Kolling Institute of Medical Research

Molecular Solutions to Medical Problems

Research Report 2007
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Introduction

For more than a decade, growth has been a regular theme in my introductory remarks to the Kolling Institute’s annual research report. Although my own major research interest is in the growth of cells and tissues, it has been the growth and development of the Kolling Institute that has particularly concerned me as Director. Benjamin Franklin said that “without continual growth and progress, such words as improvement, achievement, and success have no meaning.” This may have some truth to it, but identifying opportunities to expand the Kolling Institute, when there was no short-term prospect of additional laboratory accommodation, has presented considerable challenges. Despite this restriction, over the last decade the Kolling has expanded more than 5-fold, both by “mergers and acquisitions” of other existing research groups on the Royal North Shore Hospital (RNSH) campus, and by recruiting new researchers from outside the hospital. As a result, the Kolling Institute now includes the majority of biomedical research undertaken at RNSH as well as an increasing number of clinical and public health research programs undertaken by our member departments.

In 2006 we proudly celebrated our 75th year as the Kolling Institute – making us slightly older than the Sydney Harbour Bridge. In some ways, 2007 was a year of even greater excitement as we saw the new Royal North Shore Hospital research and education building rise from a large hole in the ground to its full height of four education and seven research floors. The formal decision to name this research and education centre the “Kolling Building” recognises the Kolling’s place at the centre of Royal North Shore Hospital’s research excellence. Planning the details of the new building, its operations and its governance, continues to be extremely time-consuming, but the investment of time at this crucial stage will certainly pay important dividends in the future smooth running of the Kolling Building and its main occupant, the Kolling Institute of Medical Research.

In 2007 we saw some changes to the Kolling’s structure, including the departure of Paul Pilowsky’s Hypertension and Stroke research group to take up a new opportunity at Macquarie University. With the changing organisation of NSW pathology services, the time also came to part company with the Laboratory and Community Genetics laboratory, part of PaLMS and a contributor to the Kolling Institute since Leslie Burnett came to the RNSH campus a decade ago. Our thanks are due to both groups for their many contributions to the culture and productivity of the Kolling Institute. A further change in 2007 was the merging of the Cancer Genetics Research group, including Functional Genomics, with the Growth Research group, to form the new Hormones and...
Cancer group, which will occupy the majority of two floors in the Kolling Building, and will contribute both the Proteomics and Genomics core laboratories.

These changes saw the Kolling Institute at the end of 2007 with seven research divisions: Hormones & Cancer, Bone & Joint, Pain Management, Neurogenetics, Cardiovascular, Renal and Perinatal Research groups. The chart below shows the group organisation at the end of 2007, with the 5 major research themes headed by the Director and four Associate Directors.

“The 2007 Research Report outlines major areas of research strength within the Kolling Institute. While physical and organisational change goes on around us, our research staff and postgraduate students have maintained their high productivity and have once again excelled…”

For the first time all of the Kolling laboratories, which are currently scattered across the RNSH campus, have the prospect of sharing physical and intellectual space in the new Kolling Building before the end of 2008 - without exaggeration, the beginning of a new era for the Kolling Institute.

The 2007 Research Report outlines major areas of research strength within the Kolling Institute. While physical and organisational change goes on around us, our research staff and postgraduate students have maintained their high productivity and have once again excelled both in attracting a high level of input to their research (competitive grants, scholarships and fellowships) and achieving excellent outputs (publications, presentations, professional service etc.). We acknowledge the vital role of the Medical Research Support Program of the NSW Office of Science and Medical Research, without which it would be impossible to provide for the administrative and support staff so essential to the Kolling Institute’s operations. We’re also very grateful to the various donors whose continuing support of the Kolling Institute’s research effort - sometimes over many years - provides opportunities to take research projects beyond the boundaries of our formal grant applications, to pilot entirely new areas, and to purchase vitally needed equipment.

We are proud to have national and international leaders in each of our research areas working within the Kolling Institute, and to present the activities of their research teams in this report. Our contributions to the international medical research effort range from understanding the most basic mechanisms of cell growth and function, to investigations in human subjects that may have immediate benefits to patients. As usual, I invite interested readers to contact the Institute for further information about any aspect of our work or to visit our website at www.kolling.usyd.edu.au.

Professor Robert C Baxter
Director
Kolling Board

In 2007 the Board of the Kolling Foundation (formerly the Northern Medical Research Foundation) also served as the Board of the Kolling Institute of Medical Research.

- Mr Chris Westworth (Chairman): Senior Partner with Ernst & Young, Sydney.
- Mr Greg Brown: Chief Executive Officer, North Shore Private Hospital.
- Professor Michael Field: Associate Dean and Head of the Northern Clinical School, Faculty of Medicine, University of Sydney.
- Mr Mark Fordree: Managing Director, Emerging Growth Capital.
- The Hon Justice Tricia Kavanagh: Judge, Industrial Relations Commission of New South Wales.
- The Hon Craig Knowles: Company Director, former Senior Minister, New South Wales Government.
- Mr Hamish McDonald: Director, Business Technology, Pfizer Australia Pty Ltd.
- Professor Carol Pollock: Professor of Medicine at the University of Sydney and Royal North Shore Hospital.
- Professor Rob Baxter: Director, Kolling Institute of Medical Research.
- Mrs Mary Bonner, General Manager, North Sydney & Ryde Health Service.

Scientific Advisory Committee

- Professor John Funder (Chair): Senior Fellow, Prince Henry’s Institute of Medical Research, Melbourne.
- Professor John Bateman, Director Musculoskeletal Disorders, Murdoch Children’s Institute, Royal Children’s Hospital, Melbourne (from November 2007).
- Professor Rob Baxter: Director, Kolling Institute of Medical Research.
- Professor Georgia Chenevix-Trench: Laboratory Head Cancer Genetics, Queensland Institute of Medical Research, Brisbane (from November 2007).
- Professor Ross Clark: Chief Technical Officer and Founder, Tercica Inc., San Francisco, USA.*
- A/Professor Christine Clarke: Head, Breast Cancer Research Group, Westmead Millennium Institute, Sydney.
- Professor Michael Field: Associate Dean and Head of the Northern Clinical School, Faculty of Medicine, University of Sydney.
- Professor Beryl Hesketh: Pro-Vice Chancellor, College of Science and Technology, the University of Sydney (until April 2007).
- Professor Peter Leedman: Deputy Director, WA Institute of Medical Research, Perth.

*With deep sadness we learnt of the death of Ross Clark in June 2008 after a long illness.

Back row L-R: John Bateman, Christine Clarke, Georgia Chenevix-Trench, Peter Leedman

Front row L-R: Michael Field, Rob Baxter, John Funder
The Institute of Bone & Joint Research (IBJR) comprises the Bone & Joint Research Group of the Kolling Institute of Medical Research. It was established to advance our knowledge and understanding of the musculoskeletal system by:

1. Conducting basic and clinical research into diseases of bone, cartilage, tendon, ligament and joints. IBJR has particular research interests in the areas of osteoarthritis, rheumatoid arthritis, osteoporosis and spinal diseases and has focused on the epidemiology, diagnosis, causes and methods of treating these conditions.

2. Promoting awareness through regular education seminars for the public about new advances in these diseases and encouraging research by liaison with patient organisations and government.

This work is achieved by clinical research as well as basic science work in the Sutton Arthritis Laboratory, Raymond Purves Laboratory and the Murray Maxwell Biomechanics laboratory.

**Research Outcomes**

- Collaborative research between the IBJR and researchers at the St Thomas Hospital in London, has continued to use the twin model to identify genetic factors in lumbar disc disease. This work was published in the number one ranked arthritis journal (Arthritis and Rheumatism). Our twin studies have also identified the genetic basis of postmenopausal bone loss. This work was published in the number one ranked bone journal (Journal of Bone and Mineral Research). Professor Sambrook wrote invited reviews in the Lancet and the New England Journal of Medicine and was elected to the Board of the International Bone and Mineral Society during 2007.

- Members of the IBJR served on Editorial boards of several international journals including the Journal of Bone and Mineral Research, Journal of Rheumatology, Osteoporosis International and Arthritis Research.

- Associate Professor Lyn March has been the President of the Australian Rheumatology Association for 2006 & 2007 and has been an invited member of both the Commonwealth DOHA and NSW Health Expert Advisory Committees for Arthritis and Osteoporosis and a member of the AIHW Steering Committee for the National Monitoring Centre for Arthritis and Musculoskeletal Conditions. In 2007 A/Prof March was invited to be the international leader of the Musculoskeletal Expert Group for the Global Burden of Diseases 2005 Project.

**2007 Highlights**

- Dr Charles Chen: Osteoporosis Australia Macquarie Bank Fellowship 2007.

**Major Sources of Funding**

- National Health & Medical Research Council
- Australian Research Council
- Amgen
- Novartis
C Murray Maxwell Biomechanics Laboratory

The Murray Maxwell Biomechanics Laboratory (MMBL) is dedicated to the investigation of mechanical properties of the musculoskeletal system. Areas of interest include spine, articular cartilage, tendon and bone biomechanics, and implant design and evaluation.

Research Outcomes

The MMBL has been working closely with a number of surgeons and industry, rapidly building a reputation as a first class biomechanics research facility. Establishment of the anatomical skill program in collaboration with the Northern Clinical Skill Centre sets the Royal North Shore Hospital apart as the only hospital in NSW where surgeons can access donated cadaveric tissue for training. This cadaveric tissue is also used in our biomechanics program for evaluating implants and surgical techniques.

Highlights

A new INSTRON testing system (funded by the USyd Large Equipment Grant Scheme), along with a dedicated computer and electronic hardware, has significantly expanded the biomechanics research program, as well as providing implant testing capabilities. A new data acquisition system has also been acquired (funded by the Rebecca Cooper Trust) and is used in conjunction with the INSTRON to collect signals and digital images from a variety of transducers and digital cameras during material testing.

Obituary

Sadly Dr C. Murray Maxwell, who established the laboratory in 1992, passed away in 2006. His contribution to orthopaedics was extensive and his enthusiasm towards research and support of the MMBL will be sadly missed.

Major Collaborations

- Raymond Purves Bone and Joint Research Laboratories, RNSH.
- Orthopaedics Dept, RNSH and the Sydney Orthopaedic Research Institute.
- Northern Clinical Skills Centre (NCSC).
- WorleyParsons Advanced Analysis Group Pty Ltd.

Major Sources of Funding

- The Lincoln Centre
- Australian Research Council Linkage grant
- Medtronic
- Arthrocare Pty Ltd
- EBI Biomet Australia
The research focus of the Raymond Purves Bone and Joint Research Labs is the study of pathobiology of diseases of the musculoskeletal system. Diseases of bone and joints more than other tissues, constitute a failure to be able to withstand the mechanical forces to which they are exposed e.g. the fracture of a bone, the rupture of a tendon or the breakdown of the cartilage that lines a joint. Our research covers three main areas:

1. Joint disease in particular osteoarthritis.
2. Spinal disorders, in particular intervertebral disc degeneration.
3. Diseases of tendon, ligament and meniscus.

Perlecan and Versican are differentially expressed (red stain) in the vertebral body (VB), around the ossification centre (OC), in the cartilage canals (CC) and intervertebral disc (IVD) of the developing spine.

Our research is unique in bringing together expertise in cell biology, biochemistry, and biomechanics. A particular strength has been in the development and use of a range of culture systems and animal models of musculoskeletal disease. In recent years this work has included both large animal models and the generation and use of genetically modified mice. Our goal is to discover the molecular mechanisms that lead to degeneration of bone and joint tissues and their failure. Our tissue culture systems and animal models provide the basis for both discovering new disease pathways and thus therapeutic targets, and in collaborative studies with the pharmaceutical industry to test novel therapies that may halt or even reverse the disease process.

Research Outcomes

We have discovered for the first time that inhibiting the breakdown of cartilage proteoglycan by a single enzyme can inhibit arthritis development, and based on this and other work specific inhibitors have now entered phase 1 human clinical trials in the USA.

Using a unique model of tendon degeneration developed in our laboratories, we have now discovered that the same enzymes that are increased in arthritis are down regulated in tendon disorders and this may lead to accumulation of cartilage-like proteoglycan and contribute to tendon failure. Early trials suggest injection of stem cells may be useful to treat tendon disease that results from overuse.
The Sutton Arthritis Research Laboratories are affiliated with the Department of Rheumatology, Royal North Shore Hospital and Institute Bone & Joint Research and Kolling Medical Research Institute. The research focuses on examining the mechanisms underlying inflammatory arthritis.

The Sutton team made a serendipitous finding when studying the anti-inflammatory role of the natural anticoagulant activated protein C (APC). In addition to arthritis, APC proved to be beneficial in preventing type I diabetes and in healing chronic wounds. The wound healing study has progressed soundly through 2006-07. The study now involves collaboration of numerous RNSH staff from various departments including Dermatology, Rheumatology, Endocrinology, Severe Burns Unit, Vascular Surgery, Pharmacy and the Clinical Governance Unit.

Chronic leg ulcers are a major public health burden associated with high direct health-care costs and substantial negative impact on the quality of life of patients and carers. Despite recent advances in wound care many ulcers still fail to heal, leading to serious complications. In 2006-07, research in the Sutton laboratory has resolved mechanisms underlying APC’s actions in wound healing. In addition, ethics approval to conduct a pilot clinical trial in patients with chronic wounds was obtained. The preliminary results of this study conducted by Kaley Whitmont, Sara Tritton and Ian Reid are exciting, with patients showing dramatic improvement in healing and no adverse reactions were identified.

The team was approved to run 3 randomised, double blind, placebo controlled clinical trials examining the efficacy of APC on i) split skin grafts, ii) burns, and iii) chronic leg ulcers. The trials are an essential step toward the validation of the therapeutic use of APC in wound healing. Topical application of APC is likely to emerge as a highly cost-effective treatment for this difficult health problem. The results have potential to make an enormous contribution to the international knowledge of wound healing as well as having a significant impact on the patients and the society as a whole with reduced public health burden.

Research Outcomes

• The National Phase of an Australian Provisional Patent Application “Treatment for Autoimmune and Inflammatory Conditions”, was entered in July 2007 and a patent application was lodged in Europe, the United States of America and Australia. PCT/AU2006/000009 (Inventors- M Xue and C Jackson).

• Ten manuscripts arising from work performed in the Sutton Laboratory were published in 2007 including J Biol Chem (No 1 in Pagerank), Arthr Rheum (the number 1 rheumatology journal), Ann Rheum Dis (number 2 rheumatology journal).

2007 Highlights

• A/Prof Chris Jackson was invited to present the research of the Sutton Laboratory at several national and international meetings including: NSW Wound Healing Society Annual meeting, Wollongong, Nov 2007; Inaugural Combined Vascular Biology Society and ANZ Microcirculation Society meeting, Hepburn Springs, Victoria, September, 2007; Australian Rheumatology Association Annual Scientific Meeting, Sydney, May, 2007; Federation of Connective Tissue Societies (FECTS) meeting, Oulu, Finland, 2006; Australian Matrix Biology Society meeting, Melbourne, 2006.

• A/Prof Jackson and Dr Kaley Whitmont represented the Sutton Lab to feature on the ABC TV news, which highlighted their recent discovery of a new wound healing agent.

• Dr Meilang Xue was awarded a prestigious Career Development award for 4 years in 2007.

• A/Prof Jackson was invited to join the Editorial Board of the journal “Pathobiology” in 2006 and Dr Meilang Xue was invited by Dr Vincent C. Hascall, the Associate Editor of JBC, to become a member in the American Society for Biochemistry and Molecular Biology (ASBMB).

• A patent application entitled “Treatment and composition for wound healing” (2001-030-AU-0) was granted in 2007 in Australia (Owner-University of Sydney, Inventors- C. Jackson and P. Sambrook).

• The groundwork research in 2007 has led to successful grants valued at >$1M to begin in 2008.

Major Collaborations

• A/Professor Chris Jackson, Dr Meilang Xue and Prof Kenji Fukudome, Saga Medical School, Nabeshima, Saga, Japan. “Cytoprotective mechanisms of action of APC.” Prof Fukudome has provided reagents which are unavailable commercially to perform experiments. Outcome: Several joint publications.

• A/Professor Chris Jackson and Prof Alan Coombes, University of Queensland. Polycaprolactone-based bicomposite scaffolds for tissue regeneration. The Sutton Laboratory provided cell culture facilities and expertise for pharmacy students to complete their projects with Prof Coombes. Outcome: joint publication and co-supervision of 2 PhD students.

• A/Professor Chris Jackson and A/Prof Shing Shun Tony To, Differential effects of photofrin, 5-aminolevulinic acid and calphostin C on glioma cells. Prof Jackson provided expertise with endothelial cell culture. Outcome: One publication.

Major Sources of Funding

• National Health & Medical Research Council

• Rebecca Cooper Medical Research Foundation

• Northern Sydney and Central Coast Area Health Service

• The Lincoln Centre
The Cardiac Technology Centre (CTC) has continued to build on its strengths in Translational Research by using sheep models. There is no substitute for this approach in studying the heart and circulation because of their dynamic nature and because small animals such as rodents mostly provide “insights” that often require intermediate testing and validation in large animal models before application in the human setting. Our aim has been to create a bridge between rapid advances in cellular and molecular biology and classical physiological measurements in whole animals. This Integrative Physiology approach is epitomized by our studies of heart damage and repair which examine the role of stem cell therapy in replacing contractile muscle and blocked blood vessels.

Our aims include refining understanding of the coronary circulation in sheep, its similarity and differences from humans, and the study of various methods for creating myocardial infarcts that are reproducible, quantifiable and credible mimics of human heart attacks. This will be the platform for study of heart repair mechanisms which use drugs, stem cells or heart assist devices. It should make our Centre increasingly attractive for collaborations with groups who wish to validate basic findings obtained in rodents or those wishing to test leading edge cellular, pharmacological and device based therapeutic candidates.

“Our aim has been to create a bridge between rapid advances in cellular and molecular biology and classical physiological measurements in whole animals.”

Our research strategy is premised on the Centre's move to the new $91 million Research & Education (Kolling) Building jointly funded by the NSW Health Department and University of Sydney, which is ahead of schedule for occupation in late 2008. This will aggregate basic and applied science groups and Clinician Scientists, with creation of synergies and sharing of highly specialised equipment. It will provide unparalleled opportunities for Translational Research with arguably the most advanced on campus large animal facility in the country with the advantages of ready access to clinical interventional and experimental surgical skills. In anticipation of this move we have totally re-equipped our laboratory with state-of-the-art hemodynamic measuring devices, probes and catheters and data analysis and archival capability. We are quite excited with the installation of a dedicated Digital Angiography Suite and with potential access to a “High Field (3 Tesla)” Magnetic Resonance Imaging facility on campus.

Our work has had a consistent flavour of device technologies which are more important in the cardiovascular system than in other fields. Sensitive measurements of the mechanical performance and energetics of the intact in vivo heart of sheep, coupled with expertise in device technology and materials science as well as in Intellectual Property, patenting and commercialisation issues have been a differentiating feature of our work.

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Research Outcomes

The following three Research Projects illustrate advances in Translational Research in the Cardiac Technology Centre.

1. **Extracellular Matrix Remodelling Post Myocardial Infarction in Sheep**
   This work demonstrated that acute myocardial infarction (MI) leads to cardiac remodelling involving structural and molecular alterations that are dependent on the extent of damage to the regional contractile performance of myocardium. Alterations in inflammatory cytokines and MMPs are seen but the postulated beneficial effect of wound healing properties of short-term administration of activated protein C (APC) did not prevent progression of events in the early post-MI period, altered early after MI in a region-specific manner that corresponds to myocardial dysfunction.

2. **Potential Role of the Interventricular Septum (IVS) in Right Heart Failure Following Use of a Left Heart Assist Device (LVAD)**
   The frequent occurrence of severe right heart failure after placement of a left ventricular assist device (LVAD) has been identified as a major problem. This is believed to be due to disruption of ventricular coupling, IVS ischemia accentuates this. We therefore created chronic IVS damage using selective catheter delivery of ethanol to the IVS and studied RV response to variable LV unloading with a "shell subtraction model" using sonomicrometer crystals. Using sham controls, we discovered that whereas high level (75%) LV unloading causes RV dilatation & compromised function, chronic septal damage actually confers protection.

3. **Tracking of Injected Mesenchymal Stem Cells (MSC) in Sheep Heart**
   Opinion remains divided as to the fate of stem cells delivered to the heart for damage repair. There is roughly equal support for a "paracrine" mechanism that sees the dying stem cells providing benefit through the associated production of cytokines that stimulate native cell growth. We demonstrated that while some traditional fluorescent dye markers damage and/or rapidly lose signal in injected MSCs the Fluorescent marker Dil maintains fluorescence both in vitro and in vivo for up to 6 weeks. This characteristic allows tracking of MSCs delivered to damaged regions of the heart.

**2007 Highlights**
- During 2007 the laboratory-based researchers in Cardiology joined with the Cardiac Technology Centre to form the Northern Cardiology Research Group.

**Major Collaborations**
- Clinical Centre of Research Excellence and Mechanical & Nanoengineering, Monash University, Melbourne.
- Cardiology Department, Royal Prince Alfred Hospital, USyd.
- Royal Hobart Hospital, Clinical School, University of Tasmania.
- Sutton Rheumatism Laboratories, USyd & RNSH.
- Department of Haematology, Dept Anatomical Pathology, Dept Nuclear Medicine, RNSH.

**Major Sources of Funding**
- National Health & Medical Research Council (NHMRC)
- North Shore Heart Research Foundation (NSHRF)
- Office of Science & Medical Research (OSMR)
Cancer research, and research into hormonal (endocrine) diseases, have been major focuses of the Kolling Institute for over 20 years. The Hormones and Cancer Group formed in 2007 from the merging of research laboratories in Cancer Genetics, Functional Genomics and Growth Research. This reorganisation, following the appointment of Professor Bruce Robinson as Dean of the Faculty of Medicine, has united the Kolling’s major cancer research teams into a single group, providing new opportunities for interaction and collaboration. The new group’s research also continues to have a strong endocrine focus, both in the cancer area (hormone-dependent cancers including breast and ovarian cancer, and cancers of endocrine organs such as thyroid, parathyroid and adrenal glands) and in areas unrelated to cancer, such as bone metabolism and endocrine actions of growth hormone and growth factors. In addition to our strong links to the hospital departments of Endocrinology and Oncology, our ongoing interactions with cancer surgeons, including the research training of junior surgeons, provide constant opportunities for the cross-fertilisation of the group’s research between the laboratory and clinic.

Research Outcomes

The new group’s research continued the interests of its component laboratories, with the Cancer Genetics laboratories focussing on genetic studies in brain, adrenal and thyroid cancer, Functional Genomics concentrating on mechanisms of parathyroid and ovarian tumorigenesis, and Growth Research laboratories particularly involved in growth-regulatory mechanisms involving the insulin-like growth factors (IGFs), their binding proteins (IGFBPs), and other growth factor signalling pathways. The Laboratory for Cellular and Diagnostic Proteomics conducted proteomic discovery projects in the areas of both cancer (disease biomarkers in breast and pancreatic cancer) and endocrinology (detection of growth hormone abuse in athletes). Specific research outcomes of the group are detailed in the following reports from the Hormones & Cancer laboratories.

2007 Highlights

- The return of NHMRC CJ Martin Fellow, Viive Howell, from the USA and the award of a Cure Cancer Australia grant for her studies in ovarian cancer.
- The arrival of Dr Burkhardt Schuett from Germany on a Growth Hormone Research Society Fellowship and Cancer Institute NSW International Collaboration Grant.
- Rob Baxter’s opening plenary talk at the Gordon Research Conference on IGFs in Physiology and Disease, Ventura, CA.
- The appointment of Bruce Robinson as Dean of the Faculty of Medicine.

Major Collaborations

- Departments of Endocrinology, Surgery and Oncology at RNSH.
- Breast Cancer Tissue Bank.
- National Brain Tumour Bank.
- Collaborative grants in cancer proteomics with University of Sydney and Macquarie University APAF (Australian Proteome Analysis Facility) groups.
- CSIRO Bioinformatics.

Major Sources of Funding

- National Health & Medical Research Council
- Australian Research Council
- The Cancer Council NSW
- Cancer Institute NSW
- Cure Cancer Australia
- Cure for Life Foundation

Group Head
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The Hormones & Cancer Research team
Adrenal Laboratory

The Adrenal Laboratory studies phaeochromocytomas, rare tumours of the adrenal medulla, frequently causing an increase in the production of adrenalin and resulting in a life-threatening elevation in blood pressure. Currently there is no reliable test to predict the behaviour of a phaeochromocytoma, in particular if the tumour will metastasise. In addition the Adrenal Laboratory studies neoplasms of the adrenal cortex, namely adrenocortical adenomas (ACAs) and adrenocortical cancers (ACCs). Overall the work of the Adrenal Laboratory focuses on identifying genes which will lead to a greater understanding of the pathogenesis of these adrenal tumours, identifying markers to assist with the early identification of malignancy and ultimately improving the clinical management of these patients and their families.

Research Outcomes

- As a surgeon, Patsy Soon has been interested in identifying markers to differentiate benign from malignant adrenocortical tumours, as tumour pathology alone does not provide this information. This work jointly supervised by Bruce Robinson, Stan Sidhu, Dindy Benn and Kerrie McDonald has used microarrays to identify genes with significantly altered gene expression between benign and malignant tumours. As a result of this work, immunohistochemical staining for IGFII and Ki‑67 is being used by Dr Anthony Gill in this hospital in assisting pathological diagnosis.

- Win-Meyer Rochow an endocrine surgeon (supervisors Bruce, Stan and Dindy) has used dHPLC as a screening tool to genotype 74 phaeochromocytoma patients for mutations in VHL, SDHB and SDHD genes. These patients have phaeochromocytomas stored in the NeuroEndocrine tumour bank and they are also being used in gene profiling studies to discriminate benign from malignant tumours.

- Marinella Messina and Dindy are studying both truncating and missense mutations in a human heterologous and a rat phaeochromocytoma cell line. A model for examining SDHB truncating and missense mutations has been developed with differing growth effects observed in cells transfected with the mutant or wild type SDHB sequence.

2007 Highlights

- Professor Bruce Robinson was appointed Dean of the Faculty of Medicine, University of Sydney and he was also invited to speak at the Endocrine Society of Australia, Annual Scientific Meeting, Christchurch, September, 2007 on ‘Gene Testing – its role in Endocrinology’.

- Patsy Soon completed her PhD thesis in December and was awarded an NHMRC Health Professional Research Training fellowship for 4 years to be held jointly in the Kolling and as a breast endocrine surgeon at Bankstown Hospital.

- Stan Sidhu was appointed Clinical Associate Professor, University of Sydney and was invited faculty to Indian Association of Endocrine Surgeons in Lucknow, November 2007, speaking on ‘The Current Management of Adrenocortical Cancer’.

- At the Royal Australasian College of Surgeons Annual Scientific Congress in Christchurch, NZ in May, Patsy was awarded the Tom Reeve prize for the best oral presentation in the Endocrine Surgery section.

- Dindy Benn was invited to speak at the Familial Cancer Meeting (kConFab) at Couran Cove in August on ‘Towards an Understanding of Phaeochromocytoma and Paraganglioma’.

Major Collaborations

- Professor Hartmut Neumann (Freiburg, Germany), Professor Charis Eng (Cleveland, Ohio, USA), Dr Mike Croxson (Auckland, New Zealand), Dr Kathy Tucker (Prince of Wales Hospital and University of New South Wales) for phaeochromocytoma work.

- Professor Jerome Bertherat (Paris, France) for adrenocortical work.

Major Sources of Funding

- Hillcrest Foundation
- Cancer Institute NSW
- National Health & Medical Research Council
- Royal Australasian College of Surgeons
- Northern Sydney Central Coast Area Health Service
It is widely believed that one of the early events leading to cancer arises from changes in the way important growth information is transferred within and between cells. In all body tissues, normal growth and function is dependent upon hormones and growth factors binding to cells and activating biochemical signals which pass from one protein to another in tightly controlled pathways. If these signalling pathways become disrupted, perhaps because of changes in the hormones and growth factors which activate them, there can be a change in the balance of cell division and cell death which may lead to uncontrolled growth and cancer.

The research carried out in the Cell Signalling Laboratory is focussed on understanding how signalling pathways function during normal cell growth, and investigating changes that occur in these pathways during the development of diseases such as cancer. We are particularly interested in the role of insulin-like growth factor binding proteins (IGFBPs) as modulators of signalling pathways in different cancer cell types. These proteins play an important part in normal cell growth and division, and understanding how their function may change during the development or progression of cancer is one of the important goals of our ongoing research.

Research outcomes

In one of the main studies being carried out in the Cell Signalling Laboratory, we are investigating how IGFBP-3, one of the six IGFBPs, may stimulate tumour growth. Some clinical studies have shown that levels of IGFBP-3 in some tumours increase as the tumour grows larger and more malignant. This was unexpected because when studied in the laboratory, IGFBP-3 usually inhibits cell division and growth. Investigation into how IGFBP-3 might be stimulating tumour growth has now led to our discovery that it may work through another signalling system, the SK system, which is now known to be very important in cancer. By changing the way this system interacts with other growth factor signalling pathways, IGFBP-3 can increase breast cancer cell division and survival. If we block the SK system using anti-cancer drugs, IGFBP-3 is no longer stimulatory to cell growth and may, in fact, become inhibitory once again. We are now investigating how IGFBP-3 changes the SK system, and the significance of this in breast cancer.

In other studies being carried out in collaboration with Visiting Fellow Burkhardt Schuett, we are investigating how another IGFBP, IGFBP-2, functions in breast and ovarian cancer. This protein is present at very high levels in the blood of women with ovarian cancer, and it is thought to be involved in ovarian cancer growth and metastasis, or spread of disease to other tissues. Understanding how IGFBP-2 functions as a metastatic agent is very important, because most deaths from ovarian cancer are due to metastasis. We are looking at how cytokines and hormones such as estrogen regulate IGFBP-2 levels in ovarian cancer cells, and whether reducing the levels of IGFBP-2 produced by cancer cells affects the way they move and invade other tissues, which is a key process in metastasis.

2007 Highlights

- Dr Martin was an invited Symposium speaker at the ESA Annual Scientific Research Meeting in Christchurch, New Zealand in September, 2007, and attended the Gordon Research Conference on IGFs in Physiology and Disease in Ventura, CA, in March 2007.
- Dr Burkhardt Schuett joined the laboratory as a Visiting Fellow from Tubingen, Germany in May, 2007.
- Paper arising from a collaborative study with Sydney Children’s Hospital describing treatment of a boy with Proteus syndrome accepted for publication in Nature Clinical Practice Oncology.

Major Collaborations

- Prof Glenn Marshall and Dr Toby Trehair, Sydney Children’s Hospital.

Major Sources of Funding

- Cancer Institute NSW
The Laboratory for Cellular and Diagnostic Proteomics analyses disease mechanisms by examining changes in the patterns of proteins in both cultured cells and patient tissues. The central technology platform in the laboratory is a protein chip mass spectrometer (MS), which uses a powerful new approach to the analysis of complex protein mixtures such as serum and cell extracts by profiling hundreds of proteins simultaneously, thus creating characteristic patterns representing various cellular states or disease conditions.

Two-dimensional difference gel electrophoresis (DIGE) has also been used successfully in 2007. Dr Liping Chung continued as the manager of this facility in 2007, funded by a Cancer Institute NSW Infrastructure Grant, and has facilitated a variety of internal and external research projects. Most of our projects were collaborative, with our various collaborating groups described below.

Research Outcomes

Our proteomic research in breast cancer during 2007 had three strands. In the first, the discovery and identification of proteins in the tissue and serum of breast cancer patients that can be used as diagnostic or prognostic disease markers, we have developed a provisional panel of three proteins or peptides that, when used in combination, allow cancer tissue to be distinguished from healthy tissue with very high reliability. When fully validated, measurement of these proteins might provide new information to help in the diagnosis of malignant breast tissue, and may be developed to assist with staging of the disease. The second area is a cell biology project to discover cellular proteins that indicate when breast cancer cells show an apoptotic (cell death) response to various chemotherapies. Dose-response curves for a range of therapies have been developed, and protein changes measured both by protein chip MS and DIGE. Proteins that reliably indicate cell death may be useful in determining when a patient has responded to chemotherapy. The third project was a biochemical investigation of the pattern of phosphorylation in the growth-regulatory protein, IGFBP-5, in breast cancer cells. New phosphorylation sites were discovered, providing information that may help to understand how this protein can cause cell death in breast cancer.

The other major cancer project in 2007 was the continuation of a study on serum and tissue biomarkers in pancreatic cancer. This has resulted in further identification of proteins of possible diagnostic value. Among non-cancer projects underway in 2007, the analysis of protein biomarkers in white blood cell extracts, to help in the detection of growth hormone abuse in athletes, yielded several related proteins that may have diagnostic utility. Further identifications are in progress. Finally, the laboratory, which aims to serve as a resource to researchers both outside and within the Kolling Institute, also hosted several external studies, under the guidance of Liping Chung.

2007 Highlights

- Highlights included the publication of papers in Molecular and Cellular Proteomics and Cellular Physiology and Biochemistry.
- The graduation of Dr Michelle Moscova who completed her PhD on proteomic analysis of ovarian cancer cells, and Dr Chris Scarlett whose PhD was on biomarker discovery in pancreatic cancer.

Major Collaborations

- Prof Richard Christopherson, School of Molecular and Microbial Bioscience, University of Sydney.
- Dr Katrina Moore and Dr Sabah Shibli, Department of Surgery, RNSH.
- Prof Ross Smith and Ms Aiqun Xue, Department of Surgery, University of Sydney.
- Prof Phil Robinson and Dr Mark Graham, Children’s Medical Research Institute, Sydney.
- Prof Ken Ho and Dr Anne Nelson, Garvan Institute, Sydney.

Major Sources of Funding

- Cancer Institute NSW
- National Health & Medical Research Council
- Northern Sydney Area Health Service
The overall objective of the Cerebral Tumour Research Group is to discover biomarkers that have prognostic and predictive significance in cerebral tumours, specifically brain and pituitary. High grade brain tumours are universally fatal and have an extraordinary capacity to migrate long distances and infiltrate the normal brain, making complete surgical removal impossible. In addition, brain tumours are highly resistant to the chemotherapy. Whilst pituitary tumours are associated with a much more optimistic survival outlook, they can cause significant morbidity and premature mortality can result from mass effect and hormonal dysfunction. The genetic factors that cause pituitary tumorigenesis are largely unknown. Consequently, the molecular targets involved in invasiveness, drug resistance and the tumorigenesis of cerebral tumours need to be identified so that new therapeutic strategies can be established to reduce further tumour spread and improve overall survival.

**Research Outcomes**

- Dr Kerrie McDonald used microarray analysis to identify IGFBP-2 and IQGAP1 protein expression as significantly useful prognostic markers for brain tumours. These markers are currently being used routinely in pathology. This work was published in 2007 and a provisional patent was taken out on the use of these markers.

- Dr Jonathon Parkinson, a neurosurgical trainee, completed his PhD examining the mechanisms of chemotherapy resistance in high grade brain tumours at the end of 2007. Dr Marinella Messina and Professor Bruce Robinson jointly supervised the work. High levels of the DNA repair gene, MGMT, have been associated with a poor patient response to temozolomide which is the most common chemotherapy administered to patients with a high grade brain tumour. Two manuscripts were accepted for publication (published 2008).

- Dr Ann McCormack also examined MGMT gene expression in pituitary tumours. This research was jointly supervised by Dr Rory Clifton-Bligh and Professor Bruce Robinson. Dr McCormack’s PhD examined the incidence of MGMT promoter methylation in a large cohort of pituitary patients and correlated low MGMT levels with patient response to temozolomide therapy.

- Dr Marianne Elston used microarray analysis to discover the loss of the gene, wif1, was a significant event in pituitary tumorigenesis. This research was jointly supervised by Dr Rory Clifton-Bligh and Professor Bruce Robinson. By restoring expression levels of Wif1 in a rat pituitary cell line, she showed that tumour cell growth was significantly suppressed, providing evidence for Wif1 as a potential tumour suppressor. This research was accepted into Endocrinology in 2007 (published 2008) and her presentation at the Endocrine Society of Australia was rewarded with the “Best Presentation from a Junior Scientist” award.

**2007 Highlights**

- Four manuscripts were accepted (3 published in 2008).
- Dr Marianne Elston was awarded the Novartis Junior Scientist Award for the best presentation at the Endocrine Society of Australia.
- Dr Jonathon Parkinson was awarded the Sanofi-Aventis Prize for the best presentation at the RNSH UTS USyd Kolling Scientific Research Meeting 2007.
- Dr Kerrie McDonald was awarded a Cure For Life Fellowship.
- Dr Kerrie McDonald was an invited speaker at the Clinical Oncology Society of Australia (COSA) meeting in Adelaide.

**Major Collaborations**

- Ms Maree O’Sullivan and Mr Glenn Stone, Mathematical and Information Sciences, CSIRO: Identification of molecular genetic markers in glioma subtypes with high density-cDNA microarrays.
- Prof Roger Reddel, Childrens Medical Research Institute (CMRI) and Dr Janice Royds, University of Dunedin, NZ: Alternative Lengthening of Telomeres and Outcome in Glioblastoma patients.
- Dr Charles Teo, Prince of Wales Hospital.
- Dr John Conaglen, Waikato Hospital, New Zealand.

**Major Sources of Funding**

- Andrew Olle Memorial Foundation
- Sydney Neuro-oncology Group
- Cure For Life Foundation
- Cancer Institute NSW
- Caledonia Foundation
- Australian Research Council LIEF
Functional Genomics Laboratory

Our laboratory studies the molecular biology of sporadic and inherited tumours, as well as generalised cellular overgrowth. In 2007 we have focused on two tumour suppressors, parafibromin and PTEN, as well as the phosphatidylinositol 3-kinase (PI3-K) pathway that is commonly upregulated in response to PTEN mutation or other genetic changes. We are also investigating a role for gonadotropins in the development of ovarian cancer.

Research Outcomes

1. Parafibromin - Understanding a Tumour Suppressor

Parafibromin is the tumour suppressor implicated in parathyroid, kidney, jaw and possibly other tumour types. Dr Michael Hahn has undertaken extensive cellular localisation studies of parafibromin and published in FEBS Letters showing parafibromin can be found in the nucleolus. This opens up a number of intriguing possibilities as to the role of nucleolar parafibromin. Along with research assistant Kristie Dickson, Michael is working on characterising binding partners of parafibromin and describing the role of this protein in healthy and cancer cells.

2. Gynaecological Cancer

Previous work undertaken collaboratively with Professor Baxter identified markers of PI3-K signalling in ovarian cancer cell line models. Dr Christine Bolitho is determining whether two of these markers, CXCL1 and interleukin-8, have functional roles in ovarian cancer. PhD candidate Lujia Gribbens is investigating markers of PI3-K signalling in endometrial cancer.

The "gonadotropin hypothesis" is one of the leading hypotheses regarding the development of ovarian cancer. Elevated levels of gonadotropin hormones are seen in postmenopausal women and have stimulatory effects on ovarian surface epithelial cells. PhD candidate Inga Mertens is investigating the pathways that might be involved in this process. Dr Vive Howell has established new collaborations in 2007 to facilitate development of mouse models of ovarian cancer to investigate these and other questions.

3. PTEN in Overgrowth and Cancer

As well as roles in cancer, activation of the PI3-K pathway has been linked to generalised cellular overgrowth. PhD candidate Wey Yeeng Chee is investigating the function of PTEN mutations known to occur in patients and determining the cellular localisation of wild-type and mutant PTEN.

4. Tumour Banking

Lynette Barrett and Ussha Pillai have established links with new surgeons in 2007 as well as maintained and strengthened many links with clinical staff to continue to develop and grow the Kolling Institute’s tumour banks. Our tumour banks represent powerful resources that enhance the Hormone and Cancer group’s translational research programs.

2007 Highlights

- The return of Dr Viive Howell to the group as a NHMRC CJ Martin Fellow after 2 ½ years postdoctoral training at the Department of Human Genetics, University of Michigan, Ann Arbor, USA under the mentorship of Professor Miriam Meisler. Viive brings extensive knowledge in mouse genetics to the group that she will be using in the first instance, to develop mouse models of ovarian cancer.

- Dr Christine Bolitho’s research into ovarian cancer signalling pathway biomarkers was recognised by a Runner-Up New Investigator Award at the RNSH-UTS-USyd-Kolling Institute XXIV Annual Scientific Research Meeting in November. Christine used this award to attend the American Association for Cancer Research Meeting in 2008.

Major Collaborations

- Dr Anthony Gill in the Department of Anatomical Pathology, RNSH, developing improved diagnostics for parathyroid tumours.

- Prof Glenn Marshall, Dr Toby Trahair, Dr Edwin Kirk and Dr Jan Walker from Sydney Children’s Hospital and the Children’s Cancer Institute Australia and Professor Rob Baxter and Dr Janet Martin investigating Proteus syndrome.

Major Sources of Funding

- Cancer Institute NSW
- NSW Cancer Council
- National Health & Medical Research Council
- Australian Research Council
- National Breast Cancer Foundation
The Gene Regulation Laboratory is interested in how cells respond to signals from the insulin-like growth factor (IGF) receptor, and how these responses are modified by other signals that influence the cells behaviour. In this context we are investigating the role of IGF and transforming growth factor-β (TGF-β) signalling in the development and progression of human osteosarcoma. These cancers are the most common primary bone tumours seen in childhood and adolescence. Despite recent advances in surgical procedures and the use of adjuvant chemotherapy, almost one third of patients with non-metastatic disease, and most patients with metastases at diagnosis, do not survive. The long-term goal of this study is to identify the IGF and TGF-β receptors as new therapeutic targets for human osteosarcoma, and to validate the use of inhibitors against these receptors in the treatment of osteosarcoma. Another research area is focused on understanding the role of the IGF binding protein, IGFBP-3, in the growth and survival of breast cancer cells, and how IGFBP-3 affects cell signalling by growth factors such as epidermal growth factor (EGF).

**Research Outcomes**

- Cell signalling pathways rarely function in isolation, and the IGF and TGF-β pathways are no exception. They are linked by the ability of TGF-β to induce the expression of the IGF binding protein, IGFBP-3, which in turn modulates signalling through the IGF receptor. Our laboratory has shown that the TGF-β-induced expression of IGFBP-3 prevents TGF-β from stimulating the growth of osteosarcoma cells, and that these effects are mediated by IGF receptor signalling. Future studies will apply these findings to animal models of human osteosarcoma with the aim of establishing an in vivo role for IGF and TGF-β signalling in the development and progression of osteosarcoma.

- In another project we are investigating the effects of IGFBP-3 on breast cancer cell growth. IGFBP-3 is well characterised for its ability to regulate the growth stimulatory and survival effects of IGFs. However, it is now clear that IGFBP-3 can exert its own biological effects independently of IGF receptor signalling. The majority of studies have examined the effects of IGFBP-3 in culture systems where IGFBP-3 has been added or over-expressed in cells. Our approach has been to examine the biological effects of IGFBP-3 following a reduction in its expression using RNA interference. In the MDA-MB-231 breast cancer cell line, down-regulating IGFBP-3 expression led to enhanced cell growth, consistent with its known role as an anti-proliferative agent in breast cancer cells. By blocking activation of the IGF-1 receptor, these effects were shown to be predominantly IGF-dependent. An ideal model in which to examine the IGF-independent effects of IGFBP-3 is the Hs578T breast cancer cell line as it does not possess a functional IGF receptor. Other work has investigated the functional interaction between IGFBP-3 and cell signalling pathways essential for the growth and survival of breast cancer cells. In this context we have shown that down-regulating IGFBP-3 decreases the expression of members of the MAPK signalling pathway. As a consequence the activation of this pathway by EGF, a growth factor which stimulates the proliferation of these cells, was found to be impaired.
Protein Structure Function Laboratory

Growth factors are fundamental in the regulation of normal development and growth. The insulin-like growth factors, IGF-I and IGF-II, are peptide hormones that are essential for early development as well as for achieving maximal growth. However, high serum levels of IGFs in adults have been associated with an increased risk for prostate, breast and colorectal cancers. Hence, the understanding of how IGFs are normally regulated is not only important for normal physiology but also for diseases like cancer.

Research Outcomes

In normal circumstances, the activity of IGFs is tightly controlled by binding to IGF-binding protein-3 (IGFBP-3) or IGFBP-5 and the formation of a complex with a third protein, acid-labile subunit (ALS), which effectively prevents the IGFs from leaving the bloodstream. We have now shown that IGFBP-5 is degraded during pregnancy and that the degrading activity increases as pregnancy progresses, indicating that there may be increased release of IGFs from these complexes during pregnancy through the degradation of IGFBP-5.

Recently, a novel mutation that caused a single amino acid substitution in the ALS protein was described in a patient that lacked ALS. When we produced this mutated version of ALS in the laboratory, we found that the mutated ALS was no longer able to form complexes with IGF-I and IGFBP-3. We propose that this results in low IGF-I and IGFBP-3 serum levels that contributed towards growth retardation of the patient harbouring this ALS mutation. These studies indicate that ALS is an important regulator of IGF-I availability and activity.

In addition to its role as a regulator of IGF activity, IGFBP-3 functions as a growth inhibitor in several cancer cell types, including breast, prostate and lung cancers. However, we have found that with prolonged exposure to IGFBP-3, breast cancer cells can overcome the IGFBP-3 effect and paradoxically become growth stimulated instead. We hypothesise that IGFBP-3 may impact on the balance between cellular processes that result in inhibition and stimulation of growth. Surprisingly, we have not found any major changes in the levels or activity of the major proteins involved in inducing programmed cell death. This would suggest that the growth stimulation in response to prolonged IGFBP-3 exposure is not due to decreased cell death.

We are continuing in our endeavours to identify novel proteins that interact with IGFBP-3 and IGFBP-5, as an initial step in understanding how these proteins can bring about effects on cellular growth independently of binding IGFs.

2007 Highlights

- The award of Cancer Institute NSW Research Scholarships to PhD students, Penny Ho, Gang Lu and Cindy Pon.
- The award of a NSCCAHS Research and Development Grant to Steve Grkovic.
- Publication that IGFBP-3 binds to nuclear hormone receptors, RARα and RXRα.
- Identification that IGFBP-3 binds to yet another nuclear hormone receptor, PPARγ, and interferes with its function in breast cancer cells. Activation of the PPARγ signalling pathway results in growth inhibition and our preliminary data suggests that IGFBP-3 synergises with PPARγ in inhibiting breast cancer cell growth. PPARγ is best known for its role in regulating the development of fat cells.

Major Collaborations

- Dr Lynette Schedlich (Gene Regulation Laboratory).
- A/Prof Stephen Twigg (Royal Prince Alfred Hospital).

Major Sources of Funding

- Australian Research Council
- Cancer Institute NSW
- Association for International Cancer Research
- Sydney University Cancer Research Fund
Our work has focused on two areas.

1. **Thyroid Cancer Genetics**

We have focussed on a fusion protein that is present in at least 50% of follicular thyroid cancers, namely PAX8-PPARγ. We have shown that PAX8-PPARγ has mixed transcriptional function, in that it stimulates some (but not all) PAX8 genes as well as some (but not all) PPARγ gene targets. For instance, we have shown that the PPARγ target genes aquaporin 7, angioptatin-like 4 and enolase 3 are all upregulated in thyroid cancers containing PAX8-PPARγ. The specific and substantial upregulation of aquaporin 7 (a glycerol channel) is particularly important as it identifies a potential source of cellular energy.

The most important PAX8 gene target that we have studied is that encoding the sodium-iodine symporter gene. This is a key target in thyroid cancer management since its expression is the means by which metastases are ablated using radioactive iodine. Since PPARγ is a receptor for thiazolidinediones (a new class of therapy for diabetes) we hypothesize that this treatment will allow re-expression of the sodium-iodide symporter in thyroid cancers that have become resistant to iodine therapy. Our basic transcriptional insights are therefore directly relevant for identifying new therapies for thyroid cancer.

“Our basic transcriptional insights are therefore directly relevant for identifying new therapies for thyroid cancer.”

2. **Phosphate and Vitamin D Regulation by FGF23**

FGF23 is currently the best candidate for ‘phosphatonin’, a hormone that promotes renal phosphate clearance, inhibits skeletal mineralization and reduces serum 1,25-dihydroxyvitamin D (1,25(OH)2D) concentrations. We and others have found that FGF23 produced by certain mesenchymal tumours is associated with a clinical syndrome of bone pain and low blood phosphate concentrations (oncogenic osteomalacia).

We have now discovered that FGF23 is elevated in patients with a genetic form of hyperparathyroidism, namely Familial Hypocalciuric Hypercalcaemia. This observation extends our understanding of the interplay between the kidney-bone-parathyroid axis of phosphate homeostasis.

We have also studied the biological effects of FGF23 on vitamin D metabolism. Several conditions associated with elevated bioactive FGF23 are known to have low active vitamin D (1,25-dihydroxyvitamin D3) levels. We have shown in vitro that FGF23 stimulates expression of an enzyme that de-activates vitamin D. Interestingly, purified FGF23 appeared to lack full biological activity which might be explained by the lack of a recently described obligate co-factor termed Klotho. Our latest work aims to over-express klotho and to study its effect on FGF23-mediated vitamin D regulation.

**2007 Highlights**

- PPARγ findings presentation at the Annual Scientific Meeting of the Endocrine Society of Australia held in Christchurch, New Zealand by Amy Au and Takafumi Taguchi.
- Ms Inge Stewart (Kolling PhD student) presented her work on FGF23 levels in a genetic model of hyperparathyroidism at the 2007 meeting of the Australian and New Zealand Bone and Mineral Society in Queenstown, New Zealand. She has now submitted her PhD thesis.

**Major Collaborations**

- Professor Ron Koenig (University of Michigan).
- Professor Catharina Larsson (Karolinska Institute).
The current focus of the tumour biology group is to determine the mechanism of action of a tumour suppressor protein, the mannose 6-phosphate/insulin-like growth factor-II receptor (M6P/IGFIIIR). Levels of this protein are decreased in a range of tumour types suggesting that it plays an important role in the development or growth of tumours.

We have previously shown that experimentally reducing M6P/IGF-IIR levels in breast cancer cells (MDA-MB231 and T47D) not only increases their ability to develop tumours in nude mice, but also increases motility, invasion and anchorage-independent growth, all properties required to develop a metastatic potential. We have therefore initiated a program of research to investigate the effect of M6P/IGF-IIR knockdown on metastatic growth of tumours and on changes in the expression of genes that may play a role in this phenotype.

Also under investigation is the role played by a soluble form of the M6P/IGF-IIR, released from cells and also found in the circulation. This protein retains binding activity for its M6P bearing ligands and for IGF-II and we have shown that it inhibits cell proliferation. One possibility being examined is that the soluble form of the receptor is the mediator of the cell associated M6P/IGF-IIR.

Research Outcomes

- Reduction of M6P/IGF-IIR in breast cancer cells (MDA-MB-231) was found to have a profound effect on their metastatic capacity in a mouse model of lung metastasis with a significant 2-fold increase in the number of mice with metastases and a 25-fold mean increase in number of metastases from cells with reduced M6P/IGFIIIR compared to control cells.

- Reduction of M6P/IGF-IIR levels by antisense knockdown in MDA-MB-231 cells led to changed expression of a number of key genes as determined by RNA microarray analysis. A number of these genes are oncogenes or tumour suppressors or proteases and may therefore play a role in the changes in tumorigenesis observed in these cells. In particular we have verified that the matrix metalloproteinases, MMP-1 and -9, have increased expression by western blotting and increased activity by zymography. The effect of these changes on tumorigenic properties of the cells is currently under investigation.

"We have ... initiated a program of research to investigate the effect of M6P/IGF-IIR knockdown on metastatic growth of tumours and on changes in the expression of genes that may play a role in this phenotype."

2007 Highlights

- Presentation at a Gordon Conference, ‘IGFs in Physiology and Disease’ on the role of HIF1alpha in the inhibition of IGFBP-1 secretion in M6P/IGF-IIIR transfected cells.

Major Sources of Funding

- Cancer Institute NSW
- University of Sydney
Our group investigates the pathogenic mechanisms involved in neurogenetic disorders with a particular interest in mitochondrial function and movement disorders. Genetic and biochemical approaches are employed to identify the molecular basis of neurogenetic disease. The group provides diagnostic support for a tertiary referral clinic for mitochondrial and movement disorders and our research focus is to develop new therapies to treat various types of neurogenetic disease. The group comprises two laboratories: the mitochondrial research laboratory and the movement disorder genetic laboratory. Current studies include the identification of new mtDNA mutations associated with mitochondrial diseases, development of new biochemical assays that may lead to better diagnosis of Parkinson's disease, validation of a genetic (DNA) chip for the improved diagnosis of genetic forms of Parkinson's disease, work to improve our understanding of the mechanisms of neuronal dysfunction in patients with both mtDNA and nDNA encoded mitochondrial disorders, epidemiological studies to determine the prevalence of genetic forms of Parkinson's disease and the development of a new neuronal model to study neurogenetic disease.

Research Outcomes

- Identification of rare genetic forms of mitochondrial disease.
- Identification of genetic markers that influence the age of onset of Parkinson's disease.
- Discovery of the prevalence of mitochondrial disease associated with MELAS 3243A>G mutation.
- Demonstration that mitochondrial haplogroups are risk factors for age-related hearing loss and age-related maculopathy.
- Demonstration that mitochondrial haplogroups modify other risk factors for age-related hearing loss and age-related maculopathy.
- Identification of patients with LRRK2 gene mutations.
- Identification of a novel LRRK2 gene mutation.
- Publication of 8 peer-reviewed articles.

2007 Highlights

- Professor Christine Klein (University of Luebeck, Germany) visited the Department of Neurogenetics in October 2007.
- Head of Department Carolyn Sue was an invited speaker at the Australian and New Zealand Association of Neurologists Neurophysiology Workshop.
- Head of Department Carolyn Sue was an invited speaker at the Australian and New Zealand Association of Neurologists Annual Scientific Meeting.
- PhD student Prachi Mehta was awarded a Kolling Institute Travelling scholarship.
- PhD student Prachi Mehta was awarded an APA PhD scholarship.
- PhD student Prachi Mehta gave birth to her first child (son).
- PhD student Farrah Tate was awarded a National Centre for Adult Stem Cell Research PhD scholarship.

Major Collaborations

- Alan Mackay-Sim (Griffith University, Qld).
- Glenda Halliday (Prince of Wales Medical Research Institute, NSW).
- Christine Klein (University of Luebeck, Germany).
- Justin Rubio (Howard Florey Institute, Vic).
- Paul Mitchell (Centre for Vision Research and Save the Sight Institute, NSW).
- John Christodoulou (Children's Hospital Westmead, NSW).
- David Thorburn (Murdoch Childrens Research Institute, Vic).

Major Sources of Funding

- National Health & Medical Research Council
- NSW Parkinson's Disease Association
- Northern Sydney Area Health Service
- National Centre for Adult Stem Cell Research
The Pain Management Research Institute (PMRI), a division of the Kolling Institute, comprises more than 60 basic and translational researchers, including 20 postgraduate students. A further 40 individuals are directly involved in clinical treatment, research and education programs.

PMRI runs an intensive research program investigating mechanisms and treatment of a wide range of persistent pain problems that many people suffer. Our research pursues the broad theme that persistent pain is a disease entity with its own symptoms, signs and underlying disorders such as abnormal sensory, spinal cord and brain neuronal physiology, neurochemistry, anatomy, and pathology.

During 2007, senior investigators at PMRI were highly successful in attracting national competitive grants from NHMRC, ARC and ANZCA. Thanks to generous support from donors, another highlight of 2007 was the opening of the Pamela and Graham Nock Behavioural Laboratories at PMRI. The Medical Foundation of the University of Sydney has also assisted our program to develop genetic approaches to analyse pain mechanism in mouse models.

The laboratories include the Brain, Body, Behaviour & Society Research Laboratory, Cellular Research Laboratory, Pain Management Human Studies Group, Neuropharmacology Laboratory, Opioids and Neuropathic Pain Laboratory, Peripheral Mechanisms and Injury Laboratory, Sensory Neuroscience Laboratory, Spinal Cord Injury Pain Clinical Research Laboratory, and the Synaptic Physiology & Plasticity Laboratory.

Research Outcomes

- **Prof Macdonald Christie, Neuropharmacology Laboratory:** Identified the therapeutic potential of a novel TTX-resistant sodium channel blocker in persistent pain. Identified the potential therapeutic targets of subtype selective nicotinic receptor blockers in nerve injury pain. Identified adaptations of calcium channels in spinal cord in persistent pain, suggesting limited utility of blockers.

- **Dr Mark Connor, Sensory Neuroscience Laboratory:** Identification of a family of endogenous modulators of T-type calcium channels that variously increase or decrease channel activity. Creation of a functional model system to investigate the effects of anti-migraine drugs on their receptor targets. Identification of the complete pathway for the synthesis of serotonin by trigeminal ganglion cells.

- **A/Prof Janet Keast, Peripheral Mechanisms & Injury Laboratory:** First detailed anatomical mapping of how spinal cord injury affects five different populations of pain-related nerve fibres in the spinal cord, showing changes that may relate to onset or maintenance of neuropathic pain. Identification of estrogenic growth responses in male pelvic autonomic neurons, suggesting new mechanisms for potentially modulating regeneration after injury. A/Prof Keast elected President, International Society for Autonomic Neuroscience (ISAN).

- **Dr Michael Nicholas, Brain, Body, Behaviour & Society Research Laboratory:** NHMRC project grant to M. Nicholas and L. Sharpe for study of pain desensitizing techniques. NHMRC project grant to M. Nicholas (PMRI) with Prof G. Murray and A/Prof C. Peck (School of Dentistry, USyd) to examine psychological factors in jaw pain. The publication by ACCESS Economics of a report on the cost of pain in Australia. Fiona Blyth was a major contributor to this report (funded by MBF).

- **Dr Peregrine Osborne, Opioids & Neuropathic Pain Laboratory:** Identification of a link between the central amygdala, which is part of the emotional brain circuitry, and anomalous increases in pain elicited by brief exposures to morphine. First demonstration of an overlap involving the major endogenous dynorphin/kappa-opioid receptor brain system, and the amygdala CRH (corticotrophin releasing hormone) system that facilitates fear, stress and anxiety. Dr Osborne was elected to the Council of the Australian Neuroscience Society as member for NSW.


- **Dr Chris Vaughan, Cellular Research Laboratory:** Identified how endogenous cannabinoids are produced within the midbrain and how they modulate pain. Identified a novel cannabis related compound that effectively alleviates an animal model of neuropathic pain. Dr Geoffrey Drew returned from the University of Heidelberg to complete his NHMRC CJ Martin Fellowship.
2007 Highlights

- Mapping pain pathways with Northern Queensland cone shell conopeptides. Scientists, led by Prof Mac Christie, are collaborating interstate and internationally (NHMRC Program Grant; $7.2M 2005-2009) to investigate conopeptides (CNPs) for pain therapy, their structure and possible sites of action. Two highly promising CNPs have progressed to initial trials in people.

- Pain following spinal cord injury (SCI): Understanding mechanisms to develop treatments. This basic research program is led by A/Prof Janet Keast (NSW Government SCIONC Program Grant $2M 2005-2008) and is one of only a few in the world to use two different models of SCI to permit intensive study of mechanisms and new treatments of SCI pain. Basic studies are closely linked to clinical studies in SCI patients, about 60% of whom have SCI pain due to mechanisms linked to nerve tissue damage.

- Mechanism underlying pelvic visceral pain. A/Prof Janet Keast and Dr Peregrine Osborne have a research program funded by the National Institutes of Health (NIH) USA (Grant $1.2m 2005-2009) to address their interest in pelvic pain problems, such as pain in the urinary bladder (e.g. “interstitial cystitis”, a frequent and severe pain problem in women).

Major Collaborations

- Prof MacDonald Christie holds an NHMRC Program Grant with A/Prof Richard Lewis, Prof Paul Alewood and Prof David Adams at The University of Queensland to identify novel targets on pain pathways for newly developed conopeptides.

- A/Prof Janet Keast was awarded $2M over 4 years commencing in 2005 for a Spinal Cord Injury and Other Neurological Conditions Research Program grant by the NSW Government to investigate mechanisms and treatments for spinal cord injury induced pain.

- A/Prof Keast is also the leader of an international team funded by the National Institutes of Health (USA) to identify mechanisms of pelvic pain.

“Our research pursues the broad theme that persistent pain is a disease entity with its own symptoms, signs and underlying disorders such as abnormal sensory, spinal cord and brain neuronal physiology, neurochemistry, anatomy, and pathology.”

Pain Management Research (cont.)
Brain, Body, Behaviour & Society Research Laboratory

Our group is studying the contribution of psychological, anatomical, physiological, and social/environmental factors to the experience of persisting pain and its management. This work extends from the clinic to community and work settings within Australia and to cross-cultural research in other countries.

Current projects include:

• Investigation of ways of limiting the aversiveness of chronic pain via a desensitization procedure (a 3-year RCT), funded by NHMRC (2007-9).
• Evaluation of an educational program for insurance claims staff in relation to awareness of pain and decision-making regarding treatment of pain. Funded by IAG (2006-8).
• Placebo responses in patients with persisting lumbar pain undergoing medial branch blocks and radiofrequency lesioning. PhD project (D Finniss).
• Post traumatic stress disorder in chronic pain patients. PhD project (M Tadros).
• Psychological processes in changing pain experience in a cognitive-behavioural pain management program. PhD project (K Kirkwood).
• The role of stretching in chronic pain (D Finniss).

2007 Highlights

• NHMRC project grant to M Nicholas (PMRI) with Prof G Murray and A/Prof C Peck (School of Dentistry, USyd) to examine psychological factors in jaw pain. Janet Benson has joined the project for her PhD.
• Key publications: in Pain, a paper (by M Nicholas, A Asghari and F Blyth) describing the use of normative data to interpret self-report scales used with chronic pain patients. Also in Pain, a topical review (by B Lyth) on overlooked psychosocial factors in chronic pain. In Annals of Internal Medicine, a paper on the outcomes of an RCT for patients with sub-acute low back pain. M Nicholas with Profs Kathryn Refshauge and Chris Maher (Physiotherapy, USyd) and M Nicholas with Prof Steven Linton (Orebro University, Sweden) on overlooked psychosocial factors in chronic pain via a desensitization procedure. In Pain, an editorial by M Nicholas on chronic pain and mental disorders. AHRMAC (2006-9).
• Two PhD students have completed their theses: Jamir Sarda, who has returned to Brazil to take up an academic position in Psychology in Florianopolis, and Kathryn Nicholson Perry.

Major Sources of Funding

• Australian Health Ministers Advisory Council (AHMAC)
• National Health and Medical Research Council (NHMRC)

Major Collaborations

• Attentional mechanisms in acute and chronic pain, M Nicholas (PMRI) with Louise Sharpe (Psychology, USyd), Kathryn Refshauge (Physiotherapy, USyd), Dr Stephen Linton (Orebro University, Sweden),), and femoral nerve blocks and radiofrequency lesioning (funded by NHMRC, 2006-9).
• Evaluating advice and exercises in treatment of sub-acute low back pain and predictors of outcome, M Nicholas with Kathryn Refshauge and Chris Maher (Physiotherapy, USyd) and M Nicholas with Profs Steven Linton (Orebro University, Sweden), and M Nicholas with A/Prof C Peck (School of Dentistry, USyd) and M Nicholas with Prof Steven Linton (Orebro University, Sweden), and M Nicholas with Profs Steven Linton (Orebro University, Sweden). AHRMAC (2006-9).
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• Key publications: in Pain, a paper (by M Nicholas, A Asghari and F Blyth) describing the use of normative data to interpret self-report scales used with chronic pain patients. Also in Pain, a topical review (by B Lyth) on overlooked psychosocial factors in chronic pain. In Annals of Internal Medicine, a paper on the outcomes of an RCT for patients with sub-acute low back pain. M Nicholas with Profs Kathryn Refshauge and Chris Maher (Physiotherapy, USyd) funded by NHMRC and APA. In Pain, an editorial by M Nicholas on chronic pain and mental disorders.
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• Two PhD students have completed their theses: Jamir Sarda, who has returned to Brazil to take up an academic position in Psychology in Florianopolis, and Kathryn Nicholson Perry.
The main focus of our research group is on how the body’s own cannabis signalling system (endocannabinoid system) works and how this might be used for the treatment of pain. This endocannabinoid system is more commonly known for being the target of the plant Cannabis sativa. Our group is examining the cellular mechanisms underlying the processing and modulation of pain and thermal sensation in the central nervous system. We are particularly interested in the involvement of the endogenous cannabinoid system in these processes and how it might be manipulated for the relief of chronic pain.

Research Outcomes

Our group has identified the mechanism by which the body’s own cannabinoid system regulates pain modulation circuits within the midbrain. We have also demonstrated that a novel class of endogenous transmitters related to cannabinoids are effective in reducing the abnormal sensation associated with models of chronic pain.

“*Our group is examining the cellular mechanisms underlying the processing and modulation of pain and thermal sensation in the central nervous system.*”

2007 Highlights

- Dr Geoffrey Drew returned from the University of Heidelberg to complete his NHMRC CJ Martin Fellowship with our group.
- Dr Paul Wrigley’s PhD thesis on cold thermal processing was accepted.
- Dr Vaughan was invited to speak at the 17th Elsevier Neuropharmacology conference, October 2007, in San Diego.

Major Collaborations

- A/Prof RJ Vandenberg and Dr M Connor (University of Sydney).
- Prof. D Piomelli (University of California, Irvine).
- Dr J Phillips (Murdoch University).

Major Sources of Funding

- National Health & Medical Research Council
- Royal North Shore Hospital Area Grant
Neuropharmacology Laboratory

Since joining the Pain Management Research Institute and the Kolling Institute of Medical Research in 2003, our group has focused on discovery of the mechanisms of potential novel therapeutics for acute and chronic pain management using cellular physiological methods in nerve cells that form pain transmission and modulatory pathways along with the mechanisms of pathological adaptation in these signalling systems.

1. In one area of research, we functionally investigate connections of spinal cord dorsal horn neurons receiving different classes of painful primary afferent input and how their molecular functions change after inflammation and nerve and spinal cord injury to produce cellular physiological adaptations that underlie persistent pain states. New medications for treating acute and chronic pain conditions may be developed from agents capable of interacting very specifically with these molecular targets in normal or pathologically adapted pain pathways.

Small molecule drugs and peptide toxins that act on pain specific receptors related to sodium channels, calcium channels, nicotinic cholinergic receptors and other targets are currently under investigation. We use novel marine snail toxins (conopeptides) and chemically modified analogues, to identify key signalling molecules in pain pathways in normal and injured tissue. Thousands of different conopeptides have evolved in these predatory snails so that their venom very rapidly inactivates the nerves of their prey. The potential utility of conopeptides in pain (one is already in clinical use) stems from their high potency to very specifically block individual types of excitability molecules on nerve cells, some of which give rise to pain states. This area is based on a collaborative NHMRC Program Grant with A/Prof Richard Lewis, Prof Paul Alewood and Prof David Adams at The University of Queensland, awarded funding of $7.16M from 2005-2009 to identify novel targets on pain pathways for newly developed conopeptides. Within this collaborative effort, our group was recently the first to identify the preclinical therapeutic potential of blockers of subtypes of sodium channels that are encoded only by pain sensing nerves entering the spinal cord and thereby treat pain resulting from nerve injury. We are continuing investigation of the mechanisms of action of novel TTX-resistant sodium channel blockers, subtype selective calcium channel blockers, subtype selective nicotinic channel blockers and acid sensing ion channel blockers in primary afferent and spinal neurons, and are examining their efficacy in neuropathic pain models. This research also forms a large part of our contribution to the SCIONC Program headed by A/Professor Keast with the aim of finding conopeptides with potential utility to treat spinal cord injury associated pain.

For more information on this program, please see “Dissecting Pain Pathways using Venom Peptides” on http://www.uq.edu.au/pain-venom/.

2. Another area of our research focuses on the mechanisms of tolerance and dependence to opioid drugs that develops in brain neurons involved in pain pathways during chronic therapy. Morphine and related opioids drugs very effectively relieve many (but not all) kinds of pain but they often lose their efficacy after prolonged treatment (tolerance). We have established that loss of opioid receptor function is associated with tolerance but this precedes receptor trafficking mechanisms thought previously by other researchers to be pivotal for tolerance.

Major Collaborations
- A/Prof Richard Lewis, Prof Paul Alewood and Prof David Adams at The University of Queensland.

Major Sources of Funding
- National Health & Medical Research Council
- NSW Ministry for Science and Medical Research
Humans often experience long periods of pain as an unwanted legacy of injury and disease. Unfortunately this chronic pain continues even when there is complete recovery from the underlying condition that triggered the pain in the first place. Our group studies biological mechanisms in the nervous system that either sustain or intensify pain for long periods, or reduce the pain-relieving properties of opioids and other analgesic drugs. We are especially interested in how chronic pain is caused by neuronal plasticity associated with pathological changes in the functioning or structure of nerve cells in pain circuits.

We are currently engaged in non-human research investigating 1) pain in the context of spinal cord and peripheral nerve injury, 2) pelvic pain and the role of circulating estrogens, 3) opioid-induced hyperalgesia, and 4) mechanisms of opioid receptor desensitization. Pain research is inherently multidisciplinary and this is reflected by our use of electrophysiological recording, functional anatomical mapping, advanced cellular imaging methods and behavioral testing in our research. Various combination of these techniques have been used to study cell lines transfected with opioid receptors, cultured sensory neurons, spinal cord and brain slices, and for whole-animal studies.

**Research Outcomes**

- Publication of the most extensive analysis to date of how an injury to the spinal cord affects the organization of the sensory circuits above the site of injury. This provides a new basis for understanding causes of at-level neuropathic pain.
- Identification of a link between the central amygdala, which is part of the emotional brain circuitry, and anomalous increases in pain elicited by brief exposures to morphine.
- First demonstration of an overlap involving the major endogenous dynorphin/kappa-opioid receptor brain system, and the amygdala CRH (corticotrophin releasing hormone) system that facilitates fear, stress and anxiety.
- Demonstration of a novel inhibitory effect of estrogen on the capsaicin receptor TRPV1 in female rat dorsal root ganglia sensory neurons. This identifies a biological mechanism by which a drop in circulating estrogens could lead to increased activity of this major pain transducer. This is consistent with clinical observations that pelvic pain is facilitated by menopause and other conditions that reduce circulating estrogens.

**2007 Highlights**

- Dr Osborne elected to the Council of the Australian Neuroscience Society as member for NSW.
- Invited presentation on “Endosomal pH determines ligand-specific endosomal sorting of the mu-opioid receptor by morphine” given by Mr David Lee to the Annual Scientific Meeting of the Australia and New Zealand College of Anaesthetists.
- Ms Shelley Forrest awarded a BSc Honours First Class by the School of Medical Science UNSW.
- PhD submission by Mr David Lee.
- Invited presentation on “Pain mechanisms in neonates and adults. Defining future directions in perinatal pain management” given by Dr Osborne to the Perinatal Society of Australia and New Zealand at their 2007 Meeting on Perinatal Pain.
- Invited presentation on “How do estrogens affect pelvic nociceptors?” given by to Dr Osborne to the Annual Meeting of the New Zealand Pain Society Annual Scientific Meeting in (Palmerston North, NZ).

**Major Collaborations**

- Dr Gavin McNally and Professor Fred Westbrook, School of Psychology, UNSW.

**Major Sources of Funding**

- National Institutes of Health (USA)
- NSW Office of Science and Medical Research (Spinal Cord Injury and Related Neurological Conditions Program)
- Australia and New Zealand College of Anaesthetists
Pain Management

Human Studies

In 2007, there has been a mix of internally initiated and industry sponsored clinical studies. Collaborative projects with the RNSH Spinal Injuries Unit and the Department of Endocrinology also continue. Human Studies projects for 2007 include:

**Mechanical Low Back Pain: - Diagnosis and Treatment**
The medial branch of the dorsal rami of the spinal nerves supplies the spinal facet joints. We are engaged in a randomized prospective placebo controlled study aimed at evaluating the utility of diagnostic medial branch blocks with local anaesthetic and the efficacy of treatment with radiofrequency lesioning. The study will also provide new insights into responses to placebo injections. A target of 100 expected patients will be enrolled by the end of 2008.

**Modified ADAPT Program for treatment of chronic pain in elderly Australians**
This randomized prospective controlled trial is evaluating the effectiveness of self management pain strategies in the older age group. The study is the first of this strategy in this age group and is funded by the Australian Government.

**Development of reproducible assessments of spinal cord injury impairment and function**
This study involves the evaluation of new techniques such as transcranial magnetic stimulation, electrical perceptual thresholds and sympathetic skin response. It is hoped that these assessment tools will be helpful in diagnosing and treating the various problems, including pain, that afflict patients with spinal cord injury.

**Treatment of pain associated with osteoarthritis of the knee and low back pain**
This is a randomized double-blind, placebo- and active-control, parallel-arm, Phase III study with controlled adjustment of dose to evaluate the efficacy and safety of CG5503 extended-release (ER) in patients with moderate to severe chronic pain due to osteoarthritis of the knee or low back pain. The study drug is a centrally acting analgesic agonist and an alpha2 adrenergic drug clonidine in spinal cord injury pain. Thus the results of this study will be of great interest to our group. Sponsored by Janssen Cilag.

**The treatment of severe neuropathic pain due to Post Herpetic Neuropathy (chronic post-shingles pain)**
This is a Phase II, double blind, placebo controlled, dose-ranging study in subjects with posttherpetic neuralgia (PHN) to evaluate the efficacy, safety, tolerability and pharmacokinetics of four doses of TAK-S83, compared with placebo. TAK-S83 is an extremely interesting drug that protects neurons from changes in the nervous system that are produced by very severe and prolonged pain. Surprisingly severe pain is associated with excess release of a very small molecule called nitric oxide (NO) which can result in the death of important neurons that “tune down” the pain signal. This is the first of a new class of drugs that attack the “disease process” in the nervous system associated with severe persistent pain. Sponsored by Takeda.

**Treatment of Severe Cancer Pain**
A second exciting new drug has been developed in our Basic Pain Research Program, in collaboration with the University of Queensland. This drug, XEN 2174, is derived from the cone shell fish in Northern Queensland and is a synthetic conopeptide which inhibits the uptake of noradrenaline by a “transporter” which transports noradrenaline across the neuronal synapse. In our basic animal studies, this drug was extremely potent in models of neuropathic pain. Changes in the noradrenaline system are an important part of the “disease process” that is associated with persistent pain. We have recently completed a multi-centre study in patients with severe cancer pain, in which XEN 2174 was administered intranally. The drug proved to be extremely potent for cancer pain and we expect to be able to proceed with more extensive studies in humans in the near future. Sponsored by Xenome.

**Treatment of Type 2 Diabetes**
PMRI has a long standing collaboration with the RNSH Department of Endocrinology which aims to develop innovative methodology for the delivery of insulin through the lungs. The same methodology is being used to develop delivery of pain relief drugs through the lungs such as fentanyl and morphine. The current study is “inhaled pre-prandial human insulin with the AERx® IDMS plus Glimepiride versus Rosiglitazone plus Glimepiride in Type 2 diabetes: a 26-week, open-label, multicentre, randomised, parallel trial to investigate safety and efficacy. In the long term, it is hoped that many diabetics will be freed from injections by the ability to deliver insulin via the lungs. It is also hoped that patients after surgery will be able to obtain pain relief with strong morphine like drugs using a hand held device which will deliver morphine directly through the lungs into the blood stream. Sponsored by NovoNordisk.

**Development of New Treatments for Neuropathic Pain in Spinal Cord Injury**
PMRI is playing a lead role into the development of improved methodology for the design and execution of randomised, double-blind, placebo-controlled, crossover studies in spinal cord injury patients who suffer from neuropathic pain. The aim of this project is to strengthen current methodologies so that they are able to detect improvement in pain end points in clinical studies. Sponsored by Pfizer.
Peripheral Mechanisms & Injury Laboratory

We are interested in the development of nerve circuits, and how adult neurons are affected by injury and inflammation. Most of our studies focus on peripheral nerves and the spinal cord, especially the pain-sensing neurons (nociceptors) and motor neurons controlling the urogenital organs (reproductive organs and lower urinary tract). We are especially interested in how neurotrophic factors and gonadal steroids (estrogens and androgens) affect pain and pelvic autonomic function.

One major goal is to understand the mechanisms underlying pelvic visceral pain (e.g. bladder pain, interstitial cystitis) and spinal cord injury pain (chronic neuropathic pain) so that better treatments can be developed. We are also investigating how pelvic autonomic neurons can regrow after injury, so that we can develop therapies to promote regeneration. The axons of these neurons are often injured during pelvic surgery such as prostatectomy, hysterectomy and lower bowel resections, and this leads to continence problems and erectile dysfunction. Our studies on developing neurons may provide us with clues about how their axons reach their target organs early in life, and may reveal mechanisms that can be used to stimulate growth and guide the injured axons to their correct locations after injury later in life.

To address these questions we use a variety of experimental approaches, including neuroanatomy, microsurgery, tract tracing, immunohistochemistry, image analysis, neuronal cultures, cell and molecular biology, organ bath pharmacology and behavioural testing.

Research Outcomes

- Identification of estrogen receptors and estrogenic growth responses in male pelvic autonomic neurons, suggesting new mechanisms for potentially modulating regeneration after injury.
- Demonstration of a remarkable degree of androgen-driven plasticity in adult male pelvic autonomic neurons, which controls how well the nerves communicate with reproductive smooth muscle.
- Discovery of a novel inhibitory effect of estradiol on the capsaicin receptor, TRPV1, in nocicepter neurons.

2007 Highlights

- A/Prof Keast elected President, International Society for Autonomic Neuroscience (ISAN) and Keynote Speaker, ISAN2007 Congress (Kyoto, Japan).
- Invited cover image for the journal Neuroscience (Volume 148: 92-104).
- New Investigator Grant (Northern Sydney and Central Coast Health) awarded to Dr Matthew Nangle.

Major Collaborations

- A/Prof James Brock, Prince of Wales Medical Research Institute.
- Prof David Handelsman, Anzac Institute.
- A/Prof Ida Llewellyn-Smith, Flinders University.

Major Sources of Funding

- National Health and Medical Research Council
- National Institutes of Health (USA)
- NSW Office of Science and Medical Research (Spinal Cord Injury and Related Neurological Conditions Program)
Sensory Neuroscience Laboratory

The Sensory Neuroscience group is tackling the problem of pain by trying to understand the special properties of nerve cells that detect different kinds of head pain. Chronic pain from the face and head affects more than 1 million Australians, and our research primarily focuses on neurons that carry information from different structures in the head to the neurons of the brain that process pain-related signals. We are interested in determining how existing pain relieving drugs affect the activity of these cells and identifying cellular targets for new analgesics.

For most of our research we use sensitive electrical recording techniques to measure the activity of single cells or of ion channels in their membranes. We make recordings from neurons isolated from trigeminal ganglia of mice which have been labelled so we know they innervate muscle or dura. These recordings, together with experiments on cloned proteins expressed in cell lines, allow us to precisely define how analgesic drugs act at the molecular level.

Research Themes

We have several major areas of interest. We are engaged in an ongoing effort to define the properties of neurons that innervate the jaw muscle and cranial dura, neurons that give rise to pain associated with temporomandibular disorders and migraine respectively. Our research into pain relieving drugs focuses on two proven classes of analgesics, opioids and triptans, and one group with great potential, the cannabinoids. We are especially interested in how opioids such as morphine and triptan antimigraine drugs act in pain-sensing neurons, and how these actions change after prolonged use of the drug. Cannabinoids were originally identified in marijuana, but the body also makes possibly dozens of molecules that have a similar analgesic effect to the plant derived drugs. We are studying how our endogenous cannabinoid molecules and plant-derived cannabinoids affect receptors and ion channels in pain-sensing neurons.

2007 Highlights

• Hamish Ross and Andrew Gilmore identified 2 potent inhibitors of T-type calcium channels, both of which may be made in the body. Andrew also showed that a novel neuromodulator was a potentiator of T-type channel activity, the first time such a molecule has been identified. These discoveries highlight the capacity of the body to regulate the activity of ion channels involved in key process such as pain sensing, and the molecules may provide useful insight into the structure and function of the channels that can be used to develop drugs to treat pain. These results were presented to several international meetings.

• Rozhin Asghari showed that trigeminal ganglia express all the proteins necessary to make the neurotransmitter serotonin, a finding that builds on work from other labs which showed the presence of one of the 3 enzymes necessary. Serotonin and its receptors are believed to play a key role in migraine, and it would be of great interest were trigeminal neurons found to make significant amounts of the neurotransmitter.

• Marika Heblinski successfully created a neuronal cell line expressing serotonin 5HT1B receptors, which are a major target of anti-migraine drugs. She showed that exposure to serotonin or an antimigraine drug for only a few minutes caused these receptors to lose their signaling capacity, and work continues to understand how this happens. Marika was supported by the RNSH WESTPAC Scholarship.

• Senior Staff Mark Connor and Emma Johnson are involved in all the above projects while continuing to explore the consequences of chronic morphine treatment for neuronal function. We successfully obtained Project funding from the NH&MRC (2008-2010), the Australia and New Zealand College of Anaesthetists (2008, with Professor Michael Cousins) and Discovery funding from the Australian Research Council (2008-2010).

Major Collaborations

• A/Prof Robert Vandenberg, University of Sydney Department of Pharmacology. Mechanism of action of arachidonoyl amino acids. We share an NH&MRC Project Grant (with Chris Vaughan), work presented by invitation at two International and one National Meeting in 2007.

• Dr Heather Bradshaw, University of Indiana. Effects of endogenous arachidonoyl amino acid conjugates on ion channels. Involves determining the cellular effects of novel compounds isolated in Indiana, including the first endogenous potentiatior of T-type calcium channel function.

Major Sources of Funding

• National Health & Medical Research Council
• Northern Sydney Area Health Project Grant
• Northern Sydney Area Health Bridging Grant
Spinal Cord Injury Pain Clinical Research Laboratory

The spinal cord injury pain clinical research group is investigating the mechanisms and management of pain following spinal cord injury, with a particular focus on the contribution of brain mechanisms. Around one third of people following spinal cord injury experience severe pain in the region of lost sensation and the pain has a major impact on their quality of life and ability to function. Despite this, the mechanisms are poorly understood and in the majority of people with pain, it is very difficult to obtain satisfactory pain relief with our current treatments.

To investigate this problem, we are using a combination of brain imaging techniques including electroencephalography, magnetic resonance spectroscopy and structural and functional magnetic resonance imaging. These will help us to identify the electrical, neurochemical and other structural and functional brain changes that may contribute to the development of pain and therefore provide targets for clinical intervention. Dr Paul Wrigley (Post-doctoral Fellow) funded by the NSW Government Spinal Cord Injury Research Grants Program coordinates these collaborative projects. Dr Luke Henderson at the University of Sydney with Dr Sylvia Gustin who is also funded by the NSW Government Spinal Cord Injury Research Grants Program provide expertise in brain imaging and have a major role in the research program.

Research Outcomes

During 2007 we published and presented a number of papers describing the physiological and psychological changes associated with pain following spinal cord injury. These include:

- Alterations in the organization of the brain in people with spinal cord injury. In people with pain, the area of the brain that normally receives messages from the lower part of the body which has now lost feeling, starts to respond to messages received from the upper part of the body such as the hand. This reorganization of the body appears to be linked to the presence of pain.

- An increase in pain in paraplegics who try to perform repetitive movements of the feet. Although unable to move, paraplegics who imagine they are moving their ankle get an increase in pain. This may occur because the imagined movement switches on parts of the brain that are involved in pain sensation, even though no messages are coming in from the legs.

- Alterations in the pattern of brain wave activity in people with pain following spinal cord injury. People with pain have an increase in activity in a certain range that suggests that there may be loss of inhibitory function in brain electrical activity that may contribute to pain.

- The negative impact of pain on people’s physical and psychological function following spinal cord injury.

2007 Highlights

- Invitation to speak at the Inaugural meeting of the Association of South East Asian Pain Societies, Manila (M Cousins)

- Invitation to speak at the Australian and New Zealand Spinal Cord Society Annual Scientific Meeting, Melbourne (P Siddall)

- Invitations to write chapters on Pain following Spinal Cord Injury for 2 of the major international texts in pain management. (P Siddall & P Wrigley)

- Participation in committee of the International Spinal Cord Society on the classification, assessment and management of pain following spinal cord injury. (P Siddall)

Major Collaborations

- Dr Luke Henderson, Department of Anatomy & Histology, University of Sydney.

- A/Professor James Middleton, Statewide Spinal Cord Injury Service, & Rehabilitation Studies Unit, The University of Sydney.

- A/Prof Michael Nicholas, Kathryn Nicholson Perry, Robin Murray, Pain Management Research Institute, University of Sydney.

- A/Prof Janet Keast, Dr Peregrine Osborne, Prof Mac Christie, Pain Management Research Institute, University of Sydney.

- Drs Sue Rutkowksi, Ros Soden and Lianne Hunt, Spinal Injuries Unit, Royal North Shore, Hospital.

- Professor Simon Gandevia, Prince of Wales Medical Research Institute, Randwick.

- Professor Vaughan Macefield, School of Medicine, University of Western Sydney.

- Dr Lea Sorensen, Professor Dennis Yue, Diabetes Centre, Royal Prince Alfred Hospital, Camperdown.

- Professor Ashley Craig, Dr Yvonne Tran, Dr Peter Boord, University of Technology, Sydney.

Major Sources of Funding

- NSW Government Spinal Cord Injury Research Grants Program

- Australian & New Zealand College of Anaesthetists
The primary interest of the Synaptic Physiology & Plasticity Laboratory is how delivery of nociceptive information to the central nucleus of the amygdala is modified by painful experiences. Acute pain provides important warnings about dangers in our environment. However, some clinical conditions produce persistent pain that outlasts the nociceptive stimuli and its useful role. Persistent or chronic pain is a debilitating condition that affects 20% of Australians and can be difficult to treat with existing therapies. The persistence of pain beyond the nociceptive stimulus suggests there are plastic changes in pain pathways that remain after the stimulus has stopped and drive the expression of persistent pain states. A better understanding of the cellular physiology of pain-induced plastic changes in pain pathways will result in better therapeutic approaches to treating persistent pain. One synaptic pathway that is critical for persistent pain is the spino-parabrachial-amygdala pathway. This pathway delivers nociceptive information to the central nucleus of the amygdala (CeA) and is critical for the development of persistent pain states. We are interested in how the delivery of nociceptive information via the spino-parabrachial pathway is altered by painful experiences. We address this by using a combination of electrophysiology, biochemical assays and immunohistochemistry. Preliminary experiments indicate this synaptic pathway is substantially changed by a mild, brief nociceptive stimulus. These changes persist for at least 3 days after the stimuli and may be indicative of changes in synaptic properties that underlie the development of chronic pain.

**Research Outcomes**

The major research outcome has been a definition of a plastic change in synaptic function produced by a brief, moderate nociceptive stimulus. This plastic change persists for several days after the stimulus. This plastic change may underlie the changes in synaptic function that result in the development of chronic/persistent pain.

**2007 Highlights**

- Elena Bagley was invited to present her work at the International Brain Research Organization meeting in Melbourne, 2007.

**Major Sources of Funding**

- National Health & Medical Research Council

“A better understanding of the cellular physiology of pain-induced plastic changes in pain pathways will result in better therapeutic approaches to treating persistent pain.”
The goal of the Perinatal Research Group is to improve the health and wellbeing of mothers and their babies through a research program that encompasses biomedical, clinical and population health research. Our aims are to:

1. Conduct high quality interdisciplinary research.
2. Build a sustainable team of enthusiastic pregnancy, childbirth and infant health researchers.
3. Make discoveries and provide research evidence that will improve the way pregnancy and childbirth are managed.
4. Ensure research findings reach those that need to know.

The group uses cutting edge in vitro and in vivo models, randomized clinical trials and epidemiological studies data to examine fetal development, pregnancy, childbirth, maternity care and health outcomes for mother and baby. The discoveries made by the group have improved the management of pregnancy and childbirth and include the formulation of new clinical tests and treatment strategies to improve the health of mothers and their babies and informed perinatal health policy.

The interests of the Perinatal Research Group can be divided into 6 distinct areas of research:

1. Immunology of normal and abnormal pregnancies.
2. Trophoblast growth and development in normal and abnormal pregnancies.
3. Placental angiogenesis.
5. Evaluating regionalised maternity care using population health data.

Perinatal Pregnancy. The Perinatal Research Group is investigating the causes of growth restriction and early birth. These problems account for the majority of admissions to newborn intensive care.
Perinatal Research (cont.)

Research Outcomes
- The Group in 2007 discovered an angiogenic factor that may be a marker of adverse pregnancy outcome and an immune modulator that may have clinical applications for the treatment of autoimmune disease. In addition the Group has pioneered new techniques to assess placental development in vitro.
- The Group oversee a major clinical trial that is recruiting in 15 countries world wide.

2007 Highlights
- The Group were awarded 3 NHMRC Project Grants.
- A provisional patent was granted for a new immune modulator.

Major Collaborations
- Professor Euan Wallace, Monash University, Melbourne.
- Professor Colin Sullivan, University of Sydney.
- Clinical trial centres in the United Kingdom, Poland, Chile, Argentina, New Zealand, Brazil, South Africa, and Israel.

Major Sources of Funding
- National Health & Medical Research Council
- University of Sydney
- Royal Australian New Zealand College of Obstetricians and Gynaecologists
- Ramsay Healthcare

“The 2007 Research Report outlines major areas of research strength within the Kolling Institute. While physical and organisational change goes on around us, our research staff and postgraduate students have maintained their high productivity and have once again excelled...”
2007 was a highly successful year for the Renal Research Laboratories. The laboratory’s key aim is to unravel the molecular mechanisms underpinning progressive kidney disease. Renal disease is now considered the single most important factor predisposing to vascular disease (ie heart attack and stroke) in the community. However the majority of renal disease is entirely asymptomatic. In general more that 70% of kidney function is lost before any symptoms appear and usually once kidney function is lost it is not reversible and dialysis remains the only option for the majority of patients. Diabetes mellitus now accounts for the majority of kidney failure in our population. Hence the Renal Laboratories focuses primarily on diabetes as a cause of kidney failure.

“Our work has highlighted the parallels between developmental biology and cancer cell biology in progressive kidney disease.”

The laboratory uses a number of approaches to achieve this aim, including studying the single cell, cells in culture, animal models of diabetes through to studies on people with diabetes. This approach allow us to determine the molecular abnormalities present at a cellular level, the interaction between cells that go to make up the kidney and then the response of the kidney to the metabolic, biochemical, physiological and molecular abnormalities that occur in the ‘whole body’ as a response to diabetes mellitus. As vascular disease goes hand in hand with diabetes a further component of our work focuses on determining the molecular mechanisms that drive vascular pathology in patients with diabetes mellitus. Once the molecular mechanisms are defined we then look for novel mechanisms that can arrest progressive disease or promote renal repair and regeneration that may act as future therapeutic targets.

The team consists of 7 post doctoral researchers, 7 PhD students and 2 research assistants.

Projects undertaken in 2007 include:

1. The isoform specific effects of transforming growth factorβ (TGFβ)and in diabetic nephropathy.
2. Differentiating the inflammatory vs the profibrotic component of progressive renal disease in diabetic nephropathy.
3. The role of the Kruppel like family of transcription factors in mediating progressive renal fibrosis.
4. Re-expression of fetal developmental markers of maturation in the epithelial to mesenchymal transformation observed in diabetic nephropathy.
5. Signalling through the serine-threonine glucocorticoid pathway (SGK-1) pathway and convergence on the epidermal growth factor receptor (EGF-R) as a unifying factor mediating salt and water retention (and consequently high blood pressure) and kidney scarring in diabetic nephropathy.
6. Stimulation of the peroxisome proliferator agonist receptors as a strategy to reduce progressive renal disease in kidney disease due to, and independent of, diabetes mellitus.
7. Mechanisms of renal repair with a focus on the BMP-7 signalling pathways.
8. The consequences of statins on renal tubular function.
9. Hypoxia inducible genes and diabetic nephropathy.

Research Outcomes

Our work has highlighted the parallels between developmental biology and cancer cell biology in progressive kidney disease. In 2007 a key focus of our work has been to elucidate the cellular abnormalities inherent in epithelial to mesenchymal transition (common to cancer cell biology) and the recapitulation of developmental signaling processes in kidney disease.
Renal Research (cont.)

2007 Highlights

• Dr John Holian was awarded the Young Investigator of the Year at the Irish Society of Nephrology.

• 2 prestigious oral presentations by Dr John Holian and Dr Scott Stanners (completed his PhD in 2007) at the American Society of Nephrology.

• Prof Carol Pollock was invited to be Guest Professor at Kings College in London in September, giving 4 lectures to diverse audiences. She additionally gave 4 further invited presentations or chaired sessions in 2007 to the Australian and New Zealand Society of Nephrology, the Cardiac Society of Australia and New Zealand and national nursing forums but declined invitations to speak at the International Society of Nephrology Meeting in Rio de Janeiro.

• We were happy to host a visit from Dr Sankar from India in 2007 to further strategic collaborations in the Asia Pacific Region.

Major Collaborations

• University of Melbourne.

• The Millenium Institute at Westmead Hospital, Sydney.

• University of Queensland.

• St Vincents Institute of Medical Research, University of Melbourne.

• University of Toronto, Canada.

• Kings College London, England.

• The Department of Physiology Tubingen, Germany.

• Sundaram Medical Foundation and Memorial Hospital, India.

Major Sources of Funding

• National Health & Medical Research Council

• The Hillcrest Foundation

• Pharmaceutical companies

• Philanthropic donations

• Australian Research Council

“In 2007 a key focus of our work has been to elucidate the cellular abnormalities inherent in epithelial to mesenchymal transition (common to cancer cell biology) and the recapitulation of developmental signaling processes in kidney disease.”
Collaborations with other researchers, research organisations, industry and academic or allied health organisations are listed below. Kolling Institute of Medical Research personnel are noted in bold in each of their collaborations.

**Dr Richard Appleyard, Ms Joanna Peterson** with Mr Umar Ansari, Dr Richard Lawson and Michael Tonkin of the RNSH Hand Surgery Unit. Investigation on the mechanical integrity of various tendon suturing techniques. Ongoing collaboration, publications.

**Dr Richard Appleyard, Helen McCarthy** with Professor Charles Archer, School of Biosciences, Cardiff University: Large animal model of articular cartilage regeneration using engineered scaffolds. International collaboration with publications.

**Dr Richard Appleyard, Dr Mark Gillies, Dr Jade Gan, Dr Dane Dabirrahmani** with Mr Shane Donahoo, WorleyParsons Pty Ltd. A close working relationship has also been formed with the WorleyParsons Advanced Analysis Group Pty Ltd. This industrial arm provides access to computation modelling including Finite Element Analysis (FEA) and Computation Fluid Mechanics (CFM). Current biomechanical research projects undertaken include: design of a femoral head resurfacing prosthesis; accelerated corrosion analysis of a total hip replacement; friction properties between bone and various implant surface coating; instrumented hammer for assessing strike force during total hip implantation; measurement of femoral bone cortical strain around a total hip stem; finite element analysis (FEA) of bone fracture around a total hip stem. Long-term collaboration with publications.

**Dr Richard Appleyard** with Dr David Parker and Dr Myles Coolican, Sydney Orthopaedic Research Institute, ‘The effect of external fixation on the strain in the anterior cruciate ligament’. This work will be presented at the next ISAKOS meeting and published in a leading orthopaedic journal.

**Dr Richard Appleyard** with Mark Haber of Wollongong University. Measurement of rotator cuff fixation techniques in a human shoulder. This work will be presented at the next ISAKOS meeting and published in a leading orthopaedic journal.

**Dr Richard Appleyard, Associate Professor Chris Little** with Professor Peter Ghosh, Mesoblast. Evaluation of the safety and efficacy of Allogeneic Mesenchymal Progenitor Cells (MPCs) in the regeneration of a medial knee joint meniscus and the retardation of cartilage injury in an ovine model of osteoarthritis. Long-term collaboration with industry.

**Dr Richard Appleyard, with Professor Andrew Ruys, Dr Qing Li, Professor Michael Swain**. Mechanical Engineering, University of Sydney. Development of patient specific implant selection criteria: Reducing the incidence of femoral fracture after hip surgery. Long-term collaboration with PhD students; successful ARC Linkage and industry funded grant, publication of numerous papers.

**Mr Levi Bassin, Professor Stephen Hunyor**, with Professor David Kilpatrick, Royal Hobart Hospital, Clinical School, University of Tasmania. Effect of Myocardial Ischaemia, Hypothermia, and subarachnoid Haemorrhage on the Wavefront of Electrical Activation and Recovery in the Myocardium: Possible Role in Arrhythmogenesis. Pursued the ECG injury patterns after heart attack and regional myocardial blood flow analysis using fluorescent microspheres.

**Professor Rob Baxter, Dr Sue Firth** with Associate Professor Stephen Twigg, Endocrinology, Royal Prince Alfred Hospital on the role of IGFBP-3 in fat cell differentiation. Outcome: joint research grant and abstracts.

**Professor Rob Baxter** with Dr X Yang, Northwestern University; Chicago, IL and Dr Bin Teh, Van Andel Research Institute, MI, USA, on IGF-IGFBP axis in renal cell carcinoma. Outcome: joint publication.

**Professor Rob Baxter** joint Chief Investigator with Professor Mark Baker and APAF, Macquarie University, University of Sydney and UNSW, in a Cancer Institute NSW Infrastructure program on cancer proteomics studies. Outcome: joint infrastructure grant.

**Professor Rob Baxter, Dr Deborah Marsh** with Associate Professor Christine Clarke, Westmead Millennium Institute, and other collaborators in a program funded by an NHMRC Enabling Grant and the Cancer Institute NSW for a national breast cancer tissue bank. Outcome: joint infrastructure grant.

**Professor Rob Baxter, Dr Liping Chung, Dr Deborah Marsh** with Dr Katrina Moore and Dr Sabah Shibli, Department of Surgery, Royal North Shore Hospital, on detection of cancer biomarkers in tissue and serum from breast cancer patients.

**Professor Rob Baxter, Dr Liping Chung** with Professor Ross Smith and Ms Aiqun Xue, Surgery, University of Sydney at RNSH on detection of cancer biomarkers in tissue and serum from pancreatic cancer patients. Outcome: joint infrastructure grants; joint publications.

**Professor Rob Baxter, Dr Sue Firth** with Professor Phil Robinson and Dr Mark Graham, Children’s Medical Research Institute, Sydney, on phosphorylation analysis of IGF binding protein-5 in breast cancer cells. Outcome: joint publication.

**Dr Fiona Blyth** with Gary MacFarlane (Dept of Public Health, University of Aberdeen). Participation in EULAR Standing Committee on Epidemiology: Workshop on Musculoskeletal Pain in Occupational Settings; Measurement and assessment of the role of psychosocial factors in the onset and outcome of symptoms.

**Dr Fiona Blyth, Professor Michael Cousins** with Dr Fran Boyle (Mater Hospital). Investigation of post-surgical pain for women with breast cancer.
Professor MacDonald Christie with Associate Professor Richard Lewis, Professors Paul Alewood and David Adams at The University of Queensland, awarded NH&MRC Program Grant $7.16M from 2005-2009 to identify novel targets on pain pathways for newly developed conopeptides.

Professor MacDonald Christie with Associate Professor Janet Keast who heads the SCIONC Program with the aim of finding conopeptides with potential utility to treat spinal cord injury associated pain.

Dr Liping Chung, Professor Rob Baxter with Professor Ken Ho and Dr Anne Nelson, Garvan Institute, on the detection of biomarkers of growth hormone abuse using serum and white cell extracts. Outcome: joint research grants, publications and abstracts.

Dr Mark Connor with Associate Professor Robert Vandenberg, University of Sydney Department of Pharmacology. Mechanism of action of arachidonoyl amino acids We share an NH&MRC Project Grant (with Chris Vaughan), work presented by invitation at 2 International and one National Meeting in 2007.

Dr Mark Connor with Dr Heather Bradshaw, University of Indiana. Effects of endogenous arachidonoyl amino acid conjugates on ion channels. Involves determining the cellular effects of novel compounds isolated in Indiana, including the first endogenous potentiator of T-type calcium channel function.

Professor Michael Cousins and Pain Management Human Studies team collaborative projects with the RNSH Spinal Injuries Unit and the Department of Endocrinology.

Ms Gabrielle Gallagher, Professor Stephen Hunyor with Associate Professor Christopher Jackson, Sutton Rheumatism Laboratories, RNSH. The basic expertise in “wet lab” techniques, biochemical measurements and wound healing has been invaluable in study of mechanisms of extracellular matrix remodelling in the progression of heart failure. Three publications resulting.

Dr Viive Howell and Dr Neal Copeland, Institute of Molecular and Cellular Biology, Singapore: Ovarian cancer modelling in mice. This is a new collaboration established in 2007 for the development of novel transgenic mouse models of ovarian cancer. Outcomes and expected outcomes: include the identification of new genes involved in ovarian cancer. New grant funding was attracted for 2008.

Professor Stephen Hunyor with Professor David Celemajer, Cardiology, Royal Prince Alfred Hospital, USyd. A Model of Varying Severity Acute Heart Failure in Sheep. Ongoing sharing of ideas, technologies and use of CTC’s large animal facilities, expertise and equipment. Induction of acute biventricular heart failure with different degree of severity achieved.

Professor Stephen Hunyor with Associate Professor Chris Ward, Department of Haematology, Dr Anthony Gill, Dept Anatomical Pathology, Associate Professor Dale Bailey & Clinical Professor Paul Roach, Dept Nuclear Medicine, RNSH. Adult Bone Marrow Stem Cell Therapy in Damage Prevention and Repair of the Heart – cellular and functional studies in sheep. Comparison is made with non-invasive, clinically relevant measurements using the Nuclear Medicine Dept’s highly sensitive SPECT/CT Imaging capability. Manuscript accepted.

Associate Professor Chris Jackson, Dr Meilang Xue with Professor Kenji Fukudome, Saga Medical School, Nabeshima, Saga, Japan. “Cytoprotective mechanisms of action of APC”, Fukudome has provided reagents which are unavailable commercially to perform experiments. Outcome: Several joint publications.

Associate Professor Chris Jackson with Professor Alan Coombes, University of Queensland. Polycaprolactone-based bicomposite scaffolds for tissue regeneration. Sutton provided cell culture facilities and expertise for pharmacy students to complete their projects with Coombes. Outcome: joint publication and co-supervision of 2 PhD students.
Research Collaborations

**Research Collaborations**

**Associate Professor Chris Jackson** with Associate Professor Shing Shun Tony To. Differential effects of photofrin, 5-aminolevulinic acid and calphostin C on glioma cells. Jackson provided expertise with endothelial cell culture. Outcome: One publication.

**Associate Professor Janet Keast** with Associate Professor James Brock, Prince of Wales Medical Research Institute: androgenic effects on development and maintenance of autonomic neurons. Outcome: joint publication.

**Associate Professor Janet Keast** with Professor David Handelsman, Anzac Institute; mechanisms of androgen and estrogen action on adult pelvic neurons. Outcome: two joint publications.

**Associate Professor Janet Keast** with Associate Professor Ida Llewellyn-Smith, Flinders University: effects of pregnancy on pelvic autonomic nerves. Outcome: new grant funding to ILS (Associate Professor Keast, Associate Investigator).

**Dr Sharon Leong, Professor Rob Baxter** with Professor Richard Christopherson, School of Molecular and Microbial Biosciences, University of Sydney, on proteomic screening for apoptotic markers in breast cancer. Outcome: joint research grants; joint infrastructure grants; joint publication.

Dr Qing Li, Dr Richard Appleyard, with Dr Li W. Mechanical Engineering, University of Sydney. Computational Scaffold Optimisation for Tissue Engineering. Long-term collaboration with PhD students; successful ARC Discovery Grant, publication of numerous papers.

**Associate Professor Christopher Little** with Professor John Bateman, University of Melbourne, Vic. Analysis of genome wide microarray and proteomic comparison of articular cartilage with the onset and progression of osteoarthritis in mice. Joint NHMRC project grant 2006-8. Manuscript accepted for publication in #1 ranked arthritis journal (Arthritis and Rheumatism); two further papers submitted to Arthritis and Rheumatism Investigator.


**Associate Professor Christopher Little** with Dr Clare Hughes, Cardiff University, UK. Investigation of proteolysis of cartilage in arthritis. Ongoing sharing of reagents including novel antibodies. Manuscript published in #1 ranked arthritis journal (Arthritis and Rheumatism) in 2007; Further manuscripts in preparation.

**Associate Professor Christopher Little** with Dr James Melrose and Professor Peter Roughley, McGill University, Montreal Canada. Investigation of proteolysis of small proteoglycans in human musculoskeletal tissues. Ongoing sharing of reagents including novel antibodies. Several publication, further; manuscripts submitted and in preparation.

**Associate Professor Christopher Little, Dr Margaret Smith** with Dr Hala Zreiqat, Sydney University, Biomedical Engineering, School of AMME. Investigation of S100 proteins in cartilage degradation and cartilage tissue engineering techniques. Several publications submitted and in review.

**Associate Professor Christopher Little, Dr Margaret Smith** with Professor Roger Smith, Royal Veterinary College, UK. Investigation of the effects of mechanical loading and stem cells on tendon degeneration and repair. Share samples and technology; research proposal to be submitted in 2008; manuscript in preparation; PhD student to visit UK and undertake collaborative experiments.

**Associate Professor Christopher Little, Dr Margaret Smith** with Dr James Melrose and Associate Professor Andrew Dart, Sydney University, Faculty of Veterinary Medicine. Large animal models of tendon injury and intervertebral disc degeneration. Shared Honors student (2008); Several published papers, manuscript accepted for publication in #1 ranked arthritis journal (Arthritis and Rheumatism, 2007); further publications in preparation.

**Associate Professor Christopher Little, Dr Margaret Smith** with Dr James Melrose and Professor Rick Read and Dr Martin Cake, Faculty of Veterinary Medicine, Murdoch University, WA. Large animal models of osteoarthritis. Long-term collaboration with shared Honours students, PhD students; successful NHMRC and industry funded grants, publication of numerous papers.

Dr Kerrie McDonald with Ms Maree O’Sullivan and Mr Glenn Stone, Mathematical and Information Sciences, CSIRO: Identification of molecular genetic markers in glioma subtypes with high density-cDNA microarrays. Outcome: A publication and a provisional patent.

Dr Kerrie McDonald with Prof Roger Reddel, Children’s Medical Research Institute (CMRI): Alternative Lengthening of Telomeres and Outcome in Glioblastoma patients. Outcome: a joint publication is anticipated in 2008.

Dr Deborah Marsh, Professor Robert Baxter with Associate Professor Christine Clarke, Ms Jane Carpenter and colleagues, Westmead Millennium Institute: Breast Tumour Biospecimen Resource. This is a multi-centre collaborative initiative to establish a state-wide breast tumour bank for NSW that is led by our Westmead collaborators. RNSH is one of six collection centres. Outcomes: collection of samples from breast tumour patients to facilitate translational research. New funding was attracted to maintain this initiative in 2008 and beyond.
Dr Deborah Marsh, Dr Janet Martin, Prof Robert Baxter with Professor Glenn Marshall, Dr Toby Trahair, Dr Edwin Kirk, Dr Jan Edwards, Sydney Children’s Hospital and Children’s Cancer Institute Australia. Collaboration has involved both studies in cell line models and clinical monitoring of a patient with Proteus syndrome to investigate the outcomes of treatment with the drug rapamycin that targets upregulated phosphatidylinositol 3-kinase (PI3-K) / mammalian target of rapamycin (mTOR) signalling. Outcome: paper in press.

Dr Deborah Marsh, Dr Michael Hahn, Dr Viive Howell with Dr Anthony Gill, Department of Anatomical Pathology, RNSH. Collaboration has involved further development of diagnostic pathological testing for parathyroid carcinoma coupled with mutation analysis in new cases. Further, a protein previously identified by microarray analysis to be upregulated in some tumours, has been additionally explored for its diagnostic value in a large cohort of parathyroid tumours. Outcome: invited review article on familial hyperparathyroidism and paper in preparation.

Dr Deborah Marsh with Professor Rob Baxter and Dr Janet Martin on the analysis of functional mutations in the tumour suppressor PTEN. Outcome: joint PhD student.

Dr Deborah Marsh with Professor Rob Baxter, Dr Janet Martin and Professor Glenn Marshall, Sydney Children’s Hospital, Sydney, on rapamycin treatment for a child with Proteus syndrome. Outcome: joint publication in press.

Dr Deborah Marsh with Professor Rob Baxter, Dr Janet Martin and Dr Michelle Jack, Department of Endocrinology, RNSH, on epigenetic regulation of genes in paediatric cancer. Outcome: joint student.

Dr James Melrose and Professor Bruce Caterson, Cardiff University, UK. Investigation of proteolysis of small proteoglycans in human musculoskeletal tissues. Ongoing sharing of reagents including novel antibodies. Manuscript submitted Arthritis Research and Therapy; further papers in preparation.

Dr James Melrose and Dr Tony Hayes, Cardiff University, UK. Confocal microscopic analysis of tensional connective tissues. Ongoing sharing of reagents including novel antibodies. Successful NHMRC project grant application – funding commenced 2008; Manuscript accepted in BioEssays further manuscripts in preparation.

Dr James Melrose and Associate Professor John Whitelock, UNSW. Investigating the role of perlecan in musculoskeletal tissues in health and disease. Shared PhD student (submitting 2008). Successful NHMRC project grant application – funding commenced 2008; ARC grant submitted 2008; publication of numerous papers.

Dr James Melrose and Professor Neil Broom, University of Auckland, NZ. Mechanobiology of disc degeneration. Ongoing sharing of ideas, technologies and equipment between the two groups, publication in preparation.

Associate Professor Michael Nicholas with Louise Sharpe (Physiotherapy, USyd); Kathryn Refshauge (Physiotherapy, USyd). Attentional mechanisms in acute and chronic pain. ARC grant.

Associate Professor Michael Nicholas with Kathryn Refshauge and Chris Maher (Physiotherapy, USyd). Evaluating advice and exercises in treatment of sub-acute low back pain and predictors of outcome. NHMRC grant.

Associate Professor Michael Nicholas with Professor Steven Linton (Orebro University, Sweden). Investigating interoceptive exposure as a pain management strategy.

Dr Peregrine Osborne with Dr Gavin McNally and Professor Fred Westbrook, School of Psychology, UNSW. Effects of acute and chronic opioid treatment on the emotional and motivational circuits in the basal forebrain. Outcome: joint publication.

Professor Carol Pollock and Professor D Johnson (University of Queensland) and Dr I McDougall (Kings College London) on pure red cell aplasia in ESA treated patients. Outcome: 2 publications in 2007.

Professor Carol Pollock and Professor P Poronnik (University of Queensland) Joint HHMRC funding on albumin uptake in tubular cells and integrated signalling mechanisms involved in angiotensin II actions on proximal tubular cells. Outcome: one publication in 2007 and one accepted for publication.

Professor Carol Pollock, Dr Bruce Cooper and Professor D Harris (Millenium Institute, University of Sydney). Joint NHMRC Funding (and significant industry support) on ‘the ideal time to commence dialysis’. Currently working towards a closer collaboration on mechanisms of progressive kidney disease. Outcome: Successful joint NHMRC funding in 2007. Joint publication.

Professor Carol Pollock, Dr Bruce Cooper and Dr Suresh Sankar (India). Joint collaborations to advance the research capacity of Dr Sankars centre in India and to promote epidemiological research. Outcome: Dr Sankar has published 2 papers in 2007 after review by the Renal research group prior to submission.

Professor Carol Pollock, Dr Xin-Ming Chen, with Associate Professor D Kelly and Dr W Qi St Vincents Institute of Medical Research University of Melbourne. Long standing collaboration, where animal research is largely conducted in Melbourne and in vitro research in Sydney. Outcome: Successful in joint NHMRC Funding in 2007. 2 publications in 2007.
Research Collaborations

Professor Carol Pollock, Dr Xin-Ming Chen with Professor R Gilbert, University of Toronto. Ongoing collaboration in progressive renal disease and alterations in transport and downstream signalling. Outcome: 3 publications in 2007.

Professor Carol Pollock, Dr Sonya Saad with Professor F Lang at the University of Tubingen. Ongoing collaboration in progressive renal disease and alterations in transport and downstream signalling. Outcome: Paper in preparation.

Professor Bruce Robinson, Dr Dindy Benn with Professor Hartmut Neumann, Freiburg, Germany and Professor Charis Eng, Cleveland, Ohio, USA as members of a large consortium studying SDH mutations. Outcome: manuscript submitted.

Professor Bruce Robinson, Dr Dindy Benn with Dr Mike Croxson, Auckland, New Zealand and Dr Kathy Tucker, Prince of Wales Hospital and University of New South Wales, studying Australasian SDH mutations. Outcome: manuscript in preparation.

Professor Bruce Robinson with Dr Gemma Figtree, Dept of Cardiology, RNSH, studying ROS-mediated signalling in cardiac myocytes. This work funded by the RNSH-Heart Research Foundation and commenced in 2008.

Professor Bruce Robinson with Dr Simon Finfer, Intensive Care Unit, RNSH on NHMRC Grant. Outcome: Trial of normoglycaemia versus conventional glycaemic control in Intensive Care patients.

Professor Bruce Robinson and Clinical Associate Professor Stan Sidhu with Professor Quan-Yang Duh, University of California, San Francisco, USA. Outcome: Malignant phaeochromocytoma samples received for joint arrays project.

Associate Professor Philip Siddall with Dr Luke Henderson, Department of Anatomy & Histology, University of Sydney.

Associate Professor Philip Siddall with Associate Professor James Middleton, Statewide Spinal Cord Injury Service, & Rehabilitation Studies Unit, The University of Sydney.

Associate Professor Philip Siddall with Associate Professor Michael Nicholas, Kathryn Nicholson Perry, Robin Murray, Pain Management Research Institute, University of Sydney.

Associate Professor Philip Siddall with Associate Professor Janet Keast, Dr Peregrine Osborne, Professor Mac Christie, Pain Management Research Institute, University of Sydney.

Associate Professor Philip Siddall with Associate Professor Janet Keast, Dr Peregrine Osborne, Professor Mac Christie, Pain Management Research Institute, University of Sydney.

Associate Professor Philip Siddall with Drs Sue Rutkowski, Ros Soden and Lianne Hunt, Spinal Injuries Unit, Royal North Shore, Hospital.

Associate Professor Philip Siddall with Professor Simon Gandevia, Prince of Wales Medical Research Institute, Randwick.

Associate Professor Philip Siddall with Professor Vaughan Maclefield, School of Medicine, University of Western Sydney.

Associate Professor Philip Siddall with Dr Lea Sorensen, Professor Dennis Yue, Diabetes Centre, Royal Prince Alfred Hospital, Camperdown.

Associate Professor Philip Siddall with Professor Ashley Craig, Dr Yvonne Tran, Dr Peter Boord, University of Technology, Sydney.

Dr Margaret Smith with Professor Nicolai Miosge, Department of Prosthodontics, University of Goettingen, Germany. International co-operative to share real time PCR primers and to investigate changes in gene expression in disease. Prot Miosge visited department in 2007 and presented a research seminar. Publication accepted 2007 and further papers in preparation.

Professor Carolyn Sue with Alan Mackay-Sim (Griffith University, Qld).

Professor Carolyn Sue Glenda Halliday
(Prince of Wales Medical Research Institute, NSW).

Professor Carolyn Sue Christine Klein (University of Luebeck, Germany).

Professor Carolyn Sue Justin Rubio (Howard Florey Institute, Victoria).

Professor Carolyn Sue Paul Mitchell (Centre for Vision Research and Save the Sight Institute, NSW).

Professor Carolyn Sue John Christodoulou (Children’s Hospital Westmead, NSW).

Professor Carolyn Sue David Thorburn (Murdoch Children’s Institute, Victoria).

Dr Chris Vaughan with Associate Professor RJ Vandenberg and Dr M Connor (University of Sydney) on NHMRC project grant 352450. Examined actions of novel endogenous cannabinoid related agents and determined the cellular targets of the agents, how they act at the cellular level, and whether they have any effect on models of chronic pain.

Dr Chris Vaughan with Professor D Piomelli (University of California, Irvine) on mechanisms of endogenous cannabinoid mediated analgesia. Unfunded. Examining how endogenous cannabinoids are produced within a midbrain region, the periaqueductal grey, which has a crucial role in pain and anxiety. The in vitro component has been studying the cellular actions of these endocannabinoids and the in vivo component has been examining the actions of these agents in chronic pain models. Dr Piomelli has supplied novel agents which modulate the endocannabinoid system.

Dr Chris Vaughan with Dr J Phillips (Murdoch University). Associate investigator on NHMRC funded project grant to examine the peripheral mechanisms involved in chronic pain states. Our group has been providing expertise and material for this project.
The Kolling Institute of Medical Research continues to actively engage in the supervision and education of students completing their undergraduate studies, masters, or doctor of philosophy. In 2007 the numbers of students working and supervised within the Kolling Institute of Medical Research included:

- Doctor of Philosophy (PhD) x 51
- Master of Medical Science (MMed) x 1
- MBBS (Hons) x 4
- Bachelor of Science with Honours (BScHons) x 2
- Bachelor of Science (BSc) x 1
- Bachelor of Health Science (BHlthSc) x 1
- Bachelor of Veterinary Science (BVSc) x 1
- Advanced Medical Science (University of Melbourne) x 1
- Postgraduate Industrial Experience Program (University of Western Sydney) x 1
- David Nelson Summer Scholars x 7

Postgraduate students activities continue to grow at the Kolling Institute of Medical Research with more than fifty students enrolled in University of Sydney PhD or Masters (by research) programs. Students have been active in publishing papers, presenting results at overseas meetings and winning awards. Kolling Institute students have also contributed to student life on campus via their involvement with the postgraduate student society, PReSS, as members of the executive. PreSS has an active role on campus organising student social events as well as a monthly student seminar series and lunch. The PReSS annual retreat was once again very successful, held in the Sydney Botanic Gardens and focusing on relaxation and oral presentation skills. The Kolling Institute Postgraduate committee continues to be active in promoting and supporting student activities. Symposia organised over two mornings to allow new students to present their thesis proposals in front of a Kolling Institute wide audience were well attended and highly successful with students setting a very high standard. A number of postgraduate workshops were also organised in conjunction with the University and Northern Clinical School. These included a two day statistics course (delivered by Dr Federica Barzi, Goerge Institute), and a very successful “Journal Article Writing” workshop (delivered by Dr Angela Ardington, Learning Centre) with Prof Rob Baxter and A/Prof Janet Keast adding useful insights from both the Editor’s and writer’s point of view.

2007 Graduations

Amy Au (PhD). The role of PPARgamma in thyroid malignancy.

Levi Bassin (MBBS Hons). Surface electrocardiogram changes during coronary microembolisation in sheep.

Sophie Chan (PhD). The role of IGFBP-3 in adipocyte differentiation and insulin sensitivity.

David Chenu (BSc Hons). Serotonergic modulation of GABAergic synaptic transmission in the midbrain periaqueductal grey of the rat.

Shelley Forrest (BSc Hons). Activation of the spino-parabrachial-amygdalar pathway by two pro-nociceptive conditions.

Jessica Hokin (BSc Hons). Anti-IgD antibody is a novel modulator of T-bet and Th1 cytokines in human PMBC.


Nicholas Kerr (MBBS Hons). Spastin mutations in patients with hereditary spastic paraplegia.

Michelle Moscova (PhD). Proteomic Analysis of phosphatidylinositol 3-kinase signalling in ovarian cancer.

Kathryn Nicholson Perry (PhD). Evaluating the utility of the biopsychosocial model in spinal cord injury-related pain and its treatment implications.

Joanna Peterson (BSc Hons). Biomechanics of mouse tendons.

Jamir Sarda Jnr (PhD). Investigation of a biophysical perspective of pain in Brazilian chronic pain patients.

Christopher Scarlett (PhD Surgery). Proteomic analysis of pancreatico-biliary malignancy.


Rachel Shepherd (PhD). The role of apoptosis in pathophysiology of mitochondrial Disorders.

Scott Stanners (PhD). Novel factors influencing renal fibrosis.

Veronica Stevens (PhD). The role of serum and glucorticoid regulated kinase in the tubulointerstitial disease of diabetic nephropathy.
Miriam Jackson. Miriam commenced her PhD in August 2006 under the supervision of Associate Professor Christopher Little and Associate Professor Christopher Jackson. She had been working as a research assistant in the Raymond Purves Research Lab since November 2004, and completed a bachelor of Medical Science with honours at the University of Western Sydney in 2005. After almost 2 years of working as a research assistant Miriam decided to undertake a PhD to further her career in research, and because “I felt there was a generous amount of support and knowledge available for students within the Kolling Institute”. Her PhD is investigating the role of activated protein C (APC) in the activation of collagenolytic matrix metalloproteinases in normal and pathological cartilage turnover. They have demonstrated that chondrocyte-derived APC could play a significant role in activation of MMPs and cartilage breakdown in arthritis, and controlling APC activity may be a novel therapeutic target. Miriam’s work is supported by the Australian Rotary Health Research Fund and the Lincoln Centre for Research into Bone and Joint Diseases. Miriam says that “so far my research has been going well with some promising results that will be published shortly thanks to the great support of my supervisors. Many challenges have also arisen including experiments not going to plan and some time off from study on maternity leave during my first year. I have obtained enough experimental data to compose my first scientific paper which has just been submitted to Arthritis and Rheumatism (Journal)”. In 2007 Miriam received a PaLMS Australasian Travel Fellowship to travel to Cairns to present at the 2007 Pan Pacific Connective tissue Societies Symposium. Her presentation was short-listed for the Young Investigator award at the RNSH/USyd/UTS/Kolling meeting in the young investigator section.

Patrick Thompson (MBBS Hons). The role of MMPs and inflammatory cytokines in bone erosion and matrix breakdown in rheumatoid arthritis- an immunohistochemical study.

Paul Wrigley (PhD). Cold thermal processing in the spinal cord.

Postgraduate Profiles

Patsy Soon. Patsy commenced her PhD in 2005 after having completed her general surgical training. Under the supervision of Professor Bruce Robinson, Clinical Associate Professor Stan Sidhu, Dr Kerrie McDonald and Dr Diana Benn, Patsy’s project aimed at identifying molecular markers which can accurately distinguish adrenocortical carcinomas from adenomas, as well as providing novel therapeutic targets for the treatment of adrenocortical carcinomas, by Loss of Heterozygosity (LOH) analysis and microarray gene expression profiling. She has found that immunohistochemistry using IGF2 and Ki-67 antibodies can accurately distinguish adrenocortical carcinomas from adenomas. Patsy has presented her findings at local, national and international meetings. She won the Tom Reeve Prize for best oral presentation in the Endocrine Section of the Royal Australasian College of Surgeons Annual Scientific Congress in Christchurch in May, 2007, for her presentation entitled “Microarray gene expression analysis of human adrenocortical tumours”. Patsy will submit her thesis in December 2007. In 2008 she will take up a part time position as a Breast/Endocrine surgeon at Bankstown hospital and continue her research into adrenocortical tumours part time under an NHMRC Health Professional Research Training Fellowship in the Kolling Institute of Medical Research.

Patsy preparing samples for an assay.
### Project & Program Grants

<table>
<thead>
<tr>
<th>Funding Source</th>
<th>Title</th>
<th>Investigators</th>
<th>Funds in 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrew Olle Foundation</td>
<td>Underexpression of prostaglandin D synthase: a key molecular event in the transition of a low grade astrocytoma to an anaplastic astrocytoma</td>
<td>K McDonald</td>
<td>$ 85,000</td>
</tr>
<tr>
<td>Association for International Cancer Research (UK)</td>
<td>IGFBP-3 as a growth inhibitor in breast cancer</td>
<td>RC Baxter, SM Firth, JL Martin</td>
<td>$ 90,344</td>
</tr>
<tr>
<td>Australian Health Ministers Advisory Council PDR</td>
<td>Chronic pain in elderly Australians: randomised controlled trial of self-management</td>
<td>M Nicholas, T Newton-John, F Blyth</td>
<td>$ 86,000</td>
</tr>
<tr>
<td>Australian &amp; New Zealand College of Anaesthetists</td>
<td>Activation of brain regions in people with neuropathic pain following spinal cord injury</td>
<td>P Siddall, J Middleton</td>
<td>$ 50,943</td>
</tr>
<tr>
<td>Australian Research Council</td>
<td>Computational scaffold for tissue</td>
<td>Q Li, RC Appleyard, W Li</td>
<td>$ 75,000</td>
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<tr>
<td>Australian Research Council</td>
<td>Proteolysis of binding protein complexes regulates IGF bioavailability</td>
<td>SM Firth, RC Baxter</td>
<td>$ 78,000</td>
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<tr>
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<td>The role of SGK in diabetic nephropathy</td>
<td>CA Pollock, XM Chen</td>
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<tr>
<td>Cancer Council NSW</td>
<td>Biomarkers of cell signalling pathways in ovarian cancer</td>
<td>DJ Marsh, RC Baxter</td>
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<tr>
<td>Cancer Institute NSW</td>
<td>Oligodendrogliomas with LOH 1p/19q: Identifying genes associated with therapeutic sensitivity</td>
<td>K McDonald, BG Robinson</td>
<td>$ 25,000</td>
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<tr>
<td>Cancer Institute NSW</td>
<td>Interactions between hypoxia, inflammation, and IGF binding proteins in ovarian cancer</td>
<td>RC Baxter, BS Schuett</td>
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<td>Diabetes Australia Research Trust</td>
<td>The role of endothelial stem cells and erythropoietin in vascular disease in patients with diabetes mellitus and/or chronic kidney disease</td>
<td>U Panchapakesan</td>
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<tr>
<td>Hillcrest Foundation</td>
<td>Unravelling tumorigenesis of phaeohromocytoma</td>
<td>BG Robinson, DE Benn</td>
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<tr>
<td>Hillcrest Foundation</td>
<td>Kruppel like transcription factors and oxidative stress in epithelial to mesenchymal transformation</td>
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<td>$ 50,000</td>
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<tr>
<td>NHMRC</td>
<td>Feasibility of flow diversion to the renal circulation in sheep</td>
<td>H Krum, J Friend, S Hunyor</td>
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## Project & Program Grants (cont.)

<table>
<thead>
<tr>
<th>Funding Source</th>
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<th>Funds in 2007</th>
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<td>NHMRC</td>
<td>Discovering which enzymes are important in joint disease</td>
<td>AJ Fosang, H Stanton, CB Little</td>
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<td>How important is collagen destruction in arthritis?</td>
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<td>NHMRC</td>
<td>Novel regulators of fat cell differentiation</td>
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<td>Pathobiology of the small leucine rich repeat proteoglycans in cartilage, intervertebral disc and tendon degeneration</td>
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<td>NHMRC</td>
<td>Proteoglycan metabolism in tendon degeneration</td>
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<td>Proteomic screening for apoptotic markers in breast cancer</td>
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<td>The role of peroxisome proliferator activated receptor gamma in sodium transport in human proximal tubule cells</td>
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<td>Epithelial-mesenchymal transformation in diabetic nephropathy: Roles of oxidative stress and KLF transcription factors</td>
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<td>Initiating Dialysis Early and Late (IDEAL) Trial</td>
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<td>Interdisciplinary Maternal Perinatal Action on Clinical Trials Collaboration IMPACT</td>
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<td>Pharmacology of peripheral pain pathways</td>
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<td>A randomised controlled trial of immediate delivery versus expectant care in women with ruptured membranes close to term</td>
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<td>NHMRC</td>
<td>Controlled clinical trial of desensitization to chronic pain</td>
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<td>Does place of birth influence a healthy start to life?</td>
<td>C Roberts, J Simpson, J Ford, J Bowen, L Taylor, N Nassar</td>
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<td>Funding Source</td>
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<td>Molecular and cellular basis for the analgesic properties of N-arachidonyl amino acids</td>
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<td>NHMRC</td>
<td>Regionalised maternity care - is there room for improvement?</td>
<td>C Roberts, J Simpson, N Nassar, L Taylor, J Morris, D Henderson-Smart</td>
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<td>NHMRC</td>
<td>Stimulus induced synaptic plasticity in the amygdala</td>
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<td>Thromboxane receptor signaling in endothelial cells</td>
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<td>NHMRC</td>
<td>Understanding immune tolerance in pregnancy to discover a new intervention for the treatment of preeclampsia</td>
<td>J Morris, E Gallery, A Ashton</td>
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<td>NHMRC</td>
<td>Why is trophoblast invasion defective in human pregnancies that develop pre-eclampsia?</td>
<td>E Gallery, C Jackson, J Morris</td>
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<td>NHMRC</td>
<td>Regeneration of pelvic autonomic axons after injury</td>
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<td>NIH (USA)</td>
<td>Effects of estrogen on bladder pain</td>
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<td>North Shore Heart Research Foundation</td>
<td>Haemodynamic effects of ANP and cANP in an ovine rapid paced heart failure model</td>
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<td>Northern Sydney Central Coast Area Health</td>
<td>The role of SELS in diabetic nephropathy</td>
<td>W Qi</td>
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<td>Northern Sydney Central Coast Area Health</td>
<td>Proteomic approaches to identify growth hormone response markers in human peripheral blood leucocytes</td>
<td>L Chung, RC Baxter, AE Nelson, KK Ho</td>
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<td>Northern Sydney Central Coast Area Health</td>
<td>Bridging Support for Senior Scientists</td>
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<td>Northern Sydney Central Coast Area Health</td>
<td>A new in vitro technique to examine the mechanisms of endocannabinoid analgesia within the midbrain periaqueductal grey</td>
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<tr>
<td>Northern Sydney Central Coast Area Health</td>
<td>Erectile dysfunction and autonomic innervation of penis in type II experimental diabetes</td>
<td>M Nangle</td>
<td>$20,000</td>
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</table>
### Project & Program Grants (cont.)

<table>
<thead>
<tr>
<th>Funding Source</th>
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<th>Funds in 2007</th>
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<tr>
<td>Northern Sydney Central Coast Area Health</td>
<td>Targeting transcription regulation of transcriptional factor T-bet as a new approach to control chronic inflammation in autoimmune diseases</td>
<td>J Morris, T Nguyen</td>
<td>$ 30,000</td>
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<td>NSW Ministry for Science and Medical Research (Spinal cord injury &amp; other neurological conditions research grants program)</td>
<td>Pain following spinal cord injury: understanding mechanisms to develop treatments</td>
<td>J Keast, M Christie, M Cousins, P Osborne, P Siddall</td>
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<td>Sydney Neuro Oncology Group</td>
<td>Brain Tumour Research</td>
<td>KL McDonald</td>
<td>$ 51,215</td>
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<tr>
<td>Sydney Neuro Oncology Group</td>
<td>Functional analysis and biomarker development of target genes in glioblastoma cell lines</td>
<td>K McDonald</td>
<td>$ 91,281</td>
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<td>University of Sydney</td>
<td>APC in cartilage breakdown</td>
<td>CB Little</td>
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<tr>
<td>University of Sydney</td>
<td>The role of the M6P/IGF-II receptor in regulating cellular function</td>
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<td>University of Sydney</td>
<td>A pilot study investigating the ability of maternal levels of Angiopoietin 2 (Ang-2) in early pregnancy to predict adverse outcomes</td>
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<td>University of Sydney</td>
<td>Studies on endometriosis and the subsequent risk of adverse pregnancy outcomes</td>
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<td>University of Sydney</td>
<td>A model of varying severity acute heart failure</td>
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<td>Alternative lengthening of telomeres and outcome of glioblastoma multiforme</td>
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<td>Novel interactions of IGFBP-3 with extracellular matrix components: Functional characterisation of the interactions in breast cancer</td>
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## Fellowships

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<tr>
<th>Funding Source</th>
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<th>Title</th>
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<td>Career Development and Support Fellowship</td>
<td>Functional genomic analyses of human tumorigenesis</td>
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<td>Cancer Institute NSW</td>
<td>Career Development and Support Fellowship</td>
<td>IGFBP-3: Regulator of growth in breast cancer cells</td>
<td>SM Firth</td>
<td>$197,600</td>
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<tr>
<td>Cancer Institute NSW</td>
<td>Career Development and Support Fellowship</td>
<td>Insulin-like growth factor binding proteins in cancer: Characterisation and mechanisms of action</td>
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<td>Cancer Institute NSW</td>
<td>Career Development and Support Fellowship</td>
<td>Mechanisms of action of a growth suppressing protein in cancer</td>
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<td>Identification of novel IGFBP-3 interacting proteins with the potential to influence cancer</td>
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<td>Cure for Life Foundation</td>
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<td>Growth Hormone Research Society</td>
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<td>Functional characterisation of the recently discovered mammalian genes, SCN1 &amp; HRPT2</td>
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<td>NHMRC</td>
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<td>Regulation of angiogenesis by thromboxane receptor activation</td>
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<td>The role of KLF transcription factors in diabetic nephropathy</td>
<td>XM Chen</td>
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<td>University of Sydney</td>
<td>Postdoctoral Research Fellowship</td>
<td>Activated protein C in the regulation of rheumatoid arthritis</td>
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**Income in 2007**

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<th>Income in 2007</th>
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## Scholarships

<table>
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<tr>
<th>Funding Source</th>
<th>Type of funding</th>
<th>Title</th>
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<tbody>
<tr>
<td>Cancer Institute NSW</td>
<td>Research Scholar Award</td>
<td>Genetics of adrenocortical tumours</td>
<td>P Soon</td>
<td>$25,000</td>
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<td>Cancer Institute NSW</td>
<td>Research Scholar Award</td>
<td>Chemotherapy and high grade glioma genetic studies</td>
<td>J Parkinson</td>
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<td>Cancer Institute NSW</td>
<td>Research Scholar Award</td>
<td>Identification of molecular genetic markers in pituitary adenoma subtypes with microarray</td>
<td>M Elston</td>
<td>$25,000</td>
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<td>Cancer Institute NSW</td>
<td>Research Scholar Award</td>
<td>Investigation of the role of PTEN in overgrowth and tumour development</td>
<td>WY Chee</td>
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<td>Extracellular matrix remodelling post myocardial infarction in sheep: role of activated protein C</td>
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<td>Role of PPARgamma: IGFBP-3 interactions in regulating breast cancer function</td>
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<td>Mechanisms of dysfunction of spinal cord inhibitory neurons in chronic pain states</td>
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<td>DEST</td>
<td>Australian Postgraduate Award</td>
<td>Mechanisms of endocannabinoid mediated analgesia within the midbrain</td>
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<td>DEST</td>
<td>Australian Postgraduate Award</td>
<td>Neurotransmitter induced endogenous cannabinoid signalling in midbrain analgesic system</td>
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<tr>
<td>DEST</td>
<td>Australian Postgraduate Award</td>
<td>Pain following spinal cord injury: the role of plasticity in spinal and brainstem pathways</td>
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<td>$19,616</td>
</tr>
<tr>
<td>Funding Source</td>
<td>Type of funding</td>
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<td>DEST</td>
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<td>The effects of anti-coagulant Activated Protein C (APC) on breast cancer cell proliferation and invasion</td>
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<td>DEST</td>
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<td>DEST</td>
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<td>Bone morphogenetic protein-and Kruppel-like factors in diabetic nephropathy</td>
<td>MG Wong</td>
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<tr>
<td>DEST</td>
<td>Endeavour International Postgraduate Research Scholarship (IPRS)</td>
<td>Investigation of the role of PTEN in overgrowth and tumour development</td>
<td>WY Chee</td>
<td>$18,840</td>
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<tr>
<td>Douglas and Lola Douglas Bequest</td>
<td>Research Scholar Award</td>
<td>Epigenetic regulation of gene expression in paediatric malignancies</td>
<td>W Lin</td>
<td>$15,000</td>
</tr>
<tr>
<td>NHMRC</td>
<td>Biomedical Postgraduate Research Scholarship</td>
<td>The role of IGFBP-5 proteolysis in regulating IGF bioavailability in pregnancy</td>
<td>X Yan</td>
<td>$21,231</td>
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<tr>
<td>NHMRC</td>
<td>Biomedical Postgraduate Research Scholarship</td>
<td>Macrophage migration inhibitory factor and kruppel-like factor 4 in diabetic nephropathy</td>
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<td>$21,231</td>
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<tr>
<td>NHMRC</td>
<td>Biomedical Postgraduate Research Scholarship</td>
<td>The role of endothelial progenitor cells and erythropoietin in vascular disease in patients with diabetic and/or chronic renal impairment</td>
<td>S Sumual</td>
<td>$19,231</td>
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<td>NHMRC</td>
<td>Medical Postgraduate Scholarship</td>
<td>The role of the mevalonate pathway in diabetic vascular disease</td>
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<td>$22,950</td>
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<td>NHMRC</td>
<td>Medical Postgraduate Scholarship</td>
<td>Why is trophoblast invasion defective in pregnancies that develop pre-eclampsia?</td>
<td>S Seeho</td>
<td>$30,600</td>
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## Scholarships (cont.)

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<thead>
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<td>NHMRC</td>
<td>Medical Postgraduate Scholarship</td>
<td>Genetics of adrenocortical tumours</td>
<td>P Soon</td>
<td>$28,600</td>
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<tr>
<td>NHMRC</td>
<td>Medical Postgraduate Scholarship</td>
<td>Identification of molecular genetic markers in pituitary adenoma subtypes with high density cDNA microarrays</td>
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<td>$28,600</td>
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<tr>
<td>NHMRC</td>
<td>Medical Postgraduate Scholarship</td>
<td>Genetics of phaeochromocytoma</td>
<td>W Meyer-Rochow</td>
<td>$31,422</td>
</tr>
<tr>
<td>NHMRC</td>
<td>Medical Postgraduate Scholarship</td>
<td>Identification of genetic markers to distinguish pituitary tumour subtypes using cDNA</td>
<td>A McCormack</td>
<td>$28,600</td>
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<tr>
<td>North Shore Heart Research Foundation</td>
<td>Scholarship</td>
<td>Development of Y chromosome FISH markers for the tracking and identification of ovine MSC cells in histological tissue samples</td>
<td>M Pokharma, C Jackson, S Saad, S Hunyor</td>
<td>$16,154</td>
</tr>
<tr>
<td>North Shore Heart Research Foundation</td>
<td>Scholarship</td>
<td>Heart damage, bone marrow progenitor cell response and stem cell therapy</td>
<td>J Seow, S Hunyor</td>
<td>$15,000</td>
</tr>
<tr>
<td>Royal North Shore Hospital</td>
<td>Cancer Memorial Research Scholarship</td>
<td>Discovering biomarkers regulated by gonadotropin signalling in ovarian cancer</td>
<td>I Mertens</td>
<td>$30,060</td>
</tr>
<tr>
<td>Rotary Club of Blacktown</td>
<td>Scholarship</td>
<td>The role of Activated Protein C in the activation of collagenolytic matrix metalloproteinases in normal and pathological cartilage turnover</td>
<td>MJ Jackson</td>
<td>$19,000</td>
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<tr>
<td>Royal Australasian College of Surgeons</td>
<td>Scholarship</td>
<td>Genetics of adrenocortical tumours</td>
<td>P Soon</td>
<td>$16,395</td>
</tr>
<tr>
<td>Royal Australasian College of Surgeons</td>
<td>Scholarship</td>
<td>Genetics of high grade gliomas and their response to chemotherapy</td>
<td>J Parkinson</td>
<td>$37,500</td>
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<tr>
<td>Royal Australasian College of Surgeons</td>
<td>Scholarship</td>
<td>Genetics of phaeochromocytoma</td>
<td>W Meyer-Rochow</td>
<td>$25,828</td>
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<tr>
<td>University of Sydney Faculty of Medicine Scholarship</td>
<td>Scholarship</td>
<td>Opioids and descending nociception control systems</td>
<td>N Pedersen</td>
<td>$8,000</td>
</tr>
<tr>
<td>University of Sydney Faculty of Medicine Scholarship</td>
<td>Scholarship</td>
<td>Regulation of receptors for anti-migraine drugs</td>
<td>M Heblinski</td>
<td>$27,680</td>
</tr>
<tr>
<td>University of Sydney International Postgraduate Award (IPA)</td>
<td>Scholarship</td>
<td>Investigation of the role of PTEN in overgrowth and tumour development</td>
<td>WY Chee</td>
<td>$19,616</td>
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<tr>
<td>Westpac</td>
<td>Postgraduate Scholarship</td>
<td>Regulation of receptors for anti-migraine drugs</td>
<td>M Heblinski</td>
<td>$30,000</td>
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</tbody>
</table>
# Industry Grants

<table>
<thead>
<tr>
<th>Funding Source</th>
<th>Title</th>
<th>Investigators</th>
<th>Funds in 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Basser Trust Perpetual</td>
<td>Pain Management Research</td>
<td>MJ Cousins</td>
<td>$ 80,000</td>
</tr>
<tr>
<td>Amgen</td>
<td>Unrestricted</td>
<td>CA Pollock</td>
<td>$ 80,000</td>
</tr>
<tr>
<td>Astra Pharmaceuticals</td>
<td>Statins and tubular proteinuria</td>
<td>U Panchapakesan, CA Pollock</td>
<td>$ 40,000</td>
</tr>
<tr>
<td>Bushell Foundation</td>
<td>Janssen-Cilag Cellular and Molecular Pain Research Laboratory</td>
<td>MJ Cousins</td>
<td>$ 75,000</td>
</tr>
<tr>
<td>EBI Biomet</td>
<td>Evaluation of knee joint kinematics pre and post application of an external fixation device</td>
<td>RC Appleyard, D Parker, M Coolican</td>
<td>$ 30,000</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>The molecular actions of peroxisome proliferators gamma in diabetic nephropathy</td>
<td>U Panchapakesan</td>
<td>$ 40,000</td>
</tr>
<tr>
<td>IAG</td>
<td>Pain research</td>
<td>MJ Cousins</td>
<td>$ 100,000</td>
</tr>
<tr>
<td>Janssen-Cilag</td>
<td>Sponsorship for the Pain Program</td>
<td>MJ Cousins</td>
<td>$ 30,000</td>
</tr>
<tr>
<td>John T Reid Charitable Trust</td>
<td>Pain Management Research Laboratory</td>
<td>MJ Cousins</td>
<td>$ 10,000</td>
</tr>
<tr>
<td>MBF</td>
<td>Pain Management Research</td>
<td>MJ Cousins</td>
<td>$ 57,342</td>
</tr>
<tr>
<td>Mesoblast Ltd</td>
<td>Evaluation of the safety and efficacy of Allogeneic Mesenchymal Progenitor Cells (IMPCs) in the regeneration of a medial knee joint meniscus and the retardation of cartilage injury in an ovine model of osteoarthritis</td>
<td>CB Little, RC Appleyard</td>
<td>$ 105,222</td>
</tr>
<tr>
<td>Mirvac</td>
<td>Pain Management Research</td>
<td>MJ Cousins</td>
<td>$ 125,000</td>
</tr>
<tr>
<td>Mundipharma</td>
<td>Sponsorship of the Pain Management Research Centre</td>
<td>MJ Cousins</td>
<td>$ 50,000</td>
</tr>
<tr>
<td>Pfizer Inc, USA</td>
<td>Evaluation of four genetically modified mice using a medial meniscal destabilization model of osteoarthritis</td>
<td>CB Little</td>
<td>$ 135,000</td>
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<tr>
<td>Pfizer Neuro Science Research Grant</td>
<td>Structural alterations of the human brain following complete spinal cord injury in people with and without neuropathic pain - a pilot study</td>
<td>P Wrigley</td>
<td>$ 46,000</td>
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<tr>
<td>Profield Foundation</td>
<td>Pain Management Research</td>
<td>MJ Cousins</td>
<td>$ 10,000</td>
</tr>
<tr>
<td>Ramsay Healthcare</td>
<td>Support to backfill position as Research Chair in NSCCAHS</td>
<td>CA Pollock</td>
<td>$ 70,000</td>
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<tr>
<td>Schering-Plough</td>
<td>Molecular characterisation of drug resistance mechanisms in high grade gliomas</td>
<td>BG Robinson, H Wheeler, K McDonald</td>
<td>$ 70,000</td>
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<tr>
<td>Trust Company</td>
<td>Pain Management Research</td>
<td>MJ Cousins</td>
<td>$ 100,000</td>
</tr>
<tr>
<td>Workcover NSW</td>
<td>Injury &amp; Pain - Prevention of progression from acute to chronic phase</td>
<td>MJ Cousins</td>
<td>$ 50,000</td>
</tr>
<tr>
<td>Xenome Ltd</td>
<td>The assessment of anti-hyperalgesic and anti-inflammatory properties of Xen0458</td>
<td>M Christie, CW Vaughan</td>
<td>$ 30,609</td>
</tr>
</tbody>
</table>
## Equipment Grants

<table>
<thead>
<tr>
<th>Funding Source</th>
<th>Title</th>
<th>Investigators</th>
<th>Funds in 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Research Council LIEF grant</td>
<td>DAKO ACIS III cellular image acquisition and analysis system</td>
<td>BD Hambly, S Bao, GA Bishop, J Black, IL Campbell, Q Dong, MD Gorrell, GE Grau, NH Hunt, NJ King, R Markham, DJ Marsh, KL McDonald, SV McLennan, KJ Rodgers, S Seth</td>
<td>$ 150,000</td>
</tr>
<tr>
<td>Caledonia Foundation</td>
<td>Delivering the right drug to the right patient</td>
<td>KL McDonald</td>
<td>$ 128,000</td>
</tr>
<tr>
<td>Clive and Vera Ramaciotti Foundation</td>
<td>RotorGene 6000 real-time PCR</td>
<td>CB Little</td>
<td>$ 25,000</td>
</tr>
<tr>
<td>NHMRC</td>
<td>Two-dimensional Gel Electrophoresis Equipment and Software</td>
<td>RC Baxter</td>
<td>$ 75,000</td>
</tr>
<tr>
<td>Rebecca Cooper Medical Research Foundation</td>
<td>Use of mouse models to investigate the mechanisms of cartilage and tendon breakdown in disease</td>
<td>CB Little</td>
<td>$ 14,346</td>
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</tbody>
</table>
## Infrastructure Grants

<table>
<thead>
<tr>
<th>Funding Source</th>
<th>Title</th>
<th>Investigators</th>
<th>Funds in 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Institute NSW</td>
<td>Cancer Functional Genomics in the Northern Hub</td>
<td>RC Baxter, DJ Marsh, RC Smith</td>
<td>$ 100,072</td>
</tr>
<tr>
<td>Cancer Institute NSW</td>
<td>Confocal microscope for cancer research in the Northern Hub</td>
<td>RC Baxter, BG Robinson</td>
<td>$ 300,000</td>
</tr>
<tr>
<td>Cancer Institute NSW</td>
<td>Tumour Bank Officer in the Northern Hub</td>
<td>DJ Marsh, RC Baxter, BG Robinson, R Smith</td>
<td>$ 65,677</td>
</tr>
<tr>
<td>NHMRC Enabling Grant</td>
<td>Breast Cancer Biospecimen Resource</td>
<td>C Clarke, R Kefford, R Balleine, RC Baxter, M Bilous, J Boyages, J Forbes, M Friedlander, P Harnett, DJ Marsh, A Morey, R Scott, A Spigelman, R Sutherland</td>
<td>$ 400,000</td>
</tr>
<tr>
<td>University of Sydney NCS RIBG</td>
<td>Camera and image acquisition software upgrade for light and fluorescence microscope</td>
<td>DE Benn, L Schedlich, K McDonald, BG Robinson</td>
<td>$ 25,000</td>
</tr>
<tr>
<td>University of Sydney NCS RIBG</td>
<td>Lab-on-a-Chip Technology</td>
<td>DJ Marsh</td>
<td>$ 35,187</td>
</tr>
<tr>
<td>University of Sydney NCS RIBG</td>
<td>Multimode plate reader</td>
<td>CB Little, C Jackson, J Morris, A Ashton</td>
<td>$ 60,000</td>
</tr>
</tbody>
</table>
**Income in 2007**

**NSW Government Medical Research Support Program**

<table>
<thead>
<tr>
<th>Funding Source</th>
<th>Title</th>
<th>Investigators</th>
<th>Funds in 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSW Ministry for Science and Medical Research - Office for Science &amp; Medical Research (OSMR)</td>
<td>NSW Medical Research Support Program</td>
<td>RC Baxter</td>
<td>$2,040,000</td>
</tr>
</tbody>
</table>

### 2007 income category percentage distribution

- **Project and Program Grants** 44%
- **OSMR Medical Research Support Program** 14%
- **Infrastructure Grants** 10%
- **Equipment Grants** 3%
- **Industry Grants** 9%
- **Scholarships** 7%
- **Fellowships** 13%
Journal articles


Blyth FM, Macfarlane GJ, Nicholas MK. The contribution of psychosocial factors to the development of chronic pain: the key to better outcomes for patients? Pain 2007;129:8-11.


Clarke EC, Appleyard RC, Bilston LE. Immature sheep spines are more flexible than mature spines. Spine 2007;32:2970-79.


Nangle MR, Keast JR. Reduced efficacy of nitricergic neurotransmission exacerbates erectile dysfunction after penile nerve injury despite axonal regeneration. Exp Neurol 2007;207:30-41.


Book Chapters


