cyclotides as scaffolds for novel drug design.

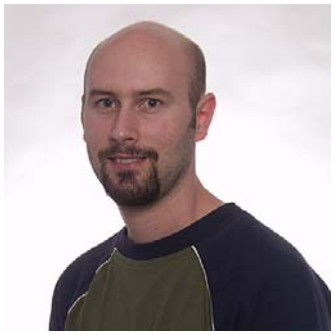
The activity of the novel cyclic peptides was tested *in vivo*. They were injected into mice before inducing the experimental equivalent of multiple sclerosis. One peptide in particular, shows very powerful activity: the mice injected with it did not fall ill, in contrast to the untreated animals that showed severe disease symptoms including limp tail and hind limb paralysis. This is an exciting result that shows the successful incorporation of an active linear peptide onto a cyclic framework. The structural information will be used in conjunction with the activity results for the successful design of the second-generation lead molecules.

Chung Fai Wong

Regulation of Squamous Differentiation by The E2F Family of Transcription Factors

Epithelial Pathobiology Group, Cancer Biology Programme
Centre for Immunology and Cancer Research
University of Queensland
Princess Alexandra Hospital

The skin is an essential organ of the body, acting as the first line of defence against dehydration, injury and infection. Structurally, the skin can be divided into two layers, the dermis and the epidermis, of which the main cell type in the epidermal layer is the keratinocyte. To maintain skin integrity and function, it is critical for keratinocytes to undergo a process known as squamous differentiation which results in keratinocytes altering in both appearance and genetic makeup. This process results in the (1) replacement of dead and damaged keratinocytes that are sloughed from the skin surface and (2) the accumulation of a range of genes that contribute to the skin's barrier properties. Disruption to this delicately-regulated process can result in the non-melanoma skin cancer, squamous cell carcinoma (SCC). This cancer accounts for approximately 20 - 30% of all non-melanoma skin cancer diagnosed and can spread to other organs of the body. Because of its life-threatening potential and incidence, treatment options focused on the origin of the cancer would be invaluable. At the molecular level, SCCs arise from a combination of deregulated keratinocyte growth and maturation. As such, genes associated with proliferation and maturation are expressed at abnormal levels. In our research, we have demonstrated that by inhibiting the gene, E2F, we are able to prevent uncontrolled growth of cancer cells and reinstate a normal process of maturation in the cancer cells. The current data would suggest that therapies targeting E2F in cancers could form the basis of a new class of anticancer agents.



Daniel F Wallace

The Liver in the Regulation of the Iron Homeostasis: Role of Hepcidin and Transferrin Receptor 2

Queensland Institute of Medical Research

Iron is essential for life. However, too much or too little can be harmful. According to the World Health Organisation up to 80% of the world's population may have iron deficiency, with 30% having anaemia (low haemoglobin). The iron overload disorder hereditary haemochromatosis is one of the most common genetic conditions, affecting 1 in 200 Australians. Excess iron in haemochromatosis can lead to liver damage, diabetes and arthritis. Most haemochromatosis is caused by mutations in the HFE gene. Other rare forms are caused by mutations in other genes such as transferrin receptor 2 (TfR2). Recent research suggests that the liver produced hormone hepcidin holds the key to most forms of haemochromatosis and anaemia. Hepcidin regulates body iron levels by reducing iron absorption in the intestine. In patients with HFE haemochromatosis hepcidin levels remain low, making the body think it is iron deficient and hence absorb too much iron. The converse is the case in the anaemia of chronic disease. Inflammation in patients with chronic diseases such as cancer, autoimmune disease and infections can cause hepcidin levels to rise and shut off iron absorption, leading to iron deficiency and eventually anaemia.

Hepcidin has proved to be a difficult molecule to study. We have produced a specific antibody to help us study the cell biology and regulation of this important molecule. Using this antibody we have shown where hepcidin goes to in liver cells and how it is regulated in mouse models of haemochromatosis and anaemia. In mice with haemochromatosis due to lack of TfR2, hepcidin levels remain low, suggesting that TfR2 as well as HFE are important for the regulation of hepcidin and the maintenance of body iron levels. Future studies are aimed at further defining the roles of hepcidin and TfR2 with the intention of identifying new therapeutic targets for the diagnosis and treatment of a wide range of iron-associated disorders, both overload and deficiency.

Katherine T. Andrews

Antiretroviral drugs as anti-malarials

Queensland Institute of Medical Research

Malaria is a parasitic disease transmitted by mosquitoes and affecting 300-500 million people annually, mainly in sub-Saharan Africa. The most lethal type of malaria is caused by the parasite *Plasmodium falciparum* and an estimated 1-2 million people die as a result of infection with this parasite each year. Unfortunately, there is currently no vaccine to protect people against malaria, and existing antimalarial drugs, such as chloroquine, are becoming less effective due the development of parasite resistance. New drugs that act on essential parasite processes are essential to combat drug resistant parasites.

Like malaria, HIV/AIDS is a major infectious disease throughout the world, particularly in developing countries where malaria is also endemic. Thus, people who are infected with both the malaria parasite and HIV may be treated with both anti-malarial and HIV drugs. This prompted us to explore the effect of HIV drugs on malaria parasite growth. Of the HIV drugs tested, we found protease inhibitors were the most effective. Five of seven HIV protease inhibitors were able to kill malaria parasites grown under laboratory conditions. Importantly, these drugs are effective against malaria at clinically relevant concentrations. We have confirmed these laboratory findings *in vivo* using mice infected with mouse malaria. The most significant results were obtained using protease inhibitor combinations of ritonavir with either saquinavir or lopinavir. These drug combinations are the same as those used to treat HIV/AIDS patients in clinical settings.

The observed inhibitory activity of antiretroviral protease inhibitors against malarial parasites raises the prospect of their use as antimalarial drugs. They have the advantage over new experimental antimalarial agents in development as they are already clinically available drugs that are widely prescribed for HIV/AIDS. Our findings have important implications for treatment strategies in co-endemic settings and suggest that appropriate choice of HIV drug combinations may also have an important role to play on malaria disease outcome.

Dagmar Wilhelm

Boy, Girl, or a Mix of Both: A Molecular and Cellular Mechanism to Reinforce Testis Development in the Male

Institute for Molecular Bioscience, University of Queensland

It is always taken for granted that everybody is either male or female. Unfortunately, this is not always the case. Disorders of sexual development in humans are surprisingly common. They range from mild genital ambiguity in up to 4% of male births to complete sex reversal (1 in 20,000 births). The arrival of an intersex baby is extremely traumatic and is commonly treated as a medical emergency. However, most of these disorders are still unexplained at the molecular level.

Our research focuses on molecular and cellular mechanisms that operate to ensure correct development of the testes and ovaries in the embryo, the first step of male or female sexual differentiation. These two completely different organs originate from a common precursor tissue in the fetus. There is one master gene, *SRY*, located on the male Y chromosome, which normally directs the cells of this tissue to develop as testicular and not ovarian cells.

We have discovered a mechanism whereby all cells in the fetal testis can be persuaded to develop as testicular cells even if their *SRY* gene is not functioning optimally. This way the intersex situation known as ovotestis (a mixture of testicular and ovarian cells) can be avoided. It involves a new signalling mechanism whereby already differentiated testicular cells instruct other cells to develop along the male pathway. We have defined this cross talk between the cells at the molecular level. Our findings may explain the low frequency of *SRY*-related intersex disorders in the human population.

Post-graduate Student Award Finalists

Grant A. Challen
Institute for Molecular Bioscience, University of Queensland
Research Funding: NIH Grant

Jennifer A. Kricker
Tissue BioRegeneration and Integration Program
School of Life Sciences
Queensland University of Technology
Research Funding: NHMRC Grant

Daniel Lee Timms
The Prince Charles Hospital
Research Funding: Prince Charles Hospital

Post-doctoral Award Finalists

Becky L. Conway-Campbell
Institute for Molecular Bioscience, University of Queensland
Research Funding: NHMRC

Maša Čemažar
Institute for Molecular Bioscience, University of Queensland
Research Funding: NHMRC, UQ Post-Doctoral Fellowship,
ARC Post-Doctoral Fellowship

Chung Fai Wong
Epithelial Pathobiology Group, Cancer Biology Programme
Centre for Immunology and Cancer Research
University of Queensland
Princess Alexandra Hospital
Research Funding: NHMRC Grant

Senior Post-Doctoral Award Finalists

Daniel F. Wallace
Queensland Institute of Medical Research
Research Funding: NHMRC and NIH

Katherine T. Andrews
Queensland Institute of Medical Research
Research Funding: NHMRC, Roche Australia and ACITHN (Australian Centre for International Tropical Health and Nutrition)

Dagmar Wilhelm
Institute for Molecular Bioscience, University of Queensland
Research Funding: ARC Grant