THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

IMB Institute for Molecular Bioscience

ANNUAL REPORT **2007**

IMB VISION STATEMENT

Creativity, motivation and intellectual freedom are the vital components of scientific discovery and technological process, and underpin the research philosophy of the Institute for Molecular Bioscience.

Our research mission is to understand the information contained in our genes and proteins – the very foundation of our existence and health.

By understanding how and why humans and animals develop the way they do, we will be better equipped to understand the basis of our differences and how and why things go wrong in disease states like cancer.

In time, our collaborative research will lead to improved therapies and diagnostics, enhancing our ability to combat common diseases and genetic disorders.

It will also give rise to new ideas, technologies and knowledge-based industries to improve the health and quality of life of future generations.

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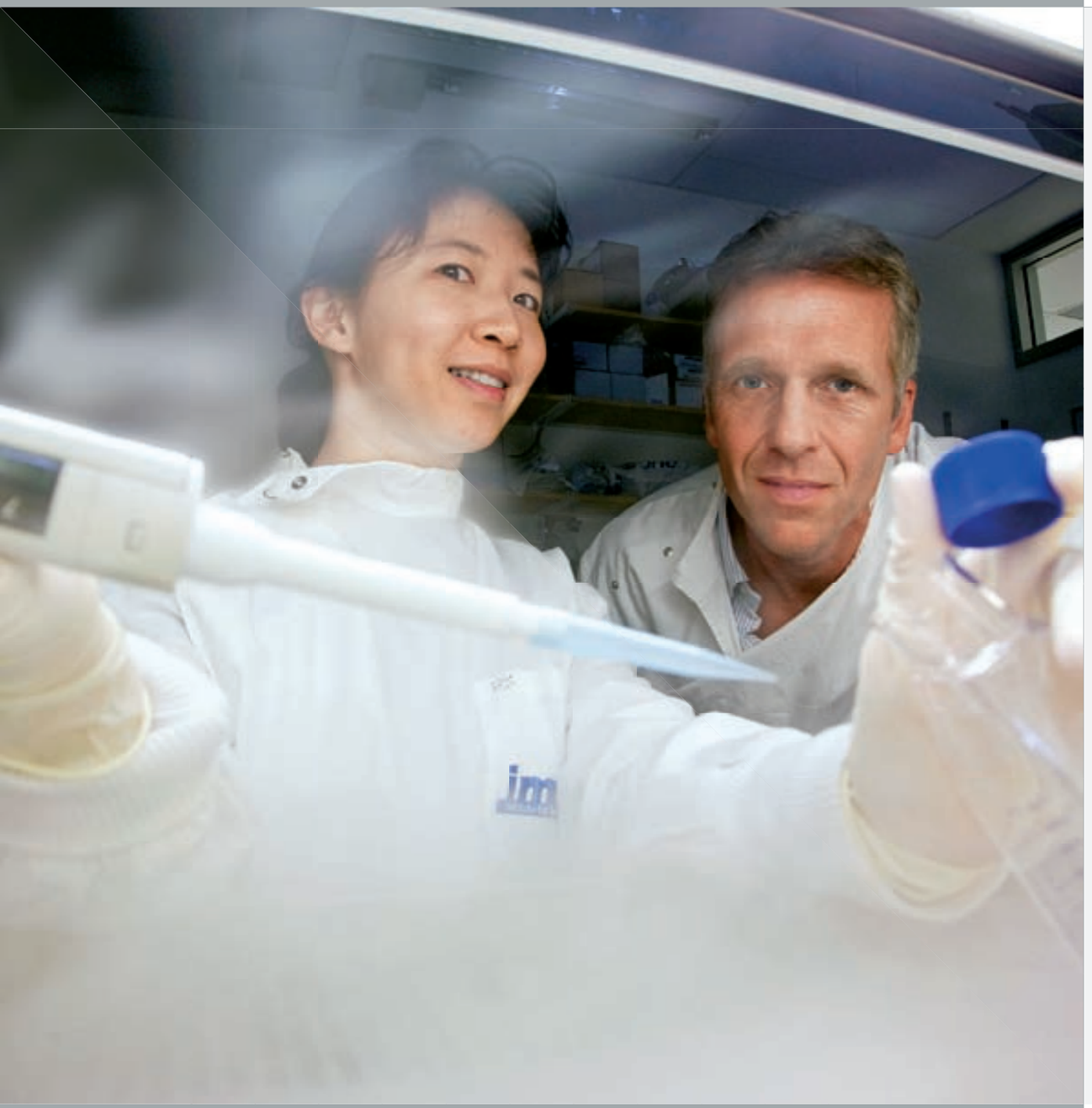
CHAIR'S MESSAGE



This is my last report as Chair of the Board of the Institute for Molecular Bioscience (IMB), before my retirement as Vice-Chancellor of The University of Queensland (UQ) on December 31, 2007.

When I arrived at UQ in 1996, there were no institutes; today, there are six: the IMB, the Australian Institute of Bioengineering and Nanotechnology, the Queensland Brain Institute, the Diamantina Institute for Cancer, Immunology and Metabolic Medicine, the Sustainable Minerals Institute and the Institute for Social Science Research.

The IMB was the first of these to be established, and there can be no doubt that it has been an unqualified success. An independent review in 2005 of the first five years of operation concluded that the IMB had surpassed expectations in all key areas, with one commentator estimating that it was "one of the two leading research institutes in Australia".

Since this review, the IMB has continued to build on its research strengths, and in the pages that follow, you will read of its achievements in 2007. The success of the IMB is due to a collection of talented people, and I would like to acknowledge their contributions and my appreciation of their efforts.

Peter Beattie and the Queensland State Government have been instrumental in the continued success of the IMB, providing not only $15 million towards the construction of the building, but also recurrent operational funding of $10 million per annum to 2014. Peter Beattie's "Smart State" vision has transformed Queensland into a powerhouse of bio research, which shows every sign of continuing under the new Premier, Anna Bligh.

Thanks must also be extended to Chuck Feeney. His generosity, through The Atlantic Philanthropies, enabled not only the construction of the IMB building, but that of several other institutes at UQ, including the Queensland Brain Institute, and the Australian Institute for Bioengineering and Nanotechnology as well as the refurbished James and Mary Emelia Mayne Centre housing the UQ art collection. World-class research requires world-class infrastructure, and Chuck Feeney's generosity has been a major driver behind the delivery of this in Queensland.

Professor John Mattick and Professor Peter Andrews were the first co-directors of the IMB. They were the driving force behind merging UQ's Centre for Molecular and Cellular Biology and Drug Design and Development Centre to establish the IMB. They are now applying their talent to other challenges: Professor Mattick stepped down as Director to concentrate on his research after receiving a Federation Fellowship, while Professor Peter Andrews is Queensland Chief Scientist.

I also acknowledge those who have contributed to the IMB in less visible, but no less meaningful ways: the IMB Board and Scientific Advisory Committee members, the staff, both research and general staff, and the students. The IMB would not be the leading research institute it is today without the contributions each of these people have made.

The establishment phase of the Institute is now over, and the IMB is building on its strong base and consolidating its world-class research reputation. In this it will be ably guided by Professor Brandon Wainwright, the current IMB Director, who in his two years at the helm has already seen considerable success and is well placed to drive the research agenda of the Institute and ensure the highest quality research output. Under the auspices of the IMB Board, which will be chaired from 2008 by my successor as Vice-Chancellor, Professor Paul Greenfield, I am confident that Professor Wainwright and the IMB will continue to go from strength to strength.

Professor John Hay, AC
UQ 2007 Vice-Chancellor

DIRECTOR'S MESSAGE

The Institute for Molecular Bioscience celebrated another successful year in 2007, with a number of our scientists receiving prestigious awards and an average 40 percent success rate over both major funding schemes (ARC and NHMRC); well above the national average. I was very pleased to acknowledge the calibre and contribution of our Group Leaders to the Institute's success at a special dinner held at Customs House in Brisbane in July 2007. Professor David Siddle, UQ's Deputy Vice-Chancellor (Research) and our guest speaker at the event, noted it is easy to overlook the personal and family sacrifices that go into producing world-class science and the dinner was one way of saying thank you to an exceptional group of people who continue to produce outstanding results on behalf of the IMB.

Professor Peter Koopman was awarded an ARC Federation Fellowship in May for his world-renowned work in the field of developmental biology. The ARC Federation Fellowship will allow him to concentrate on his research work and is richly deserved. Professor Koopman joins Professors John Mattick and David Fairlie as current IMB Federation Fellows, with IMB joint appointees Professors Kevin Burrage and Alan Mark and affiliate Professor Bostjan Kobe also holding this prestigious award. The Federation Fellowship announcement was followed shortly thereafter by Professor Koopman winning the GlaxoSmithKline Award for Research Excellence at a ceremony held in Melbourne in June. Koops is the second IMB researcher to receive this prestigious award, with Professor Melissa Little receiving the award for her work on renal disease in 2005.

Professor Jenny Stow was awarded a Smart Women: Smart State in 2007, hot on the heels of Smart Women awards for Professors Jenny Martin and Melissa Little in 2005 and 2006 respectively. Jenny Stow is researching immune cells in order to understand how they function and how they malfunction in inflammatory disease and this award recognises her outstanding contribution in this field. Our Smart Women provide excellent role models to young female researchers, showing that a successful scientific career is within their reach.

Professors Rob Parton and John Hancock were notified that they had been awarded an inaugural NHMRC Achievement Award late in 2007 for their work in Ras proteins and the dynamics and functions of the plasma membrane. These awards recognise outstanding Australians for their contributions and achievements in health and medical research.

Professor Glenn King joined the IMB in December 2006 and had an outstanding year in 2007, succeeding as chief investigator on four grant applications and as co-investigator on a further two grants. Glenn's work on environmentally friendly insecticides has already received considerable attention both in Australia and overseas and his grant success last year will enable him to extend his research to include a study of antimicrobial agents to treat antibiotic-resistant strains of golden staph.

Professor Matt Cooper, who has been at Cambridge for the last decade, was awarded one of only two prestigious NHMRC Australia Fellowships, worth $4 million. Matt is originally from Adelaide and will use the award to return to Australia to take up a Group Leader position at the IMB in 2009. We are looking forward to welcoming Matt to the IMB.

These are just some of the highlights for Institute personnel but I would like to offer my congratulations to all Group Leaders, laboratory and support staff for their efforts in 2007. Our scientists are world-class and it is through their efforts that the IMB goes from strength to strength, proving that we are indeed a smart state!

Farewells during 2007 included Professor David Hume, who left to take up a position as Director of the Edinburgh Bioscience Research Centre. David had been with us since the establishment of Centre for Molecular and Cellular Biology, one of the centres that amalgamated to form the IMB. He was Director of the ARC Special Research Centre for Functional and Applied Genomics and has had a distinguished scientific career while at the University. His appointment to the Edinburgh Bioscience Research Centre was richly deserved and we are looking forward to fruitful collaborations with that institution once David has settled into his new role. His enthusiasm, insight and vision will be missed by us all. We have said a temporary farewell to Professor Melissa Little, who was seconded as Chief Scientific Officer of the Australian Stem Cell Centre until 2011. Melissa's work in renal disease and regeneration is well known and highly regarded and she was an obvious choice for this position with the Australian Stem Cell Centre. The position is based in Brisbane at the AIBN and Melissa continues to have a lab presence at the IMB.

Activities during 2007 included our annual Dr Toshiya Yamada Memorial Lecture, in honour of the late Dr Toshi Yamada; a Group Leader scientific retreat in November; showcasing of the Institute at the University Open Day; and attendance at Bio2007 in Boston and at Ausbiotech 07 in Brisbane. Both Bio and Ausbiotech are principally trade exhibitions and IMB is ably supported by IMBcom at both events, where commercial output of research is an important topic of discussion. A visible presence at these events increases awareness of the IMB at a national and international level and supports the strategies of our major stakeholders: The University of Queensland and the Queensland State Government.

Finally, I would like to record my thanks and appreciation for the contributions of the outgoing Chairman of the IMB Board, Professor John Hay, AC, who retired as Vice-Chancellor of The University of Queensland at the end of 2007. During his twelve-year tenure at UQ, Professor Hay drove the establishment of four major research institutes at the University, including the IMB, through the brokering of a unique funding relationship between the University, the Queensland State Government and Atlantic Philanthropies. Both the building that the IMB occupies and the annual operational funding grant from the State Government are due in no small part to the efforts of Professor Hay. It was fitting, therefore, that on December 4, 2007 the IMB facility was named the John Hay Building – testament to a man who has left a lasting legacy to the University and to Queensland.

Professor Brandon Wainwright
IMB Director

DEPUTY DIRECTOR (Research) REPORT

2007 has been a highly successful year for IMB research. Our researchers continued to publish papers in high-impact journals, be invited to speak at international conferences, and receive substantial numbers of grants and fellowships. We have also established new strategies to ensure that the IMB's current success continues.

One of the most basic measurements of research performance is the quality and quantity of papers published. I am pleased to say that IMB researchers published 195 papers in 2007, many in high-impact journals including *Nature, Nature Cell Biology* and *PNAS*.

IMB continued to perform well in attracting competitive grant funding - receiving over $19 million from the National Health and Medical Research Council (NHMRC) and the Australian Research Council (ARC). This included a $5 million NHMRC Program Grant to myself and Professor Robert Parton to study the cell surface, and one of only two $4 million Australia Fellowships, awarded to Dr Matt Cooper. Dr Cooper is currently based in the United Kingdom, but will use the Australia Fellowship to move to the IMB in 2009 and continue his research on developing treatments for drug-resistant pathogens.

Altogether the IMB received $11.5 million for 14 project grants from the NHMRC, while Associate Professor Rick Sturm and Dr Rohan Teasdale both received NHMRC Senior Research Fellowships. From the ARC, the IMB received more than $2.5 million spread over seven projects. Our success rates for both agencies continue to be well above the national average, and more than half of our group leaders are now supported by fellowships, an important objective assessment of the quality of our senior researchers.

Outside the two main grant rounds, but worthy of special mention, was a $5 million grant from the National Breast Cancer Foundation awarded to a consortium of nine researchers, two of whom were IMB's Professor Mark Ragan and Professor George Muscat. This grant will allow a large-scale, long-term study of breast cancer, in which Professors Ragan and Muscat will play leading roles. You can read more about all of these grants and fellowships in our Highlights section, starting on page 9.

In addition to receiving grants for individual research programs, our research group leaders are involved in, and often lead, collaborative scientific centres. In 2007, Professor Melissa Little was appointed Chief Scientific Officer of the Australian Stem Cell Centre, and will head its scientific program, developing strategy, scientific review and management. In addition, two ARC Centres at the IMB were named Centres of Excellence, a scheme that recognises exceptional performances by Centres with an extension of funding for three years. These are the ARC Centre of Excellence in Biotechnology and Development and the ARC Centre of Excellence for Bioinformatics.

It is natural, and in fact necessary, that generational change will occur in any organisation. In 2007 Professor David Hume, who has been associated with the IMB and its predecessor, the CMCB, since 1988 was offered the directorship of a new bioscience research centre in Scotland that includes the Roslin Institute. Although we will miss David's friendship and vision, it is a fantastic opportunity and a worthy use of the talents of this world-leading genomic scientist. His research group at the IMB has been taken over by Dr Matt Sweet, formerly a Senior Research Officer within the group. Dr Sweet is one of our first true "homegrown" group leaders, as he began at the IMB as an honours student, before undertaking his PhD with Professor Hume. After completing post doctoral training overseas, Dr Sweet returned to the IMB. He has already begun to put his own stamp on the research of the group, while ensuring that it retains the high standards it achieved under Professor Hume.

Laboratory space previously rented from us by the Queensland Department of Primary Industries and Fisheries has now become available, and we will use this to house new research groups. An IMB search committee has been formed and we have already begun to receive and assess applications. Over the next two years at least six new groups will be established. These will further lift the research profile and increase the critical mass of researchers at IMB. The first one of these new group leader appointments at the very close of 2007 was Dr Brett Collins to the Division of Molecular Cell Biology.

For more details on IMB research achievements in 2007 please turn to the group leader reports beginning on page 18.

Professor John Hancock
IMB Deputy Director

DEPUTY DIRECTOR (Systems & Administration) REPORT

The research achievements detailed in the report of my fellow Deputy Director, Professor John Hancock, would not be possible without the support and expertise of the administrative and infrastructure staff of the IMB. Over 60 staff work in a range of areas including: administration, HR, finance, grants, marketing and communication, postgraduate student co-ordination, information technology services, laboratory and infrastructure management, reception, stores, building maintenance, technical services, animal house, mail and central sterilising. These staff members ensure the smooth operation of non-research services, and I would like to thank them for a job well done in 2007.

There was some movement of staff over the year. Dr James Springfield from Coherent Scientific Pty Ltd came on board to work on light and confocal microscopy and imaging systems. He will advise scientists on how they can use the IMB's microscopy resources to their full advantage in imaging research. His expertise will ensure our researchers get the most out of their equipment, and reflects the range and breadth of the microscopy equipment at the IMB. Another staff member who deserves to be acknowledged is Mileta Duggleby. Mileta was a Purchasing Officer in the finance group, and retired in 2007 after 13 years at The University of Queensland. Her warmth, wit and knowledge of her area has been much missed.

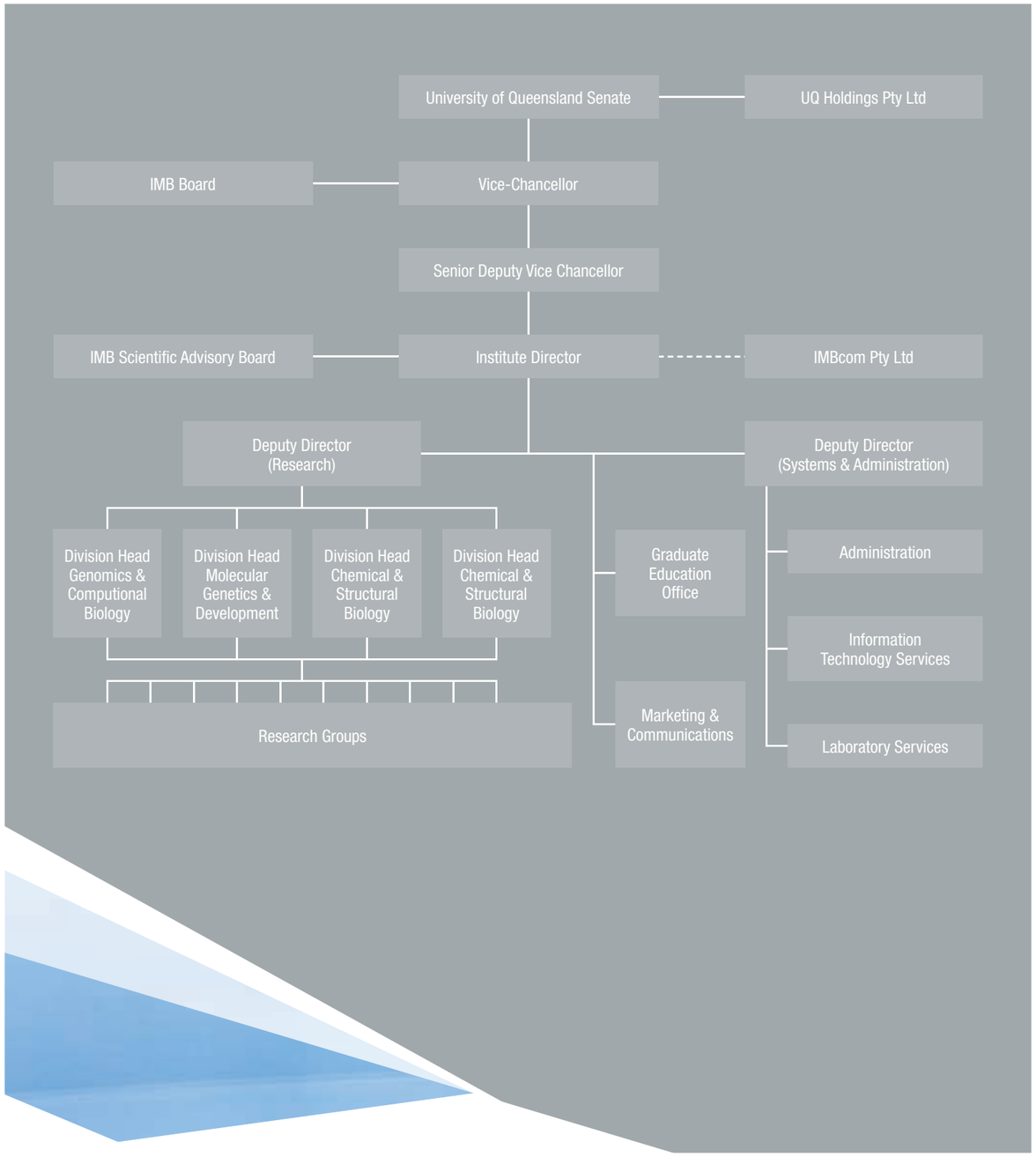
The IMB continued to embark on infrastructure upgrades in 2007, to ensure our researchers have access to world-leading equipment. One such upgrade was to the macromolecular X-ray diffraction facility, made possible through a $1m Australian Research Council Linkage Infrastructure, Equipment and Facilities Grant to Professor Jenny Martin. The new University of Queensland Remote-Op Crystallisation and X-ray (UQ ROCX) Facility includes two Formulatrix Rockimagers that allow incubation of up to 1000 crystallisation trays at each of two temperatures, automated imaging of trays, remote viewing of images, remote scoring of images, as well as searching of images/data and generation of optimised screens. This upgraded system allows diffraction images to be collected in as little as one second, beating the previous best by 59 seconds. The speed and automation of the diffraction facility means that a complete data set can be measured in a matter of minutes, and allows the overnight screening of multiple crystals without intervention. The UQ ROCX upgrade automates protein crystallisation through to structure determination and has already proven invaluable for high-throughput crystallography applications such as fragment-based screening of drug targets. Access to the facility is available on a cost-recovery basis.

Another upgrade is underway for the IMB's Zebrafish Facility, thanks to a $1.5m NHMRC Enabling Grant awarded to Associate Professor Andrew Perkins. Zebrafish are becoming a global model of choice for biomedical research due to a number of factors including: their ability to be housed cheaply, transparent eggs for easy visualisation of early developmental processes, rapid development and breeding and similarity to human gene complement. In Australia there are several strong basic research teams who have embraced zebrafish models, but until now not much specific funding has been allocated to building the necessary infrastructure. This grant will allow the IMB to expand its aquarium facilities and purchase associated research equipment such as an Illumina oligo library. This will result in a greatly enhanced ability to determine how genes work, and a pipeline for screening Australia's rich source of natural products and chemical libraries for activities against common human diseases such as cancer, dementia and muscle diseases using zebrafish models.

The Queensland Department of Primary Industries and Fisheries moved out of the 6th level of the IMB after their lease ended, freeing up a floor for us to use for our own research. This extra space will allow us to recruit new groups (see Professor Hancock's report) and shuffle our existing groups around the floors to encourage interaction, and integration of new groups. These will be spaced throughout the floors, and we are hopeful that the new ordering will result in novel and exciting collaborations.

Dr Ian Taylor
IMB Deputy Director

2007 IMB ORGANISATIONAL CHART



IMB 2007 HIGHLIGHTS

The Year In Review

highlights

$50 MILLION FUNDING FOR IMB

Queensland Premier Anna Bligh signed a $50 million funding agreement between the Queensland Government and UQ in November 2007 to fund the IMB for a further five years. The IMB was scheduled to receive operational funding from the Queensland Government until the 2008-2009 financial year, and this new agreement will extend this funding until 2013-2014.

"Continued funding for another five years will give the IMB the security it needs to conduct research which will lead to improvements in the lives of Queenslanders and people around the world," 2007 UQ Vice-Chancellor Professor John Hay, AC, said. " The State Government, through funding from its Smart State strategy, has been a key player in the success of the IMB." An independent review of the Institute's operations in its first five years showed that the IMB would generate up to 1000 jobs and grow the economy by $400 million in its first 15 years.

THE EYES HAVE IT ON MULTIPLE GENE QUESTION

A study by IMB and Queensland Institute of Medical Research scientists was the first to prove conclusively that there is no single gene for eye colour. Instead, it found that several genes determine the colour of an individual's eyes, although some have more influence than others.

"The model of eye colour inheritance using a single gene is insufficient to explain the range of eye colours that appear in humans. We believe instead that there are two major genes – one that controls for brown or blue, and one that controls for green or hazel – and others that may modify this trait," Associate Professor Rick Sturm, who headed the study, said.

GROWTH HORMONE COULD PROMOTE CANCER, ACCORDING TO IMB RESEARCHER

Growth hormone and associated proteins could be responsible for promoting many types of cancer, including breast and prostate cancer, according to Professor Mike Waters. Blocking growth hormone could thus be a useful avenue for cancer therapy, Professor Waters said. He also found that growth hormone receptor could induce tumour growth when sent to the cell nucleus.

IMB SCIENTISTS DEVELOPING CLEAN ENERGY SYSTEMS FROM MICRO-ALGAE

An international consortium established by an IMB scientist is developing a clean source of energy that could see some of our future fuel and possibly water needs being generated by solar-powered bio-reactors and micro-algae, while absorbing CO_2.

Associate Professor Ben Hankamer has established the Solar Bio-fuels Consortium, which is engineering green algal cells and advanced bio-reactor systems to produce bio-fuels such as hydrogen. Using algae has several advantages over traditional bio-fuel crops: the hydrogen can be produced using saltwater rather than fresh water, and the reactors can be placed on arid land, eliminating competition with food production for arable land and water. The energy production could also theoretically be coupled with desalination.

RESEARCH POINTS TO POSSIBLE NEW STROKE THERAPY

Research from an international team of scientists, including Professor David Fairlie from the IMB, has identified a possible new therapy for stroke that is likely to be more effective than the current treatments.

The team found that administering immunoglobulin directly into the veins via intravenous injection protected brain cells against the effects of stroke. Immunoglobulin is a class of protein manufactured by the blood to fight off foreign substances in the body.

NEW ROLE FOR LEADING QUEENSLAND STEM CELL SCIENTIST

IMB researcher Professor Melissa Little was appointed to the position of Chief Scientific Officer of the Australian Stem Cell Centre (ASCC), responsible for developing strategy, scientific review and management. She will be seconded to the ASCC until mid-2011, but will continue running her research program at the IMB where she and her team are investigating the potential of stem cells in treating chronic kidney disease.

EUROPEAN HONOUR FOR QUEENSLAND SCIENTIST

A Queensland scientist was elected as a member of one of the world's most respected scientific organizations, the European Molecular Biology Organization (EMBO). Professor John Mattick from the IMB was one of only eight scientists worldwide in 2007 to be offered Associate Membership of EMBO.

EMBO draws together top researchers from the molecular life sciences in Europe to promote excellence through targeted programs and activities. Members come from European countries, while Associate Membership is a special honour available to outstanding researchers from outside of Europe. 2007 was the first year that any Australian scientist was invited to join.

Professor Mattick's research explores the idea that so-called "junk" DNA actually functions as a sophisticated regulatory system that directs the differentiation and development of humans and other complex organisms.

RESEARCHER RETURNS TO FIGHT INSECTS WITH SPIDER VENOM

A researcher who has spent most of the past decade working in the U.S. has returned to Australia to continue working on developing environmentally friendly insect control methods based on spider venom compounds.

"Since spiders have been developing insecticidal compounds for almost 400 million years, I decided to interrogate their venoms to find natural toxins that might kill insects without harming vertebrates," Professor Glenn King, formerly of the University of Connecticut, said.

According to Professor King, the primary reasons behind his move were the advanced infrastructure and collaborative opportunities available at the IMB, while Professor Brandon Wainwright said Professor King's move from the United States to Brisbane highlighted the region's growing reputation as a hub for scientific research.

QUEENSLANDER RUNS MAJOR NEW INTERNATIONAL RESEARCH CENTRE

Professor David Hume was appointed Director of the Edinburgh Bioscience Research Centre after a worldwide search. The new research centre was created from an amalgamation of several prestigious Scottish research centres, including the Roslin Institute.

"Although we are very sorry to lose Professor Hume, it is a fantastic opportunity to lead an internationally significant research institute. His friendship, energy, intellect and vision will be very much missed by us all," Professor Brandon Wainwright, IMB Director, said.

GRADUATE TO GROUP LEADER

Dr Matt Sweet was appointed Group Leader of the former Hume group after Professor Hume's departure. Dr Sweet was previously a Senior Research Officer within the IMB, and he first entered the institute as an honours student.

The Sweet group primarily focuses on how innate immune cells detect invading pathogens and the impact of innate immune cell activation on both acute and chronic inflammation.

"Such processes underlie the basis of resistance and susceptibility to infectious disease, and for this reason have obvious importance to human health," Dr Sweet said.

UQ CELEBRATES BRAIN AWARENESS WEEK

The IMB marked Brain Awareness Week with a free public memorial lecture for a celebrated researcher whose discoveries form much of the basis of modern neurobiology. The Dr Toshiya Yamada Memorial Lecture, held on Wednesday March 14, commemorated Dr Toshiya Yamada, a neuroscientist with the IMB until his sudden death in 2001.

"This lecture is held each March and is an opportunity for us to honour Toshi's memory and to celebrate his scientific achievements," Professor Brandon Wainwright said. The 2007 lecture, co-hosted with the Queensland Brain Institute, was given by Professor Ryoichiro Kageyama, Director of the Institute for Virus Research at Kyoto University, Japan.

IMB GETS IN SYNC WITH AUSTRALIAN SYNCHROTRON

Professor Jenny Martin from the IMB was the first Queensland researcher to use the Australian Synchrotron in Victoria, which opened in 2007. Professor Martin works on chronic inflammation as well as the way adrenaline functions in the brain.

grants

FIGHTING GOLDEN STAPH AND REGENERATING SKIN SHARE IN OVER $19 MILLION OF FUNDING

The IMB was awarded over $19 million from the National Health and Medical Research Council (NHMRC) and the Australian Research Council (ARC) in the latest round of grant funding announced in late September.

This included nearly $17m from the National Health and Medical Research Council for fellowships and projects including regenerating wounded skin and fighting golden staph. Altogether, the IMB received more than $11.5 million from the NHMRC spread over 14 projects, and more than $5 million in fellowships, including a $4 million Australia Fellowship to Dr Matt Cooper (please see below for more details). From the ARC, the IMB received more than $2.5 million spread over seven projects.

2007 HIGHLIGHTS

IMB SHARES IN $9.72M CENTRES OF EXCELLENCE FUNDING

Two Australian Research Council (ARC) Centres at the IMB have been named as Centres of Excellence, a scheme that recognises exceptional performances with an extension of funding for a further three years.

The ARC Centre of Excellence in Biotechnology and Development, which has a node at IMB, will receive a further $6.42 million from 2008, while the ARC Centre for Bioinformatics, headquartered at IMB, will have its status upgraded to become a Centre of Excellence, and will receive a further $3.3 million from 2008.

MULTIMILLION-DOLLAR GRANT TO BEAT BREAST CANCER

IMB researchers Professor George Muscat and Professor Mark Ragan will be lead investigators on a $5 million National Breast Council Foundation grant that will take new approaches to treating women for whom available therapies offer little hope, and women who develop treatment resistance.

The team, which includes researchers from around the nation, will study nuclear receptors, proteins found in cells that receive information from molecules and then alter gene expression accordingly.

$4 MILLION AUSTRALIA FELLOWSHIP TO SCIENTIST

One of Australia's most prestigious fellowships for medical researchers has been awarded to Dr Matt Cooper, who will use the $4 million NHMRC Australia Fellowship to join the IMB. Dr Cooper, who is currently working in the UK, will use the fellowship to establish a research program into novel antibiotics and antifungals that combat drug-resistant pathogens, especially those that cause hospital-acquired infections.

IMB RESEARCHER HONOURED WITH LEADING FELLOWSHIP

Professor Peter Koopman received one of the highest academic accolades in Australia, being awarded an ARC Federation Fellowship for his research into developing new and vastly more efficient ways of identifying which of our 30 000 genes are important for embryonic development.

Professor Koopman is world renowned in the field of developmental biology, and was part of the team that discovered the gene that determines gender in mammals, which has been called one of the most important biological discoveries of the 20th century. He is the sixth researcher at or affiliated with the IMB to receive a Federation Fellowship.

IMB RESEARCH GETS A SMART BOOST

Professor Melissa Little received $1 million from the Queensland Government's Smart State Innovation Funding Program to further her research into cell-based regenerative therapies for chronic kidney disease.

Professor Little said the aim of the research is to enable repair to damaged kidneys and is expected to be more effective than current treatments such as dialysis.

INTERNATIONAL GRANT TO IMB RESEARCHER

Professor Rob Parton received a $408 000 grant from the prestigious Human Frontier Science Program (HFSP), which he will share with collaborators in France and India. The HFSP supports international collaborations in basic research focused on the complex mechanisms of living organisms.

Professor Parton was awarded the grant to study endocytosis, to better understand how healthy cells work and what goes wrong in disease conditions. Endocytosis describes the process whereby animal cells are constantly sampling their environment and engulfing parts of their surface membrane.

FUNDING BOOST FOR CANCER RESEARCH

Three projects led by IMB researchers received $156 000 in funding each from the Queensland Cancer Fund. Professor Brandon Wainwright's team will investigate a genetic pathway which is altered in many forms of cancer, which will lead to a better understanding of how to treat certain tumours. Professor John Hancock will study K-Ras, a protein frequently mutated in human cancers, which will allow the design of drugs to specifically target the protein. Associate Professor Rick Sturm will move a step closer to treating melanomas by studying skin cells that become malignant.

DR ROSAMOND SIEMON SCHOLARSHIP AWARDED TO IMB STUDENT

Caroline Hopkins (Little lab) from the IMB was awarded the inaugural Dr Rosamond Siemon Postgraduate Renal Research Scholarship. The scholarship is awarded to the best postgraduate student undertaking multidisciplinary, collaborative research into renal disease, repair and regeneration.

Mrs Hopkins's honours project at the IMB in 2006 investigated the potential for adult kidney cells to revert back to an embryonic form, where they could be prompted to regenerate kidney tissue. For her PhD, Mrs Hopkins will continue and expand this project. The scholarship was donated by Dr Rosamond Siemon, a historian and UQ alumnus.

US GRANT FOR OBESITY RESEARCHER

Dr Gary Leong, from the IMB and the Mater Hospital, was awarded a US$50 000 grant to study a protein that may eventually lead to treatments for diseases such as obesity and type 2 diabetes. He received the grant from the US Endocrine Society to investigate the actions of the protein Ski on muscle and fat metabolism.

QFAB CEO AWARDED CHURCHILL FELLOWSHIP

Dr Jeremy Barker, the CEO of the Queensland Facility for Advanced Bioinformatics, was awarded a Churchill Fellowship from the Winston Churchill Memorial Trust. The fellowships aim to enrich Australia by providing financial support for the Fellow to travel overseas and gain experience in their area of expertise that could not be gotten in Australia. Dr Barker travelled to the USA and the UK to study bioinformatics.

awards

IMB RESEARCH OFFERS HOPE FOR CHILDREN OF UNCERTAIN SEX

Professor Peter Koopman received what is arguably Australia's most prestigious medical research award – the GlaxoSmithKline Australia Award for Research Excellence. Professor Koopman's research offers hope to children born with sexually ambiguous genitalia and other sexual development conditions, which are more common than most people imagine.

Professor Koopman is the second IMB researcher to receive the Award in the last three years, after Professor Melissa Little's win in 2005 for her contribution to the development of new treatments for renal disease.

PRESTIGIOUS NATIONAL AWARD FOR PIGMENTATION RESEARCHER

Associate Professor Rick Sturm was awarded the Julian Wells Medal at the Lorne Genome Conference. It is awarded every year to an Australian scientist who has "made an outstanding contribution to our understanding of gene action, genome organisation or genomic evaluation," according to the prize committee. Dr Sturm has been studying the human genes that control skin, hair and eye colour for many years. He is the second IMB researcher to receive the medal, after Professor Peter Koopman in 1998.

IMB RESEARCHERS RECOGNISED IN NHMRC AWARDS

Two IMB researchers were recognised in the inaugural National Health and Medical Research Council Awards in December 2007, which recognises outstanding Australians for their contributions to health and medical research. Professors John Hancock and Robert Parton received the NHMRC Achievement Award – Program Grant for their work in studying the surface of the cell, for which they received a $5 million Program Grant earlier in 2007.

HAT TRICK OF AWARDS FOR IMB SMART WOMEN

Professor Jennifer Stow became the third woman in as many years from the IMB to win a Smart Women: Smart State award. Professor Stow received the award for her work on cells, which may lead to alternative treatments for inflammatory disease. She is researching immune cells in order to understand how they function, and then how they malfunction, in inflammatory disease and cancer. She is the third IMB researcher to receive a Smart Women: Smart State award in as many years.

SUPERB SUPERVISOR

Professor David Craik won an Award for Excellence in Research Higher Degree Supervision. He has successfully supervised to completion more than 20 PhD students, has 10 currently under supervision, and his group's publication record is outstanding. Nominations for the award must be supported by at least four people: a staff member, current research student and two former (completed) research higher degree students.

HIGHLY COMMENDED PHD STUDENTS

Four IMB PhD graduates were included on the UQ Dean's Commendation List, recognising the few postgraduate students who receive unanimously outstanding reports from their examiners, who commend them on making genuine and substantial contributions to their field of research. The four students were: Alistair Forrest (Grimmond lab), Markus Kerr (Teasdale lab), Benjamin Clark (Capon lab) and Matthew Kirkham (Parton lab).

PHD STUDENT WINS ROCHE AWARD

Rehan Villani, from Professor Brandon Wainwright's lab, won the 2007 Roche Award for Postgraduate Career Development. The award recognises the contribution of a postgraduate student to advancing research in their field in new and innovative directions. It is designed to further develop the career of the recipient by enabling them to attend conferences or present papers and publications.

After being selected as a finalist on the basis of her initial application, Mrs Villani won with her presentation, "Hedgehog Signalling: Balancing Skin Turnover and Skin Cancer".

DNA ALGORITHM WINS AMGEN AWARD

The Amgen Award for best honours student of 2007 at the IMB was won by a student from the Bailey lab who developed a discriminative algorithm for detecting motifs (repeating elements) in DNA and protein sequences. Emma Redhead's algorithm was found to be more effective than the non-discriminative approach when applied to a well-studied synthetic motif discovery problem.

IMB ADVISORY BOARD

Professor John Hay

Professor Brandon Wainwright

Professor Frank Gannon

Professor Paul Greenfield

Dr Russell Howard

Dr Peter Isdale

Professor Mick McManus

Professor Nicos Nicola

PROFESSOR JOHN HAY, AC (CHAIR)

Professor John Hay, AC, was Vice-Chancellor of The University of Queensland from 1996 until his retirement on December 31, 2007. He was previously Vice-Chancellor of Deakin University, and under his leadership both UQ and Deakin were named Australia's University of the Year by the Good Universities Guide. UQ has now won far more teaching awards than any other university.

Professor Hay has an outstanding record for attracting government and private funding, and has led UQ to establish a series of internationally recognised new research institutes: the Institute for Molecular Bioscience, the Queensland Brain Institute, the Australian Institute for Bioengineering and Nanotechnology, the Sustainable Minerals Institute, the Centre for Clinical Research and the Diamantina Institute for Cancer, Immunology and Metabolic Medicine.

In 2002 Professor Hay was appointed by the Federal Minister for Education to the Higher Education Review Reference Group. He was Chair of the Group of Eight from January 2002 to May 2003, and was Chair of Universitas 21 from 2003-2006. He is now Chair of the Carrick Institute for Learning and Teaching in Higher Education, and is a member of numerous state and national committees, including the National Library of Australia.

PROFESSOR BRANDON WAINWRIGHT (DIRECTOR)

Professor Brandon Wainwright was appointed Director of the Institute for Molecular Bioscience in late 2006. Previously, he was the Deputy Director (Research) of the IMB from 2002.

Professor Wainwright completed his undergraduate and postgraduate studies at the University of Adelaide, after which he took up a postdoctoral fellowship at St Mary's Medical School, the University of London. He remained at St Mary's for six years, eventually becoming a Medical Research Council Senior Research Fellow. In 1990, he moved back to Australia, joining the Centre for Molecular and Cellular Biology (CMCB) at The University of Queensland. Professor Wainwright stayed with the CMCB when it was merged with another UQ Centre (the Drug Design and Development Centre) in 2000 to create the Institute for Molecular Bioscience.

In addition to being Director of the IMB, Professor Wainwright continues his research into the use of genomic approaches to dissect the basis of common genetic disease. In particular, his laboratory focuses on two heritable conditions: cystic fibrosis and basal cell carcinoma of the skin, and he was responsible for the discovery of the basal cell carcinoma gene, patched.

PROFESSOR FRANK GANNON

Frank Gannon is the Director General of Science Foundation Ireland. From 1994-2007, Frank Gannon was the Executive Director of the European Molecular Biology Organisation (EMBO), Secretary General of the European Molecular Biology Council, and Senior Scientist at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany. His major research interest is the Estrogen Receptor as a Transcription Factor and he has published over 200 research articles. He serves on a number of scientific advisory boards at institutes throughout the world.

PROFESSOR PAUL GREENFIELD, AO

Professor Paul Greenfield, AO, was Senior Deputy Vice-Chancellor of The University of Queensland from 2002 to 2007, and became VIce-Chancellor on January 1, 2008. Professor Greenfield graduated with first-class honours in Chemical Engineering from the University of New South Wales (UNSW), then worked in the private sector before completing a PhD at UNSW. He then worked at CSIRO before winning a three-year fellowship to the U.S. In 1975 he joined The University of Queensland as a lecturer in chemical engineering, and a decade later became Head of Department and then Pro-Vice-Chancellor (Physical Sciences and Engineering) before being appointed an inaugural Executive Dean in 1997. Currently, he chairs several committees, including an expert advisory panel providing independent advice on delivering purified recycled water to South East Queensland. He is also a Director of several University companies including UniQuest Pty Ltd. In 2006 he was appointed an Officer in the Order of Australia for his contribution to environmental management, biotechnology and tertiary education, and in 1995, he won the Chemeca Medal, awarded jointly by the Institution of Chemical Engineers and the Institute of Engineers Australia for outstanding contribution to the profession.

DR RUSSELL HOWARD

Dr Howard is CEO of Maxygen and one of the company's founders. Since the creation of Maxygen in 1997, its core technologies have been used to create several independent businesses. Today, Maxygen is focused on optimisation and development of significantly improved proprietary versions of several marketed protein pharmaceuticals. Originally trained in biochemistry and chemistry at the University of Melbourne, Dr Howard spent over 20 years studying infectious diseases, primarily malaria. Before joining Maxygen, Dr Howard served at research institutes, biotechnology companies and a pharmaceutical company both in Australia and overseas. In addition to numerous patents, Dr Howard has over 140 publications in peer-reviewed journals.

DR PETER ISDALE, AM

Dr Peter Isdale, AM, is the CEO of IMBcom Pty Ltd., The University of Queensland's commercialisation company for the IMB. He is a former Business Director at the Australian Institute of Marine Science (AIMS), Australia's national marine research agency. He is also a former Principal Research Scientist at AIMS, and authored or co-authored more than 30 papers in his field of marine and climate research. He has 20 years of experience in the operation and governance of private, public and ASX-listed companies in Australia, Asia and the Pacific Rim. He is a Member of the Australian Institute of Company Directors. Dr Isdale currently holds five non-executive directorships in biotech companies, senior positions on Foundations around the world and is an Adjunct Professor at Texas A&M University. He holds a B.A. with first-class honours and a PhD in Marine Geomorphology (1982) from James Cook University of North Queensland.

In 2006 he was awarded as a Member in the General Division of the Order of Australia (AM) for service to marine science through research and as a contributor to the development and commercialisation of biotechnology.

PROFESSOR MICK MCMANUS

Professor Mick McManus has been Executive Dean at the Faculty of Biological and Chemical Sciences of The University of Queensland since 1998. Prior to this he was Head of the Department of Physiology and Pharmacology from 1993 to 1997, and was initially appointed to the University as Foundation Professor of Pharmacology. Mick trained as a pharmacist at Curtin University of Technology and completed his PhD at the University of Western Australia in 1978. He has held research positions in universities in Australia and London, and at the National Institutes of Health in the U.S. He was President of the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists from 2000-2001. He continues to have a strong research interest in the area of xenobiotic metabolism, especially on the role human sulfotransferases play in this process.

PROFESSOR NICOS NICOLA, AO

Professor Nicos Nicola, AO, is an ex officio member of the IMB Board, as he serves as the Chair of the IMB Scientific Advisory Council. He is Assistant Director of the Walter and Eliza Hall Institute, where he also serves as Head of the Cancer and Haemotology Division.

Professor Nicola completed both his undergraduate and postgraduate degrees at the University of Melbourne, before working for a year at Brandeis University in Massachusetts, USA. He then joined the Walter and Eliza Hall Institute in 1977. He is responsible for major discoveries including the purification of mouse G-CSF, the definition of the human equivalent of G-CSF and the purification of Leukaemia Inhibitory Factor. Professor Nicola has published over 200 journal articles and has 17 patents.

IMB SCIENTIFIC ADVISORY COMMITTEE

The Institute for Molecular Bioscience would like to acknowledge the valuable contribution that Dame Professor Anne McLaren made to the Scientific Advisory Committee. Professor McLaren, from the Institute of Cancer and Developmental Biology at the University of Cambridge, was a pioneering figure in the field of mammalian genetics and developmental biology. She served on the Committee from its inception in 2000 until her death on July 7, 2007. The IMB would like to extend condolences to her family, friends and colleagues.

Top Row: Prof. Ken-ichi Arai, Prof. Wah Chiu, Prof. David Galas, Prof. Robert Graham, Prof. Peter Gunning, Prof. Steve Kent, Prof. Edison Liu, and Prof. Chris Marshall.
Second Row: Prof. Garland Marshall, Prof. Ira Mellman, Prof. Nicos Nicola, Prof. Greg Petsko, Prof. Robert Saint, Prof. Patrick Tam, Prof. Marino Zerial and Prof. Dame Anne McLaren.

PROFESSOR KEN-ICHI ARAI

Dean, The Institute of Medical Science
The University of Tokyo, Japan

PROFESSOR WAH CHIU

Alvin Romansky Professor of Biochemistry
Director, National Center for Macromolecular Imaging
Director, Graduate Program in Structural and Computational Biology and Molecular Biophysics
Verna and Marrs McLean Department of Biochemistry and Molecular Biology
Baylor College of Medicine, USA

PROFESSOR DAVID GALAS

Vice-President
Chief Academic Officer & Norris Professor of Applied Life Sciences
Keck Graduate Institute of Applied Life Sciences, USA

PROFESSOR ROBERT GRAHAM

Executive Director
Victor Chang Cardiac Research Institute, Sydney

PROFESSOR PETER GUNNING

Head, Oncology Research Unit
Westmead Children's Hospital, Sydney

PROFESSOR STEVE KENT

Biochemistry and Molecular Biology and Chemistry
Institute for Biophysical Dynamics
The University of Chicago, USA

PROFESSOR EDISON LIU

Executive Director
Genome Institute of Singapore
National University of Singapore

PROFESSOR CHRIS MARSHALL

Chair and Director
Cancer Research UK
Centre for Cell and Molecular Biology
Institute of Cancer Research UK

PROFESSOR GARLAND MARSHALL

Department of Biochemistry and Molecular Biophysics and the Center for Computational Biology
School of Medicine
Washington University in St Louis, USA

PROFESSOR IRA MELLMAN

Chair, Department of Cell Biology
Ludwig Institute for Cancer Research
Yale University School of Medicine, USA

PROFESSOR NICOS NICOLA

Professor of Molecular Haemotology
Assistant Director
Walter and Eliza Hall Institute of Medical Research, Melbourne

PROFESSOR GREG PETSKO

Gyula and Katica Tauber Professor of Biochemistry and Chemistry
Director, Rosenstiel Basic Medical Sciences Research Center
Brandeis University, USA

PROFESSOR ROBERT SAINT

Director
ARC Special Research Centre for the Molecular Genetics of Development
Research School of Biological Sciences
Australian National University

PROFESSOR PATRICK TAM

Head, Embryology Unit
Children's Medical Research Institute
Westmead, Sydney

PROFESSOR MARINO ZERIAL

Max Planck Institute of Molecular Cell Biology
Dresden, Germany

IMB RESEARCHERS

The People & Their Passion

The highly integrated research environment at the IMB facilitates the fertile exchange of ideas and experimental approaches across the broad spectrum of molecular bioscience.

This enables a whole-of-system approach to understanding the basis of human and mammalian growth and development at the molecular, cellular and organ levels.

Only by understanding the complex molecular and cellular events that occur throughout a normal human life can scientists begin to understand abnormalities responsible for many common human diseases and to find treatments for them. IMB researchers are particularly interested in the genetic programming of mammalian development and variation, the mapping of the structure, growth and dynamics of mammalian tissues and cells, and the development of new medicines and technologies.

This research will lead to new pharmaceuticals, gene therapies, technologies and diagnostics capable of identifying, halting or even reversing the progress of many diseases.

Division of Genomics & Computational Biology

RESEARCH FOCUS

This program includes the ARC Centre of Excellence in Bioinformatics and the Queensland Facility for Advanced Bioinformatics. It intersects with the Department of Mathematics and the School of Information Technology and Electrical Engineering. It focuses on understanding the genetic programming of humans, specifically, comparative mammalian and vertebrate functional genomics; rnomics; and computational modelling of genetic and cellular regulatory networks (i.e. the Visible Cell™ project).

Research Group Leaders
Tim Bailey
Sean Grimmond
John Mattick
Mark Ragan
Rohan Teasdale

Division of Molecular Genetics & Development

RESEARCH FOCUS

This program includes IMB's participation in the Cooperative Research Centre for Chronic Inflammatory Diseases; the Centre for Biotechnology and Development; and the NIH-funded project Nephrogenix, an initiative designed to develop new therapies for renal regeneration. It focuses on urogenital development, inflammation, cell signalling and cancer, molecular genetics and molecular biology of human diseases.

Research Group Leaders
Peter Koopman
Melissa Little
George Muscat
Andrew Perkins
Rick Sturm
Brandon Wainwright
Carol Wicking

Division of Molecular Cell Biology

RESEARCH FOCUS

This program has received considerable support from the NANO Major National Research Facility; the Australian Cancer Research Foundation; Juvenile Diabetes Research Foundation International; and NIH. It is a major initiative of the IMB with the application of cryo-electron microscopy, cellular tomography, advanced visualisation and high-performance computing. It also includes the ARC Centre of Excellence in Bioinformatics. It focuses on the Visible Cell Project™; and cell architecture and trafficking.

Research Group Leaders
John Hancock
Brad Marsh
Alan Munn
Rob Parton
Jennifer Stow
Matt Sweet
Michael Waters
Alpha Yap

Division of Chemical & Structural Biology

RESEARCH FOCUS

This program has some of the most advanced equipment for structural biology in Australia, used in the development of new medicines and technologies, especially through exploration of Queensland's biodiversity. It has been responsible for a number of IMB spin-out companies based on new platform technologies for drug discovery, as well as developing novel drugs for human disease. It focuses on membrane protein structures; soluble protein and nucleic acid structures; and new drugs and therapies.

Research Group Leaders
Paul Alewood
Robert Capon
David Craik
David Fairlie
Ben Hankamer
Glenn King
Richard Lewis
Jenny Martin
Mark Smythe

Joint Appointments at the IMB

RESEARCH FOCUS

The purpose of joint appointments is to foster collaborations in teaching, research and related activities between the IMB and Schools at The University of Queensland. Joint appointments involve a split of salary between the IMB and the relevant University of Queensland School and a joint appointee's commitment to the research and teaching activities at the IMB is greater than that of affiliate appointees. Joint appointees participate in all Institute activities including laboratory research, supervision of research higher degree students, and attendance at seminars, Divisional meetings and IMB Group Leader retreats.

Research Group Leaders
Kevin Burrage
Geoff Goodhill
Alan Mark
Geoffrey McLachlan

Pattern Recognition & Machine Learning in Biology

Tim Bailey

New computational algorithms are required for the analysis of high-throughput biological data and for modelling biological systems. My group applies expertise in the development of computer algorithms - using machine learning, data mining, pattern recognition and statistical analysis - to biological problems. Using these technologies, we develop computational tools to help biologists make predictions from data.

Our recent work has focused mainly on developing computational tools for studying the process of transcriptional regulation. These include better algorithms for discovering the DNA-binding profiles of transcription factors, search algorithms for comparing DNA-binding profiles, search algorithms for predicting transcription factor binding sites (TFBSs), and a computational model of transcriptional control by a cis-regulatory element in *Drosophila*. We also developed an algorithm for predicting the statistical power of comparative genomics approaches to TFBS prediction.

We are also interested in proteins, and recently developed GLAM2, a motif discovery algorithm that allows for gaps in the motif, and DEME, a motif discovery algorithm that discovers motifs that discriminate between two sets of protein or DNA sequences. We are also studying machine learning approaches for improving protein design.

We place a strong emphasis in delivering useful computational tools to biologists. We make the algorithms we develop available as interactive tools over the web. We support these tools via websites located at IMB and UCSD. These include MEME, a tool for discovering motifs (sequence patterns) in protein and DNA sequences; MAST, a tool for scanning sequence databases for matches to known patterns; MCAST, a tool for scanning sequences for clusters of transcription factor binding sites; and Meta-MEME, a general-purpose sequence modelling tool. Some of these tools are among the most widely used bioinformatics algorithms. For example, the MEME algorithm is used via the UCSD website by over 1000 biologists around the world each month. Maintaining these websites and supporting the biologists who use them is an important commitment for us.

RESEARCH PROJECTS

- Identifying the targets of key transcription factors involved in erythropoiesis
- Identifying targets of transcription factors using functional annotation data
- Improving TFBS prediction using epigenetic modification data
- Improving TFBS prediction using comparative genomics
- Improving the training and application of models of regulation
- Improving motif discovery algorithms

KEY PUBLICATIONS

Bodén, M. (2008). Predicting nucleolar proteins using support-vector machines, in *Proceedings of the Asia-Pacific Bioinformatics Conference – APBC 2008,* Accepted.

Hawkins, J., and Bailey, T.L. (2008). "The power of phylogenetic motif models" accepted for publication at Recomb 2008.

Buske, F., and Bodén, M. (2007). Decoupling signal recognition from sequence models of protein secretion, in *Proceedings of 2007 International Symposium on Computational Models for Life Sciences – CMLS'07,* Accepted.

Dufton, L. and Bodén, M. (2007). Reducing the number of support vectors to allay inefficiency of large-scale models in computational biology, in *Proceedings of 2007 International Symposium on Computational Models for Life Sciences – CMLS'07,* Accepted.

Frith, M.C., Carninci, P., Kai, C., Kawai, J., Bailey, T.L., Hayashizaki, Y., and Mattick, J.M. (2007). Splicing bypasses 3' end formation signals to allow complex gene architectures. *Gene* **403**: 188-193.

Gupta, S., Stamatoyannopolous, J.A., Bailey, T.L., and Noble, W.S. (2007). Quantifying similarity between motifs. *Genome Biology* **8**: R24.

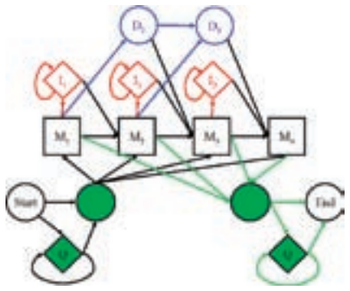
Hawkins, J., Davis, L., and Bodén, M. (2007). Predicting Nuclear Localization. *Journal of Proteome Research* **6**: 1402-1409.

Hawkins, J., Mahony, D., Maetschke, S., Wakabayashi, M., Teasdale, R.D., and Bodén, M. (2007). Identifying Novel Peroxisomal Proteins. *Proteins: Structure, Function and Bioinformatics* **69**: 606-616.

Redhead, E., and Bailey, T.L. (2007). Discriminative motif discovery in DNA and protein sequences using the DEME Algorithm. *BMC Bioinformatics* **8**: 385.

Tino, P., Hammer, B., and Bodén, M. Markovian bias of neural-based architectures with feedback connections, *Perspectives of Neural-Symbolic Integration,* Hitzler and Hammer (eds.), Springer Verlag, 2007. In press.

You, L., Zhang, P., Bodén, M. and Brusic, V. L. Understanding Prediction Systems for HLA-Binding Peptides and T-cell Epitope Identification, in *Proceedings of the 2nd IAPR Workshop on Pattern Recognition in Bioinformatics,* Singapore, Springer Verlag, 2007.



Hidden Markov model.

LAB MEMBERS

Research Fellow: Dr Mikael Bodén (seconded from ITEE)

Research Officers: Dr Martin Frith, Dr John Hawkins

Programmers: Emma Redhead, Stefan Maetschke

PhD Students: Denis Bauer, Tom Whitington

MPhil Student: Isye Arieshanti

Visitors: Professor Osamu Maruyama, Fabian Buske, Zuzana Cienikova, Liang Ma

Expression Genomics

Sean Grimmond

The central theme to my research to date has been the capture of information contained within the transcriptome and the study of transcriptome dynamics to identify key genes or transcriptional programs.

The central focus of my research is to perform global surveys of the transcriptome and to use computational mining and genomic screening techniques to uncover the genes and transcriptional programs controlling important biological processes such as cell differentiation, organogenesis, and tissue repair, as well as pathological states such as tumour initiation and progression. Over the last six years we have worked with the FANTOM consortia to re-define transcriptional output for each locus in mouse and man, with particular attention paid to: genes whose products are associated with developmental pathways, the phosphoregulators network, and the extracellular space.

Central to our research is the ability to rapidly survey transcriptome content and dynamics in model systems. The laboratory is heavily involved in creating and exploiting platform technologies to create accurate catalogues of gene expression in model systems. Microarray profiling is used to monitor the gene activity of loci, next-generation sequencing approaches have been developed to survey transcriptional complexity, and robotic in situ screening is used to put gene expression into a histological context.

The next five years will build upon these recent efforts and focus on the integration of transcriptome content, the accurate surveying of transcriptional complexity in multicellular organisms and integrating these with existing forms of data. These focus areas are outlined in more detail below:

Integration of transcriptome content is necessary to identify key transcripts and novel gene products driving key phenotypes in model systems. The combination of array and sequence tag-based profiling approaches are providing the unprecedented opportunity to survey all variant transcripts expressed from each locus in model systems. Furthermore we are able to study the role of novel RNA species in RNA-mediated control of processes (such as non-coding RNAs, repeat expression, miRNAs etc) in a non-biased fashion using next-generation sequencing approaches. We are actively pursuing these studies in models of the role of cell-cell communication in ES cell-directed differentiation and survival, the control of normal cell division and for the identification of new bio-markers associated with different subtypes of breast cancer.

Accurately surveying transcriptional complexity in multicellular organisms has the added complexity that gene expression needs to be surveyed in a histological context, if one is to accurately model gene networks controlling development and pathology. We are pioneering a joint microarray-in situ hybridisation screening regime to develop a temporal and spatial gene expression atlas of urogenital organogenesis in the mouse (as part of the NIH Genito-Urinary Development MAP program GUDMAP).

With the avalanche of data being created by these approaches, we are actively pursuing new ways to integrate these surveys with genomic, transcriptomic and epigenomic data, in an effort to make more accurate molecular control of biological processes.

RESEARCH PROJECTS

- Redefining total transcriptome content and dynamics of the mammalian transcriptome and studying the role of novel RNAs controlling cellular differentiation and development
- Creating complete transcriptional programs of models of ES differentiation, cell division and organogenesis
- Creating a combined microarray and in situ transcriptome atlas for the mammalian urogenital tract
- Analysing the transcriptome of the extracellular space in mammalian development
- Developing next-generation sequencing technologies to allow for combined genomic, transcriptomic and epigenomic profiling of model systems

KEY PUBLICATIONS

FANTOM3 Consortium and The RIKEN Genome Exploration Research Group Phase I & II Team (Grimmond, S.M. identified as one of the senior core team members.) (2006). Genome-wide analysis of mammalian promoter architecture and evolution. *Nature Genetics* **38**: 626-635.

The FANTOM Consortium and The RIKEN Genome Exploration Research Group Phase I & II Team (Grimmond, S.M. identified as a senior author.) (2005). The transcriptional landscape of the mammalian genome. *Science* **309**: 1559-1563.

LAB MEMBERS

Senior Research Officer: Dr Paul Leo

Research Officers: Dr Brooke Gardiner, Dr Alistair Forrest, Dr Nicole Cloonan, Dr Gabriel Kolle, Dr Nicola Waddell, Dr Logan Walker, Dr Ehsan Nourbkash, Dr Ben Wilson

Senior Research Assistants: Graeme Bethel, Anita Steptoe

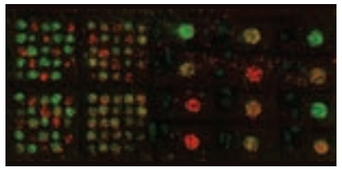
Research Assistants: Milena Gongora, Shivangi Wani, Michelle Chan

PhD Students: Geoff Faulkner, Melissa Brown

Masters Students: Rathi Thiagarjan, Ajay Panwar

Honours Student: Alan Robertson

Heatmap of kidney markers from a panel of embryonic tissues (12.5dpc).

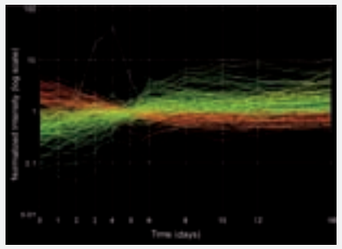


Photomicrograph of HEK cells transfected using a robotically generated cell microarray.

Rnomics: Noncoding RNA in Mammalian Evolution & Development

John Mattick

We are exploring the thesis that the genetic programming of higher organisms has been fundamentally misunderstood for the past 50 years, because of the assumption that most genetic information is transacted by proteins. It is now clear, despite the fact that only a small fraction encodes proteins, that the majority of the genomes of mammals and other complex organisms is transcribed, apparently in a developmentally regulated manner, and that most complex genetic phenomena in these organisms are RNA-directed. Working in conjunction with collaborators in Japan, Europe and the United States, we are working to characterise and understand the functions of the mammalian transcriptome, and to validate the prediction that most genetic information in mammals is conveyed by RNAs that control the trajectories of our differentiation and development. This includes the identification of small regulatory RNAs that control gene expression at various levels, including transcription and splicing, and to determine the expression patterns and function of the tens of thousands of longer non-coding RNAs that are dynamically expressed in mammalian cells. Among our recent findings we have shown that it is possible, if not likely, that most of the mammalian genome is under evolutionary selection, and demonstrated that the majority of long non-coding RNAs are expressed in the brain, many in precise cellular and subcellular locations. We also participated in the international ENCODE project to functionally analyse one percent of the human genome, and further characterised unusual features of the non-coding landscape of the genome, including ultraconserved sequences and transposon-free regions. We use advanced computational and experimental methods, integrating in silico, in vitro and in vivo approaches. The outcomes of our research will be to refine our understanding of the genomic factors underpinning human development, diversity and disease, with practical implications in medicine, genetic engineering and advanced programming of self-assembling information systems.



Dynamic expression of non-coding RNAs during embryonal stem cell differentiation.

RESEARCH PROJECTS

- Bioinformatically predicting and experimentally validating new microRNAs and other small RNAs in mouse and human
- Analysing the dynamic expression of long non-coding RNAs during differentiation of embryonal stem cells, neural stem cells, muscle, macrophages, T-cells and developing tissues such as the male and female genital ridge
- Analysing the cellular and subcellular expression patterns of non-coding RNAs in brain and other tissues
- Targeted functional analysis of selected non-coding RNAs involved in developmental processes and neurogenesis
- Re-aligning the human genome with other mammalian genomes on the basis of RNA structural rules
- Developing new algorithms for the prediction of different classes of functional non-coding RNAs
- Identifying non-coding RNAs as diagnostics and prognostic markers in cancer

KEY PUBLICATIONS

Mattick, J.S. (2007). A new paradigm for developmental biology. *Journal of Experimental Biology* **210**: 1526-1547.

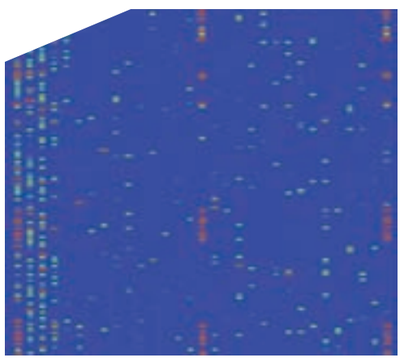
Taft, R.J., Pheasant, M., and Mattick, J.S. (2007). The relationship between non-protein-coding DNA and eukaryotic complexity. *Bioessays* **29**: 288-299.

Mattick, J.S., and Makunin, I.V. (2006). Non-coding RNA. *Human Molecular Genetics* **15**: R17-R29.

Ravasi, T., Suzuki, H., Pang, K.C., Katayama, S., Furuno, M., Okunishi, R., Fukuda, S., Ru, K., Frith, M., Gongora, M., Grimmond, S., Hume, D.A., Hayashizaki, Y., and Mattick, J.S. (2006). Experimental validation of the regulated expression of large numbers of noncoding RNAs from the mouse genome. *Genome Research* **16**: 11-19.

Bejerano, G., Pheasant, M., Makunin, I., Stephen, S., Kent, W.J., Mattick, J.S., and Haussler, D. (2004). Ultra-conserved elements in the human genome. *Science* **304**: 1321-1325.

Mattick, J.S. (2004). RNA regulation: a new genetics. *Nature Reviews Genetics* **5**: 316-323.



Validation of bioinformatically predicted small RNAs from mice using high-density arrays.

LAB MEMBERS

Research Officers: Dr Marjan Askarian-Amiri, Dr Larry Croft, Dr Marcel Dinger, Dr Martin Hansen, Dr Igor Makunin, Dr Harald Oey, Dr Michael Pheasant, Dr Giulia Solda, Dr Lorenzo Malquori

Senior Research Assistant: Ke-lin Ru

PhD Students: Paulo Amaral, Michael Clark, Chol Hee Jung, Darren Korbie, Tim Mercer, Satu Nakhuri, Cas Simons, Stefan Stanley, Stuart Stephen, Ryan Taft

MSc Students: Emmanuelle Billon, Jan Szubert

Computational Genomics

Mark Ragan

We use advanced computational and data management methods to investigate similarities and differences among genomes and the proteins they encode. Our goal is to make rigorous quantitative inferences, at both global and fine scales, about how genomes, gene and protein families, regulatory networks and cellular functions have evolved and diversified.

To deal with the large quantities of data available, we use advanced data management methods, implement high-throughput computational workflows, and develop new algorithms, approaches and software. We are particularly interested in approaches that let us interrogate diverse data types including molecular sequences and structures, signalling pathways, regulatory and molecular interaction networks, gene expression patterns, subcellular localisation and cellular function.

Genomes have diversified, both structurally and functionally, from shared ancestral states. We develop methods and employ analytical pipelines to reconstruct the paths of descent (phylogenomics) and to study processes of change through time (evolutionary genomics). We have characterised pathways of lateral genetic transfer where genetic information moves across, not within, genealogical lineages, and have developed a statistically based approach to discovery of genetically recombined regions and recombination breakpoints. We are now applying these approaches to understand genome diversification and the evolution of novel biological properties in bacterial pathogens, fish and mammals.

For more information on two specific projects, the Visible Cell™ e-project and the Modelling and Analysis of Biological Network Activity (BioMANTA) project, please see: www.visiblecell.com and www.biomanta.org

RESEARCH PROJECTS

- Automatically inferring vertical and lateral gene transmission, genetic recombination and breakpoints in pathogenic bacteria
- Investigating genome dynamics and the evolution of new protein functions in teleosts
- Fine-scale mapping of orthologous and paralogous regions of mammalian genomes
- Studying protein-protein interaction networks in cellular context
- Computationally discovering novel miRNA targets in mammalian genomes
- Integrating bioinformatic information using Semantic Web technologies
- Implementing the Visible Cell™ Project: software and data infrastructure
- Implementing a data grid for very large molecular and image datasets

KEY PUBLICATIONS

Höhl, M., and Ragan, M.A. (2007). Is multiple-sequence alignment required for accurate inference of phylogeny? *Systematic Biology* **56**: 206-221.

Beiko, R.G., and Hamilton, N. (2006). Phylogenetic identification of lateral genetic transfer events. *BMC Evolutionary Biology* **6**: 15.

Beiko, R.G., Harlow, T.J., and Ragan, M.A. (2006). Searching for convergence in phylogenetic Markov chain Monte Carlo. *Systematic Biology* **55**: 553-565.

Chan, C.X., Beiko, R.G., and Ragan, M.A. (2006). Detecting recombination in evolving nucleotide sequences. *BMC Bioinformatics* **7**: 412.

Garcia Castro, A., Rocca-Serra, P., Stevens, R., Taylor, C., Nashar, K., Ragan, M.A., and Sansone, S-A. (2006). The use of concept maps during knowledge elicitation in ontology development processes. *BMC Bioinformatics* **7**: 267.

Beiko, R.G., Chan, C.X., and Ragan, M.A. (2005). A word-oriented approach to alignment validation. *Bioinformatics* **21**: 2230-2239.

Beiko, R.G., Harlow, T.J., and Ragan, M.A. (2005). Highways of gene sharing in prokaryotes. *Proceedings of the National Academy of Sciences USA* **102**: 14332-14337.

Garcia, A., Thoraval, S., Garcia, L.J., and Ragan, M.A. (2005). Workflows in bioinformatics: meta-analysis and prototype implementation of a workflow generator. *BMC Bioinformatics* **6**: 87.

Mar, J.C., Harlow, T.J., and Ragan, M.A. (2005). Bayesian and maximum likelihood phylogenetic analyses of protein sequence data under branch-length differences and model violation. *BMC Evolutionary Biology* **5**: 8.

LAB MEMBERS

Senior Research Officers: Dr Nicholas Hamilton

Research Officers: Dr Aaron Darling, Dr Karin Kassahn, Dr Simon Wong

Research Webmaster: Dr J. Lynn Fink (to 4/2007)

Database and Application Developers: Oliver Cairncross, Dr Ingrid Jakobsen, Dr Tim McComb, Tim Sullivan, David Wood

Data Grid Developers / Administrators: Kimberly Begley (Griffith University/APAC), Mhairi Marshall (ARC Centre of Excellence/APAC)

Queensland Facility for Advanced Bioinformatics Senior Team: Jeremy Barker (CEO), Dr Dominique Gorse (Technical Manager from 5/2007), Dr David Hansen (Technical Manager to 5/2007)

BioMANTA-Pfizer: Dr Melissa Davis, Dr Muhammad Shoaib Seghal

QosCosGRID: Dr Pamela Burrage, Dr Krzysztof Kurowski

Scientific Programmer: Chikako Ragan

Manager, ARC Centre of Excellence in Bioinformatics: Lanna Wong

PhD Students: Cheong Xin Chan, Alex Garcia, Chang Jin Shin

Masters Student: JooYoung Choi

Honours Student: Andrés Esteban-Marcos

International Interns: Arnab Saha Mandal (Indian Institute of Technology, Kharagpur)

Research Trainees: Vinh Dang, Liam McIntyre

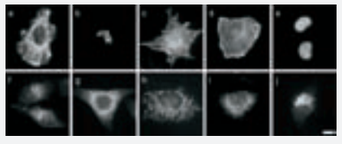
Computational Cellular Biology

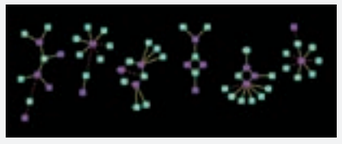
Rohan Teasdale

Individual cells contain a number of distinct sub-compartments, termed organelles. These organelles compartmentalise distinct biochemical pathways and cell-based physiological processes. Many proteins reside in one specific compartment while others are dynamically localised in multiple compartments. My research group is investigating how individual proteins are compartmentalised and defining the protein machinery responsible for their transport with a focus on the mammalian endosomal system.

Using a multidisciplinary approach combining computational biology with cell biology techniques, we investigate all aspects of this process. My research combines computational analysis across entire proteomes with focused investigation into individual proteins. Consequently, there are two overlapping streams of work:

Subcellular Localisation - Determination of the subcellular localisation or compartmentalisation is an essential step in characterising the protein's function across all types of biomedical research, and its modulation needs to be considered when developing pharmaceutical agents. Our major long-term objective is to document the subcellular localisation of every protein within the mouse proteome. This will be achieved by a combination of experimental evidence, computational prediction and data mining.





Endosomal Dynamics – The endosomal/lysosomal system of mammalian cells is a highly dynamic organelle and the trafficking pathways within the endosomal system are fundamental for a wide variety of key cellular processes. My group is developing cellular and computational approaches to identify novel mammalian proteins associated with the endosomal system. A major current focus of the group is the characterisation of the mammalian retromer complex. We have implicated this complex, using real-time microscopy and molecular interaction techniques, in the sorting of numerous membrane receptors, including EGFR, within the endosomal system. With my group, Dr B. Collins has determined the high-resolution crystal structures of individual retromer proteins and is currently attempting to determine the structure of the entire complex. Currently we are undertaking a systems biology approach to examine the biogenesis of macropinosomes.

RESEARCH PROJECTS

- Annotating the membrane organisation of mammalian secretory pathway proteins
- Maintaining and updating LOCATE: A Mouse Protein Subcellular Localisation Database - http://locate.imb.uq.edu.au
- Developing algorithms for prediction of protein features
- Developing computational approaches to analyse image and real-time microscopy data
- Studying endosome dynamics, macropinocytosis and retromer
- Investigating the systems biology of the mammalian endosome

KEY PUBLICATIONS

Hamilton, N.A., Pantelic, R.S., Hanson, K., and Teasdale, R.D. (2007). Fast automated cell phenotype image classification. *BMC Bioinformatics* **8**: 110.

Sprenger, J. Fink, J.L., Karunaratne, S., Hanson, K., Hamilton, N., and Teasdale, R.D. (2007). LOCATE: A Mammalian Protein Subcellular Localization Database. *Nucleic Acids Research* **36** (Database issue).

Aturaliya, R.N., Fink, J.L., Davis, M.J., Teasdale, M.S., Hanson, K.A., Miranda, K.C., Forrest, A.R.R., Grimmond, S.M., Suzuki, H., Kanamori, M., Kai, C., Kawai, J., Carninci, P., Hayashizaki, Y., and Teasdale, R.D. (2006). Subcellular Localisation of Mammalian Type II Membrane Proteins. *Traffic* **7**: 613-625.

Davis, M.J., Hanson, K.A., Clark, F., Fink, J.L., Zhang, F., Kasukawa, T., Kai, C., Kawai, J., Carninci, P., Hayashizaki, Y., and Teasdale, R.D. (2006). Differential use of endoplasmic reticulum signal peptides and transmembrane domains is a common occurrence within the variable protein output of transcriptional units. *PLOS Genetics* **2**: e46.

Kerr, M., Lindsay, M., Luetterforst, R., Hamilton, N., Simpson, F., Parton, R., Gleeson, P.A., and Teasdale, R.D. (2006). Visualisation of macropinosome maturation by the recruitment of sorting nexins. *Journal of Cell Science* **119**: 3967-3980.

LAB MEMBERS

Senior Research Officers: Dr Brett Collins, Dr Nick Hamilton, Dr Zheng Yuan

Research Officers: Dr Lynn Fink, Dr Markus Kerr, Dr Stefan Maetschke, Dr Suzanne Norwood

Research Assistants: Seetha Karunaratne, Shane Zhang

PhD Students: Rajith Aturaliya, Melissa Davis, Daniel Shaw, Josefine Sprenger, Jack Wang

How Genes Regulate Embryo Development

Peter Koopman

Our group specialises in studying genes controlling the formation of various organs in the developing embryo. In particular we are striving to understand the events that regulate the development of functional male and female gonads and the formation of the blood and lymphatic vessels.

The discovery of the gene SRY, which acts as a single switch to initiate the male pathway of development, was over a decade ago. However, few pivotal genes up- or down-stream of SRY have been identified since then, and the exact interactions and functions of those such as SOX9 and WT1 remain elusive. Our lab specialises in the identification and characterisation of genes in this pathway using techniques such as microarray screening and transgenic mouse models created via pronuclear injection, tetraploid aggregation and RNAi.

Of particular interest are those genes that shape the somatic cell environment of the gonad in addition to those that co-ordinate germ cell entry into mitotic arrest or meiosis. The recent discovery in our lab that retinoic acid controls germ cell meiosis entry in the female gonad has provided a pivotal point to understanding this process. Current projects are also focused on identifying the timing and mechanism of sex differentiation in the animal models of bovine and cane toads, in an effort to manipulate sex ratios and population numbers respectively.

A second major focus in our group includes investigating the function of Sox genes during embryo development. Specifically we are investigating the role of SOX18 in angiogenesis and the formation of the lymphatic system. The significant discovery that disruption of SOX18 leads to a delay of tumour formation has highlighted SOX18 as a potential target for antiangiogenic therapy of human cancers.

The study of embryo development gives us profound insight into mechanisms of disease and cancer. In particular, a detailed knowledge of sex determination will have vast biomedical significance, with up to 80 percent of human sex reversal cases currently unexplained. The use of new technologies and the availability of multiple species' genomes may allow us to better understand these cases, and aid in new therapies for patients. Our research also has the potential to assist the industrial sector through possible pest management and livestock sex-ratio manipulation contributing to the Australian economy and agricultural sectors.

RESEARCH PROJECTS

- Understanding Sex Determination and Gonadal Development
- Studying the Development of Male Germ Cells
- Investigating Sox Gene Function and Evolution
- Studying the Molecular Genetics of Vascular and Lymphatic Development
- Developing Daughterless Cane Toads
- Triggering Male-Only Offspring Production in Beef Cattle

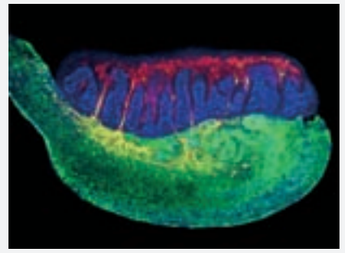
KEY PUBLICATIONS

Wilhelm, D., Palmer, S., and Koopman, P. (2007). Sex determination and gonadal development in mammals. *Physiological Reviews* **87**: 1-28.

Bowles, J., Knight, D., Smith, C., Wilhelm, D., Richman, J., Mamiya, S., Yashiro, K., Chawengsaksophak, K., Wilson, M.J., Rossant, J., Hamada, H., and Koopman, P. (2006). Retinoid signaling determines germ cell fate in mice. *Science* **312**: 596–600.

Wilhelm, D., and Koopman, P. (2006). The makings of maleness: Towards an integrated view of male sexual development. *Nature Reviews Genetics* **7**: 620-631.

Young, N., Hahn, C.N., Poh, A., Dong, C., Wilhelm, D., Olsson, J., Muscat, G.E.O., Parsons, P., Gamble, J.R., and Koopman, P. (2006). Effect of disrupted SOX18 transcription factor function on tumor growth, vascularization, and endothelial development. *Journal of the National Cancer Institute* **98**: 1060-1067.



Recombinant organ culture with GFP expressing mesonephros (green) and wild type testis allows analysis of cell migration into the testis during development. Migrating endothelial cells integrate with endogenous vasculature (yellow and red respectively) which separate forming testis cords (blue).

LAB MEMBERS

Senior Research Officers: Dr Josephine Bowles, Dr Catherine Browne, Dr Dagmar Wilhelm

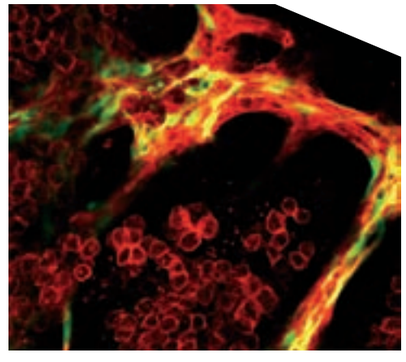
Research Officers: Dr Annemiek Beverdam, Dr Mathias Francois, Dr Terje Svingen, Dr Brett Hosking, Dr Kallayanee Chawengsaksophak

Research Assistants: Tara Davidson, Deon Knight, Desmond Tutt, Allen Feng, Vy Truong, Arief Mulyadi, Danielle Wilson

Admin Assistant: Rebekka van Kampen

PhD Students: Katherine Ewen, Juan Carlos Polanco, Stephen Bradford, Alexander Combes, Cassy Spiller, Diana Farkas, John Abramyan

UROP Students: James Holland



Platelet endothelial cell adhesion molecule (red) vividly outlines germ cell clusters and endothelial cells in a recombinant organ culture. Migrating endothelial cells marked by GFP (green) integrate into the endogenous population to establish testis vasculature.

Renal Development, Disease & Regeneration

Melissa Little

The central theme of this laboratory is the molecular basis of kidney development, disease and repair.

Each of us has a pair of kidneys that functions to excrete waste products in the form of urine. The kidneys therefore play an important role in maintaining fluid balance, blood volume and electrolyte balance. On top of this, they regulate blood pressure, bone density and number of red blood cells via the production of specific growth factors.

Chronic kidney disease (CKD) is a devastating disease and an expensive one to treat. Once this condition has reached end-stage renal failure, it can only be treated with dialysis or transplantation. Each year, more than 4000 Australian adults will be diagnosed with CKD, which cost the health system $1.8 billion dollars in 2006. This cost is likely to escalate to $4.7 billion by 2010. There is an urgent need to develop novel therapies as the rate of CKD is rising at 6-8 percent per annum, primarily due to increasing rates of Type II diabetes and obesity, and as only 1 in 4 patients will be lucky enough to receive a kidney transplant.

Our laboratory is acknowledged internationally for our work in defining the genes involved in normal kidney development and in dissecting the molecular basis of renal disease. The long-term aim of our laboratory is to develop novel cell-based or factor-based therapies for both acute and chronic kidney disease. Such therapies will grow out of our understanding of the processes involved in normal kidney development.

RESEARCH PROJECTS

- Characterising the function of potential adult renal stem cells
- Characterising the cap mesenchyme on a molecular level
- Creating an atlas of gene expression during urogenital development
- Investigating the role of the resident tissue macrophage in renal regeneration
- Analysing the role of specific growth factors in renal development, repair and regeneration
- Screening the directed dedifferentiation of proximal tubule cells using lentiviruses
- Characterising the role of Crim1 in kidney and vascular development

KEY PUBLICATIONS

Little, M., Brennan, J., Georgas, K., Davies, J., Davidson, D, *et al.* (2007). A high-resolution anatomical ontology of the developing murine genitourinary tract. *Gene Expression Patterns* **7**: 680-699.

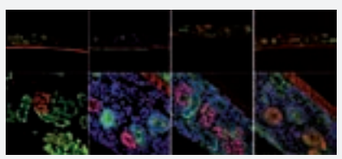
Pennisi, D.J., Wilkinson, L., Kolle, G., Sohaskey, M.L., Gillinder, K., Piper, M.J., McAvoy, J., Lovicu, F., and Little, M.H. (2007). Crim1KST264/KST264 mice display a disruption of the Crim1 gene resulting in perinatal lethality with defects in multiple organ systems. *Developmental Dynamics* **236**: 502-511.

Rae, F., Woods, K., Sasmono, T., Campanale, N., Taylor, D., Ovchinnikov, D., Grimmond, S., Hume, D.A., Ricardo, S., and Little, M.H. (2007). Characterisation and trophic functions of murine embryonic macrophages based upon the use of a CSF-1R-EGFP transgene reporter. *Developmental Biology* **308**: 232-246.

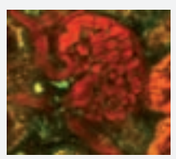
Wilkinson, L., Gilbert, T., Pennisi, D., Challen, G., Ruta, L.-A., Kett, M., Cummings, M., and Little, M.H. (2007). Crim1KST264/KST264 mice implicate Crim1 in the regulation of VEGF–A activity during glomerular vasculature development. *Journal of the American Society of Nephrology* **18**: 1697-1708.

Challen, G.A., Bertoncello, I., Deane, J., Ricardo, S., and Little, M.H. (2006). Kidney side population cells represent a non-haematopoietic but heterogeneous population with multilineage and renal potential. *Journal of the American Society of Nephrology* **17**: 1896-1912.

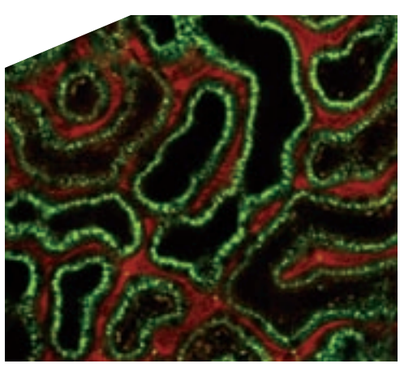
Little, M.H. (2006). Regrow or repair – potential regenerative therapies for the kidney. *Journal of the American Society of Nephrology* **17**: 2390-2401.

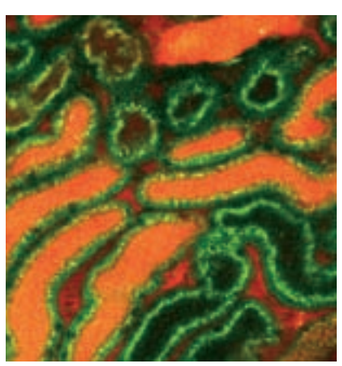


Reaggregation assay – proof of concept.



Live imaging (70kDa Rhodamine-dextran) of adult kidneys shows profound leakiness across the GBM.





Rhodamine-dextran is evident in proximal tubules of KST264 adults.

LAB MEMBERS

Research Officers: Dr Thierry Gilbert, Dr Lorine Wilkinson, Dr David Pennisi, Dr Fiona Rae, Dr Joan Li

Research Assistants: Kylie Georgas, Bree Rumballe, Jess Ineson, Emmanuelle Lesieur, Han Chui, Crystal McGirr

PhD Students: Genevieve Kinna, Michael Lusis, Caroline Hopkins

Nuclear Receptors, Skeletal Muscle & Metabolic Disease

George E.O. Muscat

Nuclear Hormone Receptors (NRs) control metabolism in metabolic, cardiovascular and endocrine organs. The importance of NRs in safeguarding human wellbeing is underscored by the curative efficacy of medicinals that target dysfunctional hormone signalling in the context of inflammation, cancer, endocrine and metabolic diseases. Nuclear hormone receptors function as agonist-dependent DNA-binding factors that translate nutritional (eg. dietary lipids), metabolic and pathophysiological signals into gene regulation. Proteins have been identified that belong to the NR superfamily on the basis of sequence identity, but the molecules that regulate their activity are unknown and they are denoted as orphan NRs. The orphans provide a platform for the unearthing of new signalling cascades that may have potential therapeutic utility.

Many orphan NRs are expressed in skeletal muscle, a peripheral tissue that accounts for ~40 percent of the total body mass and energy expenditure, and is a major site of fatty acid and glucose oxidation. Moreover, this lean tissue is involved in cholesterol efflux, expresses myostatin and cytokines that control inflammation, energy expenditure, lean body mass and adiposity. Consequently, muscle has a significant role in insulin sensitivity, the blood lipid profile, and energy balance. Therefore, the tissue has a notable role in the development of metabolic disease, and it is not surprising that NRs and skeletal muscle are emerging as targets in the battle against diabetes and obesity.

Surprisingly, the function of these orphan NRs in skeletal muscle metabolism has not been examined. The objective of our current research is to examine the role of orphan NRs in skeletal muscle cell and animal models. We will test the hypothesis that the orphan NR4A and 1F subgroups regulate lipid and energy homeostasis in skeletal muscle. Recently, our group has provided evidence for regulatory crosstalk between beta-adrenergic and Nuclear Receptor (NR) 4A signalling in slow-twitch oxidative soleus muscle and fast-twitch glycolytic tibialis anterior muscle in the context of oxidative metabolism. The process involved PKA, MAPK and phosphorylation of CREB. Secondly, we have utilised several mouse models to demonstrate that NR1F subgroup is involved in the regulation of (i) serum and liver triglycerides and (ii) adiposity.

In addition, in collaboration with Dr Gary Leong (joint IMB/Mater Hospital) and Dr Edna Hardeman at Children's Medical Research Institute, Sydney, we are utilising the Ski transgenic mouse model to investigate the role of the ski gene in the metabolic changes associated with increased skeletal and decreased fat mass.

RESEARCH PROJECTS

- Examining the role of the NR1D and F subgroups (Rev-erb and RORs) in lipid homeostasis and inflammation
- Elucidating the role of the NR4A subgroup (Nur77, NOR-1) in skeletal muscle energy balance and adrenergic signalling
- Determining the role and function of the Ski gene in body composition and metabolism via modulation of NR-dependent metabolism in skeletal muscle, fat and liver

KEY PUBLICATIONS

Pearen, M.A., Myers, S.A., Raichur, S., Ryall, J.G., Lynch, G.S., and Muscat, G.E. (2008). The Orphan Nuclear Receptor, NOR-1, a Target of {beta}-Adrenergic Signaling, Regulates Gene Expression that Controls Oxidative Metabolism in Skeletal Muscle. *Endocrinology* Epub ahead of print

Raichur, S., Lau, P., Staels, B., and Muscat, G.E. (2008). Retinoid-related orphan receptor gamma regulates several genes that control metabolism in skeletal muscle cells: links to modulation of reactive oxygen species production. *Journal of Molecular Endocrinology* **39**: 29-44.

Smith, A.G., Luk, N., Newton, R.A., Roberts, D.W., Sturm, R.A., and Muscat, G.E. (2008). Melanocortin-1 receptor signalling markedly induces the expression of the NR4A nuclear receptor subgroup in melanocytic cells. *Journal of Biological Chemistry* Epub ahead of print

Myers, S.A., Wang, S.C., and Muscat, G.E. (2006). The chicken ovalbumin upstream promoter-transcription factors modulate genes and pathways involved in skeletal muscle cell metabolism. *Journal of Biological Chemistry* **281**: 24149-24160.

Pearen, M.A., Ryall, J.G., Maxwell, M.A., Ohkura, N., Lynch, G.S., and Muscat, G.E. (2006). The orphan nuclear receptor, NOR-1, is a target of beta-adrenergic signaling in skeletal muscle. *Endocrinology* **147**: 5217-5227.

Smith, A.G., and Muscat, G.E. (2006). Orphan nuclear receptors: therapeutic opportunities in skeletal muscle. *American Journal of Physiology: Cell Physiology* **291**: C203-17.

LAB MEMBERS

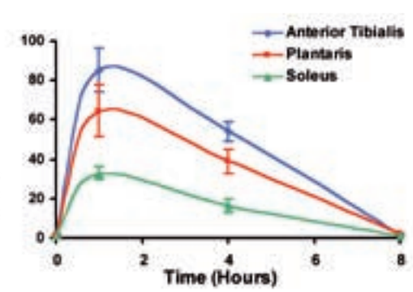
Research Officers: Dr Patrick Lau, Dr Stephen Myers, Dr Mary Wang, Dr Aaron Smith

Research Assistants: Rebecca Fitzsimmons, Rachel Burow

PhD Students: Michael Pearen, Sathiya Ramakrishnan, Suryaprakash Raichur, Lisa Crowther

Dr Gary Leong (Joint appointment Senior Research Officer, IMB, and Staff Specialist, Mater Childrens Hospital, NHMRC Clinical CDA & QLD Smart State Clinical Research Fellow)

Research Assistant: Nick Martel



Muscat2.tif - β 2-adrenergic agonist increases NR4A2/Nurr1 mRNA expression in slow oxidative (soleus) and fast glycolytic (tibialis anterior & plantaris) skeletal muscle.

Blood Development

Andrew Perkins

Our group is interested in the transcriptional regulation mesoderm specification. We are primarily concerned with transcriptional hierarchies and how transcription factors work within biochemical and genetic pathways, and also how deregulation of such programs leads to cancer. Our group uses mouse and zebrafish model systems to examine gene function in vivo, and a wide variety of biochemical assays to examine gene function in vitro.

We have four primary focus areas:

1. Transcriptional hierarchies which are active during embryonic stem (ES) cell differentiation into mesoderm-derived tissues such as the kidney and blood. The methodologies used include: directed differentiation of ES cells in various recombinant growth factors, gene targeting and BAC recombineering for generating reporter ES cell lines and mice in which stem cells can be followed by epifluorescence and FACS, expression profiling and chromatin immuno-precipitation.

2. Transcriptional regulation of erythropoiesis. Mutations in the globin genes are the most common genetic mutations worldwide. These mutations are responsible for thalassaemia and sickle cell disease, which cause serious morbidity and mortality around the world. We are interested in trying to decipher the complex process of haemoglobin switching at a molecular level. The long-term goal is to design new drugs that target key regulators of this process and thereby reactivate foetal haemoglobin in adults.

3. Zebrafish are used as a vertebrate model for dissection of some of the earliest transcriptional events which underpin morphogenetic movements which lead to the generation and 'education' of stem cells within the mesoderm germ layer. Once again we are concerned primarily with the activities of key 'master regulator' transcription factors of zinc finger and homeodomain classes. We have established expression profiling in zebrafish and have established assays and systems for study of morphogenesis.

4. The role played by the Kruppel-like factor (KLF) family of zinc finger genes in normal differentiation and human skin, colon and blood cancers.

RESEARCH PROJECTS

- Studying transcriptional hierarchies active during ES cell differentiation into mesoderm-derived tissues
- Investigating the transcriptional regulation of erythropoiesis
- Studying morphogenesis using zebrafish models
- Investigating the role of KLFs in differentiation and cancer

KEY PUBLICATIONS

Bruce, S.J., Gardiner, B.B., Burke, L.J., Cridland, S., Steptoe, A., Flanagan, J., Gongora, M., Grimmond, S.M., and Perkins, A.C. (2007). Dynamic transcription programs during ES cell differentiation towards mesoderm in serum versus serum-free (BMP4) culture. *BMC Genomics* **8**: 365.

Bruce, S.J., Rossiter, A.L., Steptoe, A.L., Busslinger, M., Bertram, J.F., and Perkins, A.C. (2007). A late Kidney Gene Expression Program within Mouse Embryoid Bodies. *Differentiation* **75**: 337-349.

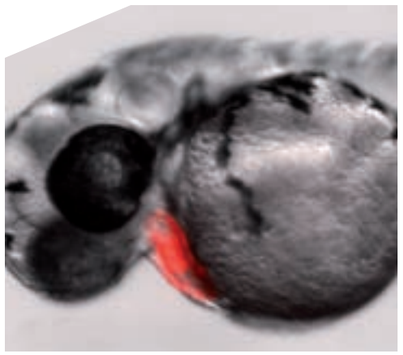
Gardiner, M.R., Gongora, M.M., Grimmond, S.M., and Perkins, A.C. (2007). A global role for zebrafish klf4 in embryonic erythropoiesis. *Mechanics of Development* **124**: 762-764.

Wilkins, S.J., Yoong, S., Verkade, H., Mizoguchi, T., Plowman, S.J., Hancock, J.F., Kikuchi, Y., Heath, J.K., and Perkins, A.C. (2007). Mtx2 directs zebrafish morphogenetic movements during epiboly by regulating microfilament formation. *Developmental Biology* **314**: 12-22.

Hodge, D., Coghill, E., Maguire, T., Keys, J., Hartmann, B., Weiss, M., McDowall, A., Grimmond, S., and Perkins, A.C. (2006). A global role for EKLF in definitive and primitive haematopoiesis. *Blood* **107**: 3357-3370.

Papathanasiou, P., Perkins, A.C., Cobb, B.S., Ferrini, R., Sridharan, R., Hoyne, G.F., Nelms, K.A., Smale, S.T., and Goodnow, C.C. (2003). Widespread failure of hematolymphoid differentiation caused by a recessive niche-filling allele of the Ikaros transcription factor. *Immunity* **19**: 131-144.

Perkins, A.C., Sharp, A.H., and Orkin, S.H. (1995). Lethal β-thalassemia in mice lacking the erythroid CACCC-transcription factor EKLF. *Nature* **375**: 318-322.



LAB MEMBERS

Senior Research Officer: Dr Janelle Keys (Cooley's Anemia Post-doctoral Research Fellow)

Research Officers: Dr Christine Neyt, Dr Stephen Bruce

Senior Research Assistants: Angela Lawton, Anita Steptoe

Research Assistants: Aliesha Griffin, Natalie Eriksson

PhD Students: Simon Wilkins, Simon Cridland, Melissa Gardiner, Michael Tallack, Paulo Amaral, Tom Whittington

Human Pigmentation Genetics, Melanocyte Biology & Melanoma

Rick Sturm

The genetic and cellular understanding of human pigmentary traits is vital to assess an individual's response to sun exposure and their risk of skin cancer. We are investigating loci within the human genome that are responsible for an individual's pigmentation phenotype and identifying polymorphic alleles of these genes. A number of proteins essential to normal melanin biosynthesis have so far been identified and include the enzymes tyrosinase, tyrosinase-related protein-1 and dopachrome tautomerase (TYR, TYRP1 and DCT), while the P-protein (OCA2) is associated with blue eye colour, and the melanocortin-1 receptor (MC1R) is responsible for red hair colour. Furthermore, recent population-specific polymorphisms within the MATP (SLC45A2) and NCKX5 (SLC24A5) protein-coding regions have been correlated with the degree of pigmentation in human skin.

Our group has found that coding region variation within the MC1R gene can result in altered receptor activity and that this underlies the association with the red hair and fair skin phenotype (RHC). Nine common alleles have been studied and designated as either R (strongly associated with the RHC phenotype) or r (with lower penetrance). Using immunofluorescence and ligand binding studies, we have found that melanocytic cells expressing MC1R show strong surface localisation of the wildtype receptor but markedly reduced cell surface expression of some R variants. Moreover, MC1R variants can exert dominant negative activity on the wildtype receptor indicative of the ability of the receptor to homodimerize. We have also conducted genotyping studies to investigate the role of the OCA2 locus in inheritance of eye colour and other pigmentary traits associated with skin cancer risk in white populations. SNPs spanning the OCA2 region were typed in a collection of 3839 adolescent twins, their siblings, and parents. The highest association for blue:non-blue eye colour was found for a major haplotype block mapping within the first intron of the OCA2 gene, notably this haplotype (TGT) representing 78.4 percent of alleles. The TGT/TGT diplotype found in 62.2 percent of samples was the major genotype seen to modify eye colour, with a frequency of 0.905 in blue or green compared to only 0.095 in brown eye colour.

Investigations into pigment cell biology have utilised cultures of both murine and human melanocytes, as well as numerous melanoma cell lines. We have published conditions for the isolation and propagation of human epidermal melanocyte precursors, termed melanoblasts, using medium supplemented with a range of growth factors and which differentiate into melanocytes upon mitogen withdrawal. Recent publications have suggested that melanoma may arise from the malignant transformation of melanocytic precursor cells residing in the skin. Our proposal is to study potential differences in the transcriptional and signalling network of skin-derived precursor (SKP) cells, when grown in vitro as spheroids and differentiated into melanocytes. We aim to identify the differentiation and regulatory pathways active in normal melanocyte growth that differ to those responsible for melanoma development, and formation of spheroids from melanoma cell lines.

RESEARCH PROJECTS

- Understanding skin cancer risk phenotypes through studying the interaction of genes involved in skin, hair and eye colour
- Undertaking parallel genetic and cellular analysis of human melanogenesis
- Investigating eye colour as a genetic trait
- Researching melanocytic spheroids as a model for melanoma development and metastasis

KEY PUBLICATIONS

Beaumont, K.A., Shekar, S.N., Newton, R.A., James, M.R., Stow, J.L., Duffy, D.L., and Sturm, R.A. (2007). Receptor function, dominant negative activity and phenotype correlations for MC1R variant alleles. *Human Molecular Genetics* **16**: 2249-2260.

Duffy, D.L., Montgomery, G.W., Chen, W., Zhao, Z.Z., Le, L., James, M.R., Hayward, N.K., Martin, N.G., and Sturm, R.A. (2007). A three-SNP haplotype in the intron 1 of OCA2 explains most human eye color variation. *American Journal of Human Genetics* **80**: 241-252.

Sturm, R.A. (2006). A golden age of human pigmentation genetics. *Trends in Genetics* **22**: 464-468. (Journal Cover)

Beaumont, K.A., Newton, R.A., Smit, D.J., Leonard, J.H., Stow, J.L., and Sturm, R.A. (2005). Altered cell surface expression of human MC1R variant receptor alleles associated with red hair and skin cancer risk. *Human Molecular Genetics* **14**: 2145-2154.

Duffy, D.L., Box, N.F., Chen, W., Palmer, J.S., Montgomery, G.W., James, M.R., Hayward, N.K., Martin, N.G., and Sturm, R.A. (2004). Interactive effects of MC1R and OCA2 on melanoma risk phenotypes. *Human Molecular Genetics* **13**: 447-461. (Journal Cover)

Sturm, R.A., and Frudakis, T.N. (2004). Eye colour: portals into pigmentation genes and ancestry. *Trends in Genetics* **20**: 327-332. (Journal Cover)

LAB MEMBERS

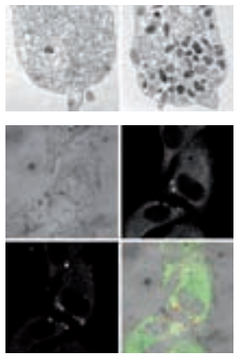
Research Officer: Dr Anthony Cook

Research Assistants: Darren Smit, Caroline Sturm, Amy Thurber

PhD Students: Helene Johanson, Luke Kirkwood, Don Roberts, Kimberley Beaumont

Honours Student: Wen Lim

Undergraduate Student: Poh Yuen Chin



Melanocytes and melanosomes.

Tissue Repair & Cancer

Brandon Wainwright

Using genomic approaches our group mapped and isolated genes affecting two human genetic conditions, cystic fibrosis (CF) and naevoid basal cell carcinoma syndrome (NBCCS). From this work has emerged a focus upon the pathways that lead to inflammation, tissue repair and proliferation in the context of these two diseases. In particular the patched gene, discovered from our studies on NBCCS, has defined a signalling pathway known as the ("hedgehog pathway") which appears to be mutated or perturbed in a wide range of tumour types, including lung, gastro-intestinal, skin, pancreatic, prostate, brain and ovarian cancer. This has led us to focus on the role of hedgehog signalling, not only in cancer but also on the regulation of stem cell compartments. Increasingly it appears that in some tumour types there are cells known as "cancer stem cells" which reside within the tumour and are responsible for the overall phenotype. Currently such cells can be partially defined functionally but their molecular signature remains elusive. We believe that the patched/hedgehog pathway defines many of the characteristics of such stem cells and is a powerful starting point for understanding tumour biology and the development of new therapeutics.

Given that cancer represents a state of unregulated cell growth, it is likely that the pathways that lead to cancer are also involved in the normal process of tissue growth and repair. Several of our studies are particularly directed at the role of the hedgehog (and other pathways) in repair and regeneration. In our laboratory this is a developing theme and focused upon the lung. From our studies on cystic fibrosis we are gaining an understanding of how infection and inflammation in this disorder damage the lung epithelium and severely compromise lung function. At the same time, in order to provide new therapeutic avenues, we are analysing the molecular signature of repair of the lung epithelium using the patched/hedgehog pathway as a start point. The processes of inflammation, damage, repair and cancer are intimately connected and to gain an insight into one process enables progress in all to be made. This will lead us to a better understanding of how cell-based therapies might be used to treat lung diseases as well as likely provide valuable insights into the mechanism of lung cancer.

As part of our experimental approach our laboratory makes extensive use of transgenic and knockout mice. However at all points we refer back to the human diseases under study and have major activities based around mutation analysis, transcriptomics and proteomics of human material, integrating the data from all systems.

As a result of these studies we have a particular interest in the interface between developmental cell biology and human genetics, and in therapeutic interventions such as gene or cell therapies.

RESEARCH PROJECTS

- Controlling neuronal stem cells and CNS by the patched/hedgehog pathway
- Investigating the molecular basis of primary brain tumours
- Controlling the stem cell niche in mammalian epidermis and skin cancer
- Studying infection, inflammation and repair in cystic fibrosis mice and cystic fibrosis infants
- Controlling lung regeneration following injury

KEY PUBLICATIONS

Ingram, W., McCue, K., Tran, T., Hallahan, A., and Wainwright, B. (2007). Sonic hedgehog regulates Hes1 through a novel mechanism that is independent of canonical Notch pathway signalling. *Oncogene* **27**: 1489-1500.

McMorran, B., Patat, S., Carlin, J., Grimwood, K., Jones, A., Armstrong, D., Galati, J., Cooper, P., Byrnes, C., Francis, P., Robertson, C., Hume, D., Borchers, C., Wainwright, C., and Wainwright, B. (2007). Novel neutrophil-derived proteins in bronchoalveolar lavage fluid indicate an exaggerated inflammatory response in pediatric cystic fibrosis patients. *Clinical Chemistry* **53**: 182-91.

Adolphe, C., Hetherington, R., Ellis, T., and Wainwright, B. (2006). Patched1 functions as a gatekeeper by promoting cell cycle progression. *Cancer Research* **66**: 2081-2088.

Adolphe, C., Narang, M., Ellis, T., Wicking, C., Kaur, P., and Wainwright, B. (2004). An in vivo comparative study of sonic, desert and Indian hedgehog reveals that hedgehog pathway activity regulates epidermal stem cell homeostasis. *Development* **131**: 5009-5019.

LAB MEMBERS

Senior Research Officer: Dr Tammy Ellis

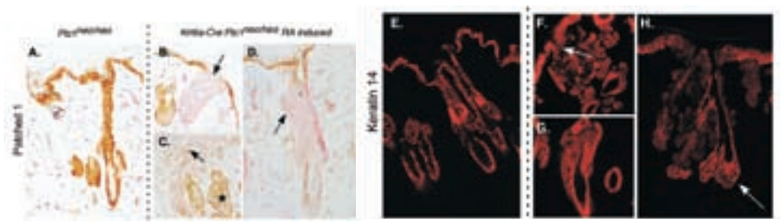
Research Officers: Dr James Palmer, Dr Richa Dave, Dr Elaine Costelloe

Research Assistants: Ailsa McCormack, Melissa Bourboulas

PhD Students: Karen McCue, Rehan Villani, Uda Ho, Elaine Haase, Jonathon Robson, Lena Constantin, Azita Ahadizadeh

Masters Student: Ann-Marie Michalski

Honours Student: Larissa Upward



Loss of patched leads directly to skin tumours.

Developmental Genes & Human Disease

Carol Wicking

Defects arising from abnormal embryonic development are a major cause of infant mortality and childhood disability. Many such disorders are characterised by anomalies of the limbs and craniofacial region, suggesting a conservation of the molecular development of these structures. Using the mouse as a model system, we aim to identify and characterise novel molecules contributing to the development of the limb and face, with particular emphasis on genes regulated by the Hedgehog signalling pathway. Because of the importance of Hedgehog and other developmental signalling pathways in tumorigenesis, many of these genes will also be important in cancer.

Using genomics-based approaches we have identified a number of novel or poorly characterised genes with potential roles in embryonic development and disease. For those genes of interest we are undertaking a more detailed characterisation at both the cell and whole-organism level. We employ standard cell biology and biochemical techniques to shed light on the cellular role of these molecules, and in some cases are using transgenic or knockout approaches in the mouse to elucidate function. We are currently pursuing analysis of a protein that we have shown regulates cell migration. Our ultimate aim is to correlate the genes we identify with human disease, and we are currently analysing a number of genes for a role in tumour formation and/or progression.

The limb bud has long been considered a paradigm for analysis of embryonic development, and Hedgehog signalling is a key determinant of patterning in the vertebrate limb. We are therefore using a number of mouse models of Hedgehog signalling to further explore the function of this pathway in limb development.

RESEARCH PROJECTS

- Studying conditional knockout of the Hedgehog receptor patched in the developing mouse limb
- Identifying and analysing genes regulated by the transcription factor Gli3 in the developing limb
- Identifying and analysing genes expressed in the facial primordia
- Analysing a novel regulator of cell migration on a cellular level

KEY PUBLICATIONS

Bennetts, J.S., Rendtorff, N.D., Simpson, F., Tranebjaerg, L., and Wicking, C. (2007). The coding region of *TP53INP2,* a gene expressed in the developing nervous system, is not altered in a family with autosomal recessive non-progressive infantile ataxia on chromosome 20q11-q13. *Developmental Dynamics* **236**: 843-852.

Bennetts, J.S., Fowles, L.F., Berkman, J.L., Lammerts van Bueren, K., Richman, J.M., Simpson, F., and Wicking, C. (2006). Evolutionary conservation and murine embryonic expression of the gene encoding the SERTA domain-containing protein CDCA4 (HEPP). *Gene* **374**: 153-165.

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Simpson, F., Lammerts van Bueren, K., Butterfield, N., Bennetts, J.S., Bowles, J., Adolphe, C., Simms, L.A., Young, J., Walsh, M.D., Leggett, B., Fowles, L.F., and Wicking, C. (2006). The PCNA-associated factor KIAA0101/p15PAF binds the potential tumour suppressor product p33ING1b. *Experimental Cell Research* **312**: 73-85.

McGlinn, E., Lammerts van Bueren, K., Fiorenza, S., Mo, R., Poh, A., Forrest, A., Soares, M.B., Bonaldo, M., Grimmond, S., Hui, C.C., Wainwright, B., and Wicking, C. (2005). Pax9 and Jagged1 act downstream of Gli3 in vertebrate limb development. *Mechanisms of Development* **122**: 1218-1233.

Simpson, F., Martin, S., Evans, T., Kerr, M., James, D.E., Parton, R.G., Teasdale, R.D., and Wicking, C. (2005). A novel Hook-related protein family and the characterisation of Hook-related protein 1. *Traffic* **6**: 442-458.

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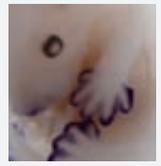
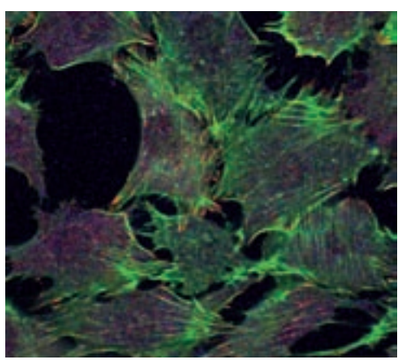
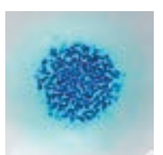


Whole mount in situ hybridisation in mouse embryos is used to determine spatio-temporal gene expression.



Immunofluorescence analysis to reveal subcellular localisation of proteins can provide insight into function.



High density micromass culture established from limb mesenchymal cells and stained with Alcian blue to detect sulfated proteoglycans associated with cartilage. This method is used to study chondrogenesis in vitro.

LAB MEMBERS

Senior Research Officer: Dr Fiona Simpson (RD Wright Fellow)

Research Officer: Dr Kerry Manton

Research Assistant: Vicki Metzis

PhD Students: Natalie Butterfield, Liam Town

Honours Student: Amanda Bain

Visiting Student: Diane Schluep (Netherlands)

Plasma Membrane Microstructure & Signal Transduction

John Hancock

Our group studies mammalian intracellular signalling. We are especially interested in the function of Ras proteins. These small GTP binding proteins operate as molecular switches in signal transduction pathways and are present in a mutant, activated state in many human tumours. Understanding the basic biology of Ras has major implications for the development of novel anticancer therapeutics.

Specifically, we are investigating how the Ras membrane anchors cooperate with the G-domain and peptide sequences flanking the anchor to drive lateral segregation. Our work suggests new models are needed to explain how lipidated proteins interact with, and use, the plasma membrane to generate signalling platforms.

We remain interested in how confinement of signalling complexes onto a 2D surface in general, and in plasma membrane microdomains in particular, regulates the kinetics and sensitivity of Raf/MEK/Erk signal output. Similarly, as we develop our spatial and proteomic maps of the plasma membrane, we can address how the composition and organisation of the membrane alters in response to specific growth factors. The integration of complex spatial, kinetic and biochemical data sets increasingly requires mathematical modelling to generate and test our novel hypotheses of microdomain structure and function.

We also have a major interest in characterising the K-ras ER to plasma membrane trafficking pathway and studying the biology of Ras prenyl binding proteins such as PDE delta.

RESEARCH PROJECTS

- Molecular mapping of the proteins and lipids of plasma membrane microdomains
- Electron microscopic visualisation and quantitative characterisation of surface microdomains to build up a high-resolution 2D map of the microdomains of the inner plasma membrane
- Investigating the dynamic regulation of microdomain localisation of Ras and Ras-interacting proteins in response to physiological stimuli
- Characterising the mechanism(s) whereby K-ras is transported to the plasma membrane
- Mathematically modelling Ras signal transduction
- Monte Carlo modelling of plasma membrane microdomain dynamics

KEY PUBLICATIONS

Tian, T., Harding, A., Inder, K., Plowman, S.J., Parton, R.G., and Hancock, J.F. (2007). Plasma membrane nanoswitches generate high-fidelity Ras signal transduction. *Nature Cell Biology* **9**: 905-914.

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Nicolau Jr., D.V., Burrage, K., Parton, R.G., and Hancock, J.F. (2006). Identifying optimal lipid raft characteristics required to promote nano-scale protein-protein interactions on the plasma membrane. *Molecular Cell Biology* **26**: 313-323.

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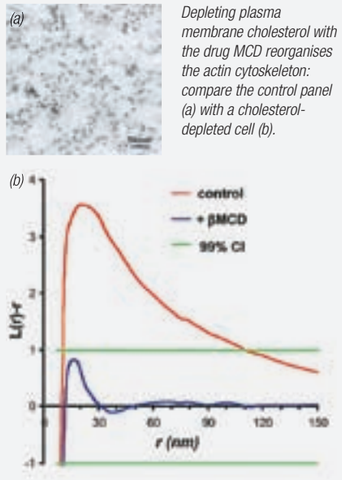
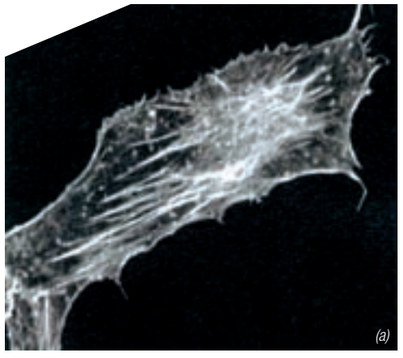
Harding, A., Tian, T., Westbury, E., Frische, E., and Hancock, J.F. (2005). Subcellular localization determines MAP Kinase signal output. *Current Biology* **15**: 869-873.

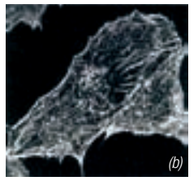
Plowman, S., Muncke, C., Parton, R.G., and Hancock, J.F. (2005). H-ras, K-ras and inner plasma membrane raft proteins operate in nanoclusters with differential dependence on the actin cytoskeleton. *Proceedings of the National Academy of Sciences USA* **102**: 15500-15505.

Roy, S., Plowman, S., Rotblat, B., Prior, I.A., Muncke, C., Parton, R.G., Henis, Y.I., Kloog, Y., and Hancock, J.F. (2005). Individual palmitoyl residues serve distinct roles in H-Ras trafficking, microlocalization and signaling. *Molecular Cell Biology* **25**: 6722-6733.



Depleting plasma membrane cholesterol with the drug MCD reorganises the actin cytoskeleton: compare the control panel (a) with a cholesterol-depleted cell (b).





Cholesterol depletion also causes the lipid raft marker protein GFP-Th, imaged on intact plasma membrane sheets by immunogold labelling (a) to de-cluster: immunogold-point patterns are analysed using spatial statistics (b).

LAB MEMBERS:

Research Officers: Dr Michael Hanzal-Bayer, Dr Michelle Hill, Dr Sarah Plowman, Dr Daniel Abankwa, Dr Kerry Inder

Research Assistants: Annette Lane, Dorothy Loos, Natasha Ray, Nicholas Ariotti

PhD Students: Andrew Goodall, Kwang-Jin Cho

M.Phil Student: Daniel Nicolau Jr.

Structure-function Studies of The Endocrine Pancreas – Comparative Studies of Mouse & Human Pancreatic Islet Biology

Brad Marsh

The ß-cells of the endocrine pancreas are the sole source of insulin in mammals. Death of the ß-cells, or their abnormal processing, trafficking and/or secretion of insulin, results in the disease commonly known as diabetes. This disease is one of Australia's national health priority areas and represents the fastest-growing epidemic internationally. More than 230 million people worldwide currently live with the disease, but this number is expected to rise to 350 million within 20 years. In 2007, the world spent an estimated US$215-375 billion to care for diabetes and its complications. In particular, type 1 diabetes is one of Australia's fastest-growing chronic diseases, and represents a life-long autoimmune disease that usually begins in childhood and results in premature death through health complications. Type 1 diabetes cannot be prevented, and a cure remains to be found.

Our group's research is focused on understanding the basic mechanisms related to ß-cell function and dysfunction from a structural cell biology perspective, so that we can precisely identify how and where defects in these steps occur. By necessity, this work has led us to develop or advance techniques for the improved preservation and imaging of pancreatic ß-cells in situ within pancreatic islets of Langerhans isolated from both mice and humans, so that we are positioned to reliably elucidate the basic cell biology and physiology of the ß-cell — and islet biology more generally — through comparative studies of islet cell structure-function.

To complement our move toward an integrated or more holistic approach to understanding cells as examples of complex systems, we have undertaken a multi-scale/multi-resolution approach whereby we have started reconstructing entire mammalian (ß) cells in 3D at both high (≤5nm) and intermediate (15-20nm) resolutions. These approaches underpin the Visible Cell™ project (www.visiblecell.com) coordinated between the IMB and the Australian Centre of Excellence in Bioinformatics (ACB) at The University of Queensland. Our group's data will uniquely inform advanced in silico studies of 3D cell and molecular organisation in mammalian cells that are focused on developing the capacity to model and predict cellular differentiation during normal development, as well as the pathophysiology of chronic diseases like type 1 diabetes.

NEW RESEARCH PROJECTS

As the only Australian research group within the nPOD program (Network for Pancreatic Organ donors with Diabetes) in North America, we are currently working to establish high-resolution structural studies of human islet tissue from islet autoantibody-positive donors to detect/compare early changes in islet cell health and topology against baseline data that we are now acquiring regularly from human islets isolated from both normal/healthy and type 2 diabetic (T2D) donors obtained within Australia. These human studies will be carried out concurrently with key mouse models for T1D and viral uptake/infection of islet cells.

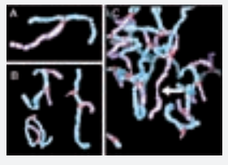
KEY PUBLICATIONS

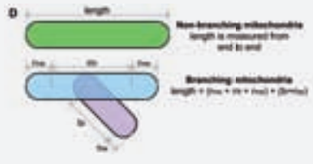
Noske, A.B., Costin, A.J., Morgan, G.P., and Marsh, B.J. (2008). Expedited approaches to whole cell electron tomography and organelle mark-up in situ in high-pressure frozen pancreatic islets. *Journal of Structural Biology* **161**: 298-313.

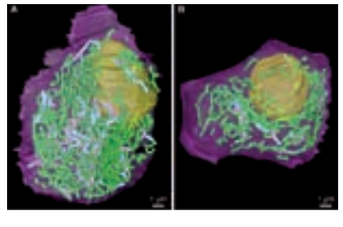
Brunham, L.R., Kruit, J.K., Pape, T.D., Timmins, J.M., Reuwer, A.Q., Vasanji, Z., Marsh, B.J., Rodrigues, B., Johnson, J.D., Parks, J.S., Verchere, C.B., and Hayden, M.R. (2007). Beta-cell ABCA1 influences insulin secretion, glucose homeostasis and response to thiazolidinedione treatment. *Nature Medicine* **13**: 340-347.

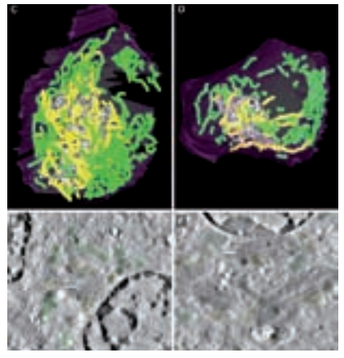
Marsh, B.J., Soden, C., Alarcón, C., Wicksteed, B.L., Yaekura, K., Costin, A.J., Morgan, G.P., and Rhodes, C.J. (2007). Regulated autophagy controls hormone content in secretory-deficient pancreatic endocrine beta-cells. *Molecular Endocrinology* **21**: 2255-2269.

Uchizono, Y., Alarcón, C., Wicksteed, B.L., Marsh, B.J., and Rhodes, C.J. (2007). The balance between proinsulin biosynthesis and insulin secretion: where can imbalance lead? *Diabetes, Obesity and Metabolism* **9**: 56–66.









LAB MEMBERS

Research Officers: Dr Isabel Morrow, Dr Tobias Richter, Dr Neelima Pottekkat Sidharthan

Research Assistants: Janette Galea, Jaclyn Goh, Garry Morgan, Timothy Pan

PhD Students: Adam Costin, Alex Foo, Andrew Noske, Peter van der Heide

Visiting Scholar: Meike Leuger

Fungal Genetics Applied to Human Disease & Crop Protection

Alan Munn

High-throughput approaches have facilitated the identification of genes whose expression is altered during development or in disease. Identification of the genes affected is, however, only a starting point. There is an increasing realisation that a single gene and its product(s) often have multiple and sometimes diverse, complex, and even antagonistic roles in the cell. Understanding the role(s) of the affected genes and their products is essential for translation of basic discoveries into outcomes for human health. For many disease genes and their products the available functional data are severely limited or non-existent. Much of the work in the Munn group has focused on understanding the role(s) of genes and their products linked to human diseases. Assigning functions to disease genes has relied very heavily on genetic approaches using model organisms. Yeast (a unicellular fungus) is the most powerful and widely used of these model organisms. Not every human disease gene or drug target is present in the yeast genome, but several hundred are represented. Study of these yeast genes can provide the clues needed to interpret high-throughput human data and translate this knowledge into outcomes for human health.

For example, the actin cytoskeleton is a protein scaffold, present in both humans and yeast, comprising building blocks known as actin filaments. The actin cytoskeleton undergoes dynamic changes and these govern changes in cell shape and internal organisation. Our results suggest that some cytoskeletal proteins may have the ability to permanently alter the conformation and physiological activity of proteins they transiently interact with. The process we have uncovered may play a profound, but as yet largely unexplored, role in human maladies such as cancer, immunodeficiency and neurological diseases.

Virus infection is another area where human and yeast processes are similar. Viruses hijack and utilise host cell machineries during infection. This makes these host machineries potential anti-viral drug targets. Work from a number of virology groups has identified the endosomal sorting machinery as a host cell machinery utilised by an especially diverse group of viruses (e.g. ebola, herpes, HIV, hepatitis B, mumps). In healthy cells this machinery works to package and dispose of cellular waste products. In infected cells, however, it packages and exports viruses. Discoveries made in the Munn group over the past year have identified how this machinery is targeted to membranes and assembles into an active complex – processes that may provide opportunities for therapeutic intervention in viral infection.

Using yeast as a model organism has also allowed our group to work on pathogens that affect plants. *Fusarium graminearum* is a pathogenic filamentous fungus. *Fusarium* infects wheat plants and not only reduces crop yields by destroying the grain, but also contaminates the remaining grain with potent toxins. We have identified a set of *F. graminearum* genes that are expressed at elevated levels during infection. Some of these fungal genes may be essential for pathogenicity.

RESEARCH PROJECTS

- The actin cytoskeleton in health and disease
- Endosomal sorting machinery as a novel target for antivirals
- Fungal pathogens of wheat

KEY PUBLICATIONS

Desmond, O.J., Manners, J.M., Stephens, A.E., Maclean, D.J., Schenk, P.M., Gardiner, D.M., Munn, A.L., and Kazan, K. (2008). The Fusarium mycotoxin deoxynivalenol elicits hydrogen peroxide production, programmed cell death and defence responses in wheat. *Molecular Plant Pathology* In press

Vajjhala, P.R., Nguyen, C.H., Landsberg, M.J., Kistler, C., Gan, A., King, G.F., Hankamer, B., and Munn, A.L. (2008). The Vps4 C-terminal helix is a critical determinant for Vps4 assembly and ATPase activity and has elements conserved in other members of the meiotic clade of AAA ATPases. *FEBS Journal* **275**: 1427-1449.

Thanabalu, T., Rajmohan, R., Meng, L., Ren, G., Vajjhala, P.R., and Munn, A.L. (2007). Verprolin function in endocytosis and actin organisation: roles of the Las17p (yeast WASP)-binding domain and a novel C-terminal actin-binding domain. *FEBS Journal* **274**: 4103-4125.

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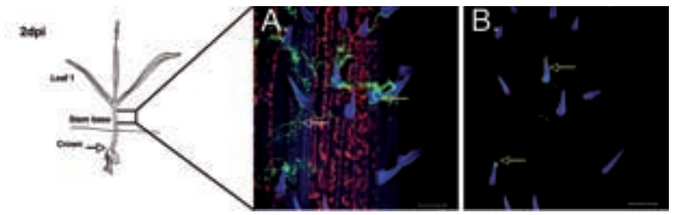
Wiradjaja, F., Ooms, L.M., Tahirovic, S., Kuhne, E., Munn, A.L., Piper, R., Mayinger, P., and Mitchell, C.A. (2007). Inactivation of the phosphoinositide phosphatases Sac1p and Inp54p leads to accumulation of phosphatidylinositol 4,5-bisphosphate on vacuole membranes and vacuolar fusion defects. *Journal of Biological Chemistry* **282**: 16295-16307.

LAB MEMBERS

Research Officer: Dr Parimala Vajjhala

PhD Students: Gang Ren, Amber Stephens (CSIRO-IMB Joint PhD Student)



Fusarium *spores germinating on wheat stem surface, highlighting the affiliation the germ tubes have for the stem hairs, growing around and up the hairs.*

The Cell Surface in Health & Disease

Rob Parton

Our group is interested in the organisation, dynamics, and functions of the plasma membrane. The properties of the plasma membrane rely on the specialisation of the plasma membrane into microdomains of specific function. We have particularly focused our attention on caveolae, a fascinating domain of the cell surface with a distinct structure. Caveolae have been implicated in regulation of cell growth and in maintaining the balance of lipids in the cell. In addition, caveolae and caveolins, the major proteins of caveolae have been implicated in a number of disease states including tumour formation, atherosclerosis, and muscular dystrophy. To study caveolae function and, in particular, the link between lipid regulation and cancer, we are using caveolae-null mice, cells lacking caveolins, and zebrafish embryos. These systems are also being used to study the role of caveolae in muscle and the molecular changes associated with muscular dystrophy. In 2007 we discovered a new caveolar coat protein, which regulates caveolae formation. An additional aim of our work is to understand the link between caveolae and lipid-filled organelles termed lipid droplets, which are major storage organelles involved in obesity. We have shown that caveolins are essential for the formation of lipid droplets during liver regeneration.

RESEARCH PROJECTS

- Caveolae, cancer and cholesterol: investigating the link between caveolins, cell cycle regulation and cholesterol regulation (with Professor John Hancock)
- Caveolae and caveolin-3 in muscle: analysing the role of caveolin-3 and caveolae in muscle development and in muscular dystrophy
- Caveolae and obesity: dissecting the role of caveolins and Rab proteins in lipid droplet formation and function in adipose tissue and during liver regeneration
- Caveolins and caveolin-interacting proteins in zebrafish: using zebrafish as a model system to understand the role of caveolae during development and the effect of muscular dystrophy mutants of caveolin-3 on muscle structure and function
- Clathrin-independent endocytosis: characterising the structure and function of a novel endocytic pathway in mammalian cells and the zebrafish
- Caveolae formation and structure: studying caveolae biogenesis and caveolae structure in health and disease using electron tomography (with Dr Brad Marsh) and novel cell systems

KEY PUBLICATIONS

Hill, M.M., Bastiani, M., Luetterforst, R., Nixon, S., Kirkham, M., Kirkham, A., Nixon, S.J., Walser, P., Abankwa, D., Ooschot, V.M.J., Martin, S., Hancock, J.F., and Parton, R.G. (2007). PTRF-cavin, a conserved cytoplasmic protein required for caveola formation and function. *Cell* **132**: 113-124.

Parton, R.G., and Simons, K. (2007). The multiple faces of caveolae. *Nature Reviews Molecular Cell Biology* **8**:185-194.

Fernandez, M.A., Albor, C. Ingelmo-Torres, M., Nixon, S.J., Ferguson, C., Kurzchalia, T., Tebar, F., Enrich, C., Parton, R.G., and Pol, A. (2006). Caveolin-1 is essential for liver regeneration. *Science* **313**: 1628-1632.

Kirkham, M., Fujita, A., Chadda, R., Nixon, S.J. Kurzchalia, T.V., Sharma, D.K., Pagano, R.E., Hancock, J.F., Mayor, S., and Parton, R.G. (2005). Ultrastructural identification of uncoated caveolin-independent early endocytic vehicles. *Journal of Cell Biology* **168**: 465-476.

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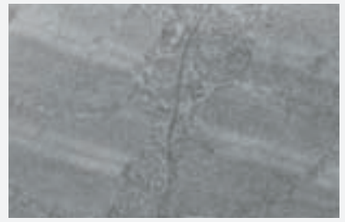
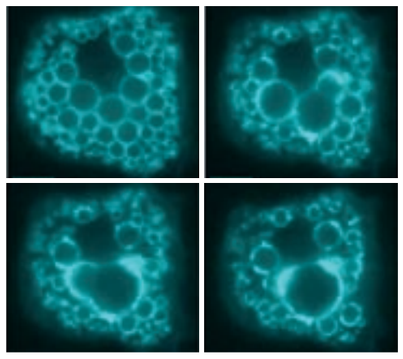


Electron micrograph of muscle in a cryofixed zebrafish embryo (collaboration with Rick Webb, CMM).



Video sequence showing fusion of lipid droplets (labelled with a blue fluorescent marker) in an adipocyte.

LAB MEMBERS

Senior Research Officer: Dr Sally Martin

Research Officers: Dr Manuel Fernandez, Dr Michelle Hill, Dr Isabel Morrow#, Dr Susan Nixon, Dr Tobias Richter, Dr Piers Walser, Dr Lars Kuerschner#, Dr Harriet Lo#

Research Assistants: Robert Luetterforst, Rachel Hancock, Nicole Schieber#

PhD Students: Mark Howes, Michele Bastiani, Samantha Murphy

Visiting Scientists: Dr. Katia Cortese, Viola Oorschot#, Dr. Cynthia Corley-Mastick#, Prof Jean Gruenberg#, Prof Gisou van der Goot#

part of year

Protein Trafficking in Human Disease

Jennifer Stow

Our research group studies protein trafficking in human and animal cells with the aim of mapping the cellular organelles and molecules that function in the secretion and endocytosis of disease-related proteins. In this work we use a range of cellular, molecular and biochemical approaches. Trafficking is a highly dynamic process and studies in this field have been greatly enhanced by the development of fluorescent probes and microscopic techniques for imaging in living cells. Live cell imaging, combined with other forms of microscopy, has thus become a major core technology for the research in our group.

In epithelial cells we are studying E-cadherin, an essential adhesion protein and a vital tumour suppressor. E-cadherin is trafficked to and from the cell surface to regulate cadherin-based cell–cell adhesion and to jointly regulate other proteins, including growth factor receptors. The pathways and molecules involved in E-cadherin trafficking have seminal roles in epithelial cell polarity, the integrity of epithelial tissues and in the transition of normal epithelial cells to cancer cells. A main goal of this work is to understand how E-cadherin trafficking functions during the opposing processes of morphogenesis and cancer progression. As a model system for these experiments we are growing epithelial cells in mini-organ cultures where the effects of gene expression or gene silencing can be analysed using fluorescence imaging and computer modelling.

Cells of the immune system secrete tightly orchestrated arrays of cytokines to control immune responses. In macrophages we are studying the secretion of pro-inflammatory cytokines such as TNF, IL-6 and IL-1. In addition to their roles in immunity, these cytokines all contribute to the onset and progression of chronic inflammatory diseases, and understanding how they are trafficked and secreted may lead to the development of new therapeutic strategies in inflammation. Gene expression arrays, live cell imaging, FACS and biochemical approaches are used to map out intracellular pathways for cytokine trafficking and secretion. Based on recent findings, we are now also studying the pathways for phagocytosis or ingestion of different microbes by macrophages.

RESEARCH PROJECTS

- Mapping trafficking pathways using live cell imaging; fluorescence imaging and 4D computer modelling
- Studying E-cadherin trafficking: morphogenesis, tubulogenesis and tumorigenesis in cyst cultures
- Investigating regulated endocytosis of E-cadherin for growth factor signalling in cancer cells
- Researching protein sorting and cell polarity in epithelial cells
- Studying trafficking and secretion of inflammatory cytokines in macrophages
- Investigating phagocytosis in macrophages

KEY PUBLICATIONS

Manderson, A.P., Kay, J.G., Hammond, L.A., Brown, D.L., and Stow, J.L. (2007). Subcompartments of the macrophage recycling endosome direct the differential secretion of IL-6 and TNFalpha. *Journal of Cell Biology* **178**: 57-69.

Bryant, D.M., Kerr, M.C., Hammond, L.A., Joseph, S.R., Mostov, K.E., Teasdale, R.D., and Stow, J.L. (2007). EGF induces macropinocytosis and SNX1-modulated recycling of E-cadherin. *Journal of Cell Science* **120**: 1818-1828.

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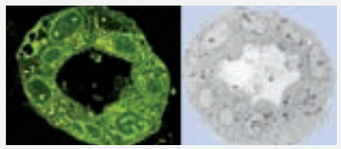
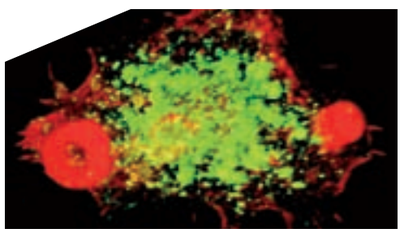
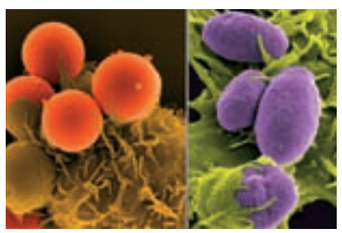
Murray, R.Z., Kay, J.G., Sangermani, D.G., and Stow, J.L. (2005). A role for the phagosome in cytokine secretion. *Science* **310**: 1492-1495.



Transmission electron micrographs of a section through human breast cancer cells.



Immunofluorescence image of a macrophage displaying large phagocytic cups (Red).



Scanning electron microscope images of macrophages ingesting foreign particles.

LAB MEMBERS:

Research Officers: Dr Fiona Wylie, Dr Esther Reefman, Dr Marion Desclozeaux, Dr Sandrine Roy, Dr Tony Manderson

Research Assistants: Darren Brown, Tatiana Khromykh, Juliana Venturato, Teresa Munchow

PhD Students: Carolin Offenhauser, Jason Kay, Daniele Sangermani, Wang Bo, Luke Hammond

Honours Students: Huong Le, Regine Pei Low

Pathogen Surveillance, Innate Immunity & Inflammation

Matt Sweet

The major research streams of this group are innate immunity, inflammation and bone biology. Our work in innate immunity focuses on elucidating the mechanisms by which macrophages sense invading pathogens. The detection of specific molecular components of bacteria, viruses, intracellular parasites and helminths by macrophages enables these cells to coordinate the most appropriate host response to deal with an infectious challenge. We have previously concentrated on the recognition of bacterial CpG-containing DNA by macrophages, but have more recently focused on elucidating the detection systems for viral DNA in the cytoplasm and helminth products at the cell surface. Characterisation of such detection systems not only allows us to understand infectious disease processes, but also provides an opportunity to modulate immune responses for therapeutic applications.

Macrophages are not only important for anti-microbial responses, but they also contribute to the pathology of both acute and chronic inflammatory diseases. Within the CRC for Chronic Inflammatory Diseases we have focused on identifying novel macrophage-expressed genes as candidate regulators of inflammation in the specific disease areas of Rheumatoid Arthritis and Chronic Obstructive Pulmonary Disease. Our focus in 2007 has been on the identification of novel secreted or cell-surface macrophage-specific proteins and our major goal for 2008 is to validate the involvement of these proteins in inflammation.

Osteoclasts are a cell lineage closely related to macrophages that have a specialised role in bone resorption and maintenance of bone homeostasis. Dysregulated osteoclast function contributes to several diseases including osteoporosis, arthritis and osteolytic bone diseases. Our group is identifying osteoclast-specific genes and characterising their contribution to the pathology of bone disease. We have also defined a novel macrophage population that is associated with bone surfaces: osteomacs. Future research is aimed at characterising osteomac function in bone biology.

RESEARCH PROJECTS

- Investigating novel genes and signalling pathways in macrophages that regulate inflammation
- Studying molecular mechanisms that enable innate immune cells to sense and respond to different types of pathogen
- Characterising prostaglandin synthases in inflammation
- Investigating regulation of gene expression in osteoclasts
- Developing novel biomaterials for use in bone repair
- Characterising osteomacs, a macrophage population associated with bone surfaces

KEY PUBLICATIONS

Schroder, K., Spille, M., Pilz, A., Lattin, J., Bode, K.A., Irvine, K.M., Burrows, A.D., Ravasi, T., Weighardt, H., Stacey, K.J., Decker, T., Hume, D.A., Dalpke, A.H., and Sweet, M.J. (2007). Differential effects of CpG DNA on IFN-beta induction and STAT1 activation in murine macrophages versus dendritic cells: alternatively activated STAT1 negatively regulates TLR signaling in macrophages. *Journal of Immunology* **179**: 3495-3503.

Meadows, N.A., Sharma, S.M., Faulkner, G.J., Ostrowski, M.C., Hume, D.A., and Cassady, A.I. (2007). The expression of Clcn7 and Ostm1 in osteoclasts is coregulated by microphthalmia transcription factor. *Journal of Biological Chemistry* **282**: 1891-1904.

Ripoll, V.M., Irvine, K.M., Ravasi, T., Sweet, M.J., and Hume, D.A. (2007). Gpnmb is induced in macrophages by IFN-gamma and lipopolysaccharide and acts as a feedback regulator of proinflammatory responses. *Journal of Immunology* **178**: 6557-6566.

Irvine, K.M., Burns, C.J., Wilks, A.F., Su, S., Hume, D.A., and Sweet, M.J. (2006). A CSF-1 receptor kinase inhibitor targets effector functions and inhibits pro-inflammatory cytokine production from murine macrophage populations. *FASEB Journal* **20**: 1921-1923.

Aung, H.T., Schroder, K., Himes, S.R., Brion, K., van Zuylen, W., Trieu, A., Suzuki, H., Hayashizaki, Y., Hume, D.A., Sweet, M.J., and Ravasi, T. (2006). LPS regulates proinflammatory gene expression in macrophages by altering histone deacetylase expression. *FASEB Journal* **20**: 1315-1327.

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LAB MEMBERS

Senior Research Fellow: Dr Ian Cassady

Senior Research Officers: Dr Ian Ross, Dr Kate Stacey, Dr Elizabeth Fowler

Research Officers: Dr Kate Irvine, Dr Dmitry Ovchinnikov, Dr Allison Pettit, Dr Liza-Jane Raggatt, Dr Jack Flanagan, Dr Kate Schroder, Dr Jodie Robinson, Dr Nicholas Meadows, Dr Vera Ripoll, Dr Tara Roberts

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Lab Manager: Greg Young

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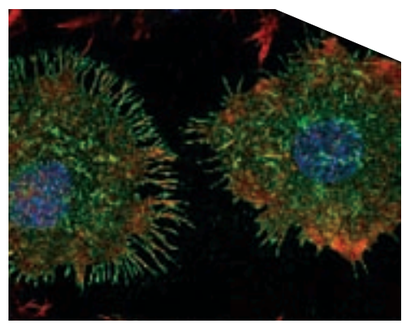
PhD Students: Andy Wu, Wendy van Zuylen, Ming Chang, Jane Lattin, Felicia Goh, Adi Haji Idris, Kylie Alexander, Angela Trieu, Melanie Andrews

Honours Students: Carol Burnton, Jessica Malcolm, Larisa Labzin

Undergraduate Students: Hanneke Peeters, Rachel Thijssen



Plasma membrane localisation of a macrophage-specific protein

Role Of Growth Hormone & Related Cytokines in Growth, Cancer, Metabolism & Obesity

Mike Waters

Adult height is determined by the actions of growth hormone (GH) during childhood and adolescence. In the adult, growth hormone is an important metabolic agent regulating body composition, opposing the actions of insulin. In old age, growth hormone status determines lifespan, at least in animal models. We study the means used by growth hormone to achieve these changes, using a variety of approaches directed to the growth hormone receptor, from high-resolution protein structures to genetically engineered animals.

The growth hormone receptor determines the degree of the cell response to growth hormone, which we originally cloned collaboratively with Genentech. Through FRET, BRET, crystallography and targeted mutagenesis we have developed a new model of how the GH receptor is activated by GH, involving realignment of receptor subunits within a constitutive dimer. An extension of this model describes how a rearrangement of an extracellular b-loop of the GH receptor selectively controls ERK activation without influencing Stat5 activation through the use of an alternate: Src kinase.

By creating targeted knock-in mutations to signalling domains within the GH receptor cytoplasmic domain, we have shown that enhancement of postnatal somatic growth by GH is dependent on its ability to activate the transcription factor Stat5. Because these mice become strikingly obese after six months of age, we are currently investigating the role of Stat5a/b in control of lipid and carbohydrate metabolism using tissue-targeted gene deletion of Stat5a/b.

The surprising finding that the growth hormone receptor is located in the cell nucleus of dividing cells has led us to discover that nuclear localising the receptor artificially can result in cancer. The mechanism involved is being actively pursued as a potential therapeutic target, and complements the recent realisation that GH acts as a tumour promoter.

Modulation of target tissue response to hormone stimulation is an important aspect of physiology. Regulation of reproductive function is particularly dependent on levels of expression of the SOCS genes, which determine tissue sensitivity to GH and the related cytokine, prolactin. In this context, we study the roles of CIS and SOCS-3 and their regulation in control of reproductive function, and in the etiology of breast cancer.

RESEARCH PROJECTS

- Investigating the mechanism of activation of growth hormone and related cytokine receptors
- Researching the role of nuclear localised growth hormone receptor in cell proliferation and oncogenesis
- Researching the role of GH-dependent Stat5 in lipid and carbohydrate metabolism
- Researching the role of suppressors of cytokine signalling in prolactin and GH physiology
- Researching the role of GH in promoting breast and prostatic cancer

KEY PUBLICATIONS

Barclay, J.L., Anderson, S.T., Waters, M.J., and Curlewis, J.D. (2007). Regulation of Suppressor of cytokine signalling-3 by GH in pro-B cells. *Molecular Endocrinology* **21**: 2503-2515.

Conway-Campbell, B.L., Wooh, J.W., Brooks, A.J., Gordon, D., Brown, R.J., Lichanska, A.M., Chin, H.S., Barton, C.L., Boyle, G.M., Parsons, P.G., Jans, D.A., and Waters, M.J. (2007). Nuclear targeting of the growth hormone receptor results in dysregulation of cell proliferation and tumorigenesis. *Proceedings of the National Academy of Sciences USA* **104**: 13331-13336.

Waters, M.J., and Barclay, J.L. (2007). Does GH drive breast and other cancers? *Endocrinology* **148**: 4533-4535.

Anderson, S.T., Barclay, J.L., Fanning, K.J., Kusters, D.H., Waters, M.J., and Curlewis, J.D. (2006). Mechanisms underlying the diminished sensitivity to prolactin negative feedback during lactation: reduced Stat5 signalling and upregulation of CIS expression in tuberoinfundibular dopaminergic neurons. *Endocrinology* **147**: 1195-1202.

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Brown, R.J., Adams, J.J., Pelekanos, R.A., Wan, Y., McKinstry, W.J., Palethorpe, K., Seeber, R.M., Monks, T.A., Eidne, K.A., Parker, M.W., and Waters, M.J. (2005). Model for growth hormone receptor activation based on subunit rotation within a receptor dimer. *Nature Structural & Molecular Biology* **12**: 814-821.

Rowland, J.E., Lichanska, A.M., Kerr, L.M., White, M., D'Aniello, E., Maher, S.L., Brown, R.J., Teasdale, R., Noakes, P.G., and Waters, M.J. (2005). In vivo analysis of growth hormone receptor signalling domains and their associated transcripts. *Molecular and Cellular Biology* **25**: 66-77.

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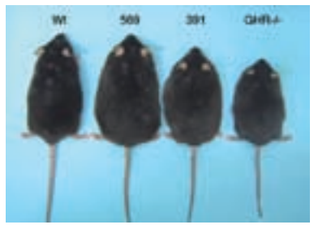
LAB MEMBERS

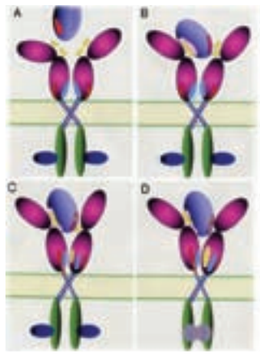
Research Officers: Dr Andrew Brooks, Dr Johanna Barclay, Dr Tim McPhee

Visiting Research Fellow: Dr Mayumi Ishikawa

Research Assistants: Kathryn Tunny, Linda Kerr



Marked adiposity in mature male mice lacking growth hormone receptor (GHR-/-), lacking ability to generate STAT5 in response to GH (receptor truncated at 391), or able to generate only 30% of the normal STAT5 response to GH (receptor truncated at 569).



Diagrammatic representation of mechanism of growth hormone receptor activation by hormone binding. The hormone possesses two receptor binding sites which are asymmetrically placed. Engagement of both receptor binding sites by the hormone results in the relative rotation of the receptor subunits, rotating the associated JAK2 kinases together so that they can cross-phosphorylate and autoactivate, initiating signalling.

Cadherin Adhesion & Tissue Organisation: Molecular Mechanisms & Morphogenetic Consequences

Alpha Yap

Cells are the building blocks of our bodies. Interactions between different cells are important to shape our developing bodies, and a range of diseases occur when those interactions are disturbed, including cancer and inflammation. My laboratory studies one set of cell-to-cell interactions, those that occur when cells attach to one another. We focus on the cadherin family of cell-cell adhesion receptors. These critically determine the ability of cells to recognise one another and organise into coherent tissues. The importance of these receptors is emphasised by the fact that loss of cadherin function promotes cancer progression in epithelial tissues (such as the breast and colon) – the commonest form of human cancers. By understanding the basic biological mechanisms of cadherin-mediated cell recognition we thus hope to provide vital insights into the basis of developmental patterning and common human diseases.

Currently we focus on understanding how cadherins cooperate with the actin cytoskeleton, long believed to be central to cadherin function. Our experience makes it increasingly clear that this cooperation involves a complex interplay between adhesion receptors and diverse distinct states of the cytoskeleton that are coordinated by a variety of signalling pathways at the cell membrane. In particular, our work demonstrates that cadherins function as adhesion-activated cell signalling receptors that stimulate pathways to regulate the actin cytoskeleton, thereby influencing cell shape, adhesion, and cell-cell cohesion. Relevant signals include the Rho family GTPases, Src family kinases and PI3-kinase. These affect a range of cytoskeletal regulators, including actin nucleators, cross-linking proteins, scaffolds and the myosins II and VI.

RESEARCH PROJECTS

- Cadherin-activated cell signalling: coordinating protein and lipid kinases at cell adhesions
- Analysing Arp2/3 activity at cadherin contacts: molecular regulators and functional consequences
- Regulation of the actin cytoskeleton by E-cadherin
- Cooperation between cadherins and Myosin motors at cell-cell contacts
- Cooperativity between cadherins and microtubules
- The morphogenetic consequences of cadherin-activated cell signalling and cooperativity with the actin cytoskeleton

KEY PUBLICATIONS

Maddugoda, M.P., Crampton, M.S., Shewan, A.M., and Yap, A.S. (2007). Myosin VI and vinculin cooperate during the morphogenesis of cadherin cell-cell contacts in mammalian epithelial cells. *Journal of Cell Biology* **178**: 529-540.

McLachlan, R.W., Kraemer, A., Helwani, F.M., Kovacs, E.M., and Yap, A.S. (2007). E-Cadherin adhesion activates c-Src signaling at cell-cell contacts. *Molecular Biology of the Cell* **18**: 3214-3223.

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Stehbens, S.J.*, Paterson*, A.D., Crampton, M.S., Shewan, A.M., Ferguson, C., Akhmanova, A., Parton, R.G., and Yap, A.S. (2006). Dynamic microtubules regulate the local accumulation of E-cadherin and activity of Myosin 2 at cell-cell contacts. *Journal of Cell Science* **119**: 1801-1811. (*Equal contributions.)

Shewan, A.M., Maddugoda, M., Kraemer, A., Stehbens, S.J., Verma, S., Kovacs, E.M., and Yap, A.S. (2005). Myosin 2 is a key target for Rho kinase necessary for the local concentration of E-cadherin at cell-cell contacts. *Molecular Biology of the Cell* **16**: 4531-4542.

Helwani, F.M.*, Kovacs*, E.M., Paterson, A.D., Verma, S., Ali, R.G., Fanning, A.S., Weed, S.A., and Yap, A.S. (2004). Cortactin is necessary for E-cadherin-mediated contact formation and actin organization. *Journal of Cell Biology* **164**: 899-910. (*Equal contributions.)

Verma, S., Shewan, A.M., Scott, J.A., den Elzen, N.R., Helwani, F.M., Miki, H., Takenawa, T., and Yap, A.S. (2004). Arp 2/3 activity is necessary for efficient extension of cadherin adhesive contacts. *Journal of Biological Chemistry* **279**: 34062-34070.

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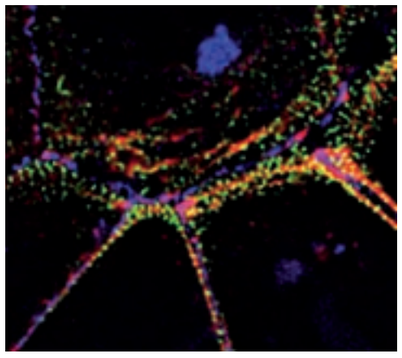
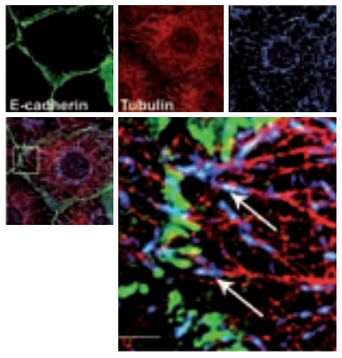
Kovacs, E.M., Goodwin, M., Ali, R.G., Paterson, A.D., and Yap, A.S. (2002). Cadherin-directed actin assembly: E-cadherin physically associates with the Arp 2/3 complex to direct actin assembly in nascent adhesive contacts. *Current Biology* **12**: 379-382.





LAB MEMBERS

Research Officers: Dr Nicole den Elzen, Dr Matthew Crampton, Dr Michael Smutny

Research Assistants: Suzie Verma, Carmen Buttery

PhD Students: Madhavi Maddugoda, Angela Jeanes, Robert McLachlan, Sabine Mangold, Samantha Stehbens

Left Picture: Myson II (green) accumulates with actin filaments (red) at E-cadherin cell-cell adhesions (blue).

Right Picture: Microtubules (red) decorated at the ends with CLIP170 (blue) extend into E-cadherin adhesions (green).

Design & Discovery of Bioactive Peptides & Proteins

Paul Alewood

The overall focus in the group (www.uq.edu.au/alewood/) is the identification of bioactive molecules that have the potential to play important roles in human health and wellbeing. Some specific interests include: the discovery and total synthesis of potent and selective peptides (toxins) from Australia's venomous creatures; the chemical synthesis of proteins and bioactive peptides; development of new synthetic and analytical chemistry; and protein structure and function. Special emphasis is placed on determining the structure-function relationships of natural and designed molecules. Current research programs involve: the discovery, isolation and characterisation of toxins from snakes, spiders, cone snails, platypus, ticks and scorpions; mimetics of calcium-binding inflammatory proteins from the S100 class; the chemical engineering of disulfide-rich peptides and proteases; elucidating the structure and function of milk proteins and their role in human health; and uncovering new pain pathways in chronic pain. This has led to the development of three new classes of drugs addressing chronic pain and congestive heart failure.

RESEARCH PROJECTS

- Identification and characterisation of novel peptides from Australian animals that target ion channels, transporters and receptors
- Dissecting pain pathways with receptor-selective toxins
- Antiinflammatory protein mimetics
- Discovery of new bioactive peptides and proteins from bovine and human milk
- Development of enabling new synthetic chemistry to access disulfide-rich peptides and small bioactive proteins and enzymes (up to 200 residues)
- Design and synthesis of novel molecules that mimic peptide structure and function (peptidomimetics)

KEY PUBLICATIONS

Dutertre, S., Ulens, C., Büttner, R., Fish, A., van Elk, R., Kendel, Y., Hopping, G., Alewood, P.F., Schroeder, C., Nicke, A., Smit, A.B., Sixma, T.K., and Lewis, R.J. (2007). AChBP-targeted α-conotoxin correlates distinct binding orientations with nAChR subtype selectivity. *EMBO Journal* **26**: 3858-3867.

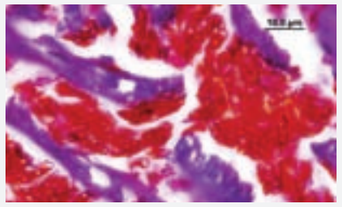
Lewis, R.J., Schroeder, C.I., Ekberg, J., Nielsen, K.J., Loughnan, M., Thoma, L., Adams, D., Drinkwater, R., Adams, D.J., and Alewood, P.F. (2007). Isolation and structure-activity of mu-conotoxin TIIIA. A Potent Inhibitor of Tetrodotoxin-Sensitive Voltage-Gated Sodium Channels. *Molecular Pharmacology* **71**: 676-685.

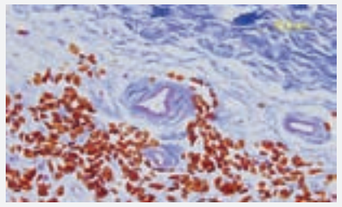
Armishaw, C.J., Daly, N., Nevin, S., Adams, D.J., Craik, D.J., and Alewood, P.F. (2006). Alpha-selenoconotoxins: A new class of potent alpha 7 neuronal nicotinic receptor antagonists. *Journal of Biological Chemistry* **281**: 14136-14143.

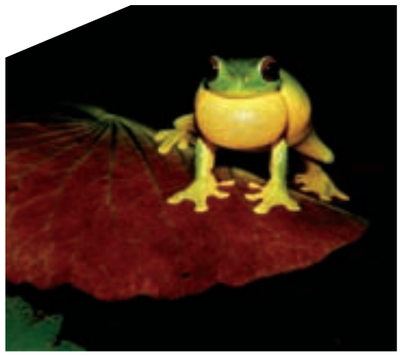
Holland, J.W., Deeth, H.C., and Alewood, P.F. (2006). Resolution and characterisation of multiple isoforms of bovine k-casein following by 2-DE a reversible cysteine-tagging enrichment strategy. *Proteomics* **6**: 3087-3095.

Fry, B.G., Wickramaratana, J.C., Lemme, S., Beuve, A., Garbers, D., Hodgson, W.C., and Alewood, P.F. (2005). Novel natriuretic peptides from the venom of the inland taipan *(Oxyuranus microlepidotus)*: isolation, chemical and biological characterization. *Biochemical and biophysical research communications* **327**: 1011-1015.

Sharpe, I., Gehrmann, J., Loughnan, M., Thomas, L., Adams, D., Atkins, A., Craik, D.J., Adams, D., Alewood, P.F., and Lewis, R.J. (2001). Two new classes of conopeptides inhibit the alpha1-adrenoceptor and the noradrenaline transporter. *Nature Neuroscience* **4**: 902-907.







LAB MEMBERS

Research Manager: Dianne Alewood

Senior Research Officer: John Holland

Research Officers: Dr Gene Hopping, Dr Aline Dantas, Dr Andrea Vernal, Dr Raj Gupta, Dr Tom Durek, Dr Lachlan Rash, Dr Jean Jin, Dr Marion Loughnan, Dr Boris Zhang

Research Assistants: Aaron Poth, Zoltan Dekan

PhD Students: Marcus Muttenthaler, Rod Morales, Jen Smith, Kalyani Abondi

Visiting Students: Len Sorensen (Danish Pharmaceutical University), Debby Feytens (Free University of Belgium)

Biodiscovery: From Biodiversity & Biology to Bioactives & Beyond

Rob Capon

The Capon research group (CMB) has a thematic biodiscovery focus that employs a collaborative multi-disciplinary approach to exploring Australian biodiversity to discover valuable molecular products that have potential application as pharmaceuticals and research tools. Specialists in the acquisition, detection, isolation, structure elucidation and synthesis of bioactive molecules, the research group is well equipped with modern chromatographic and spectroscopic technologies, and innovative chemical and biological approaches to molecular discovery. The breadth of biodiversity explored ranges across terrestrial and marine ecosystems, and includes plants, animals and microbes. The array of novel molecules studied is equally broad, and extends across all biosynthetic classes and includes many molecules with unprecedented structural features, and a wide spectrum of biological properties. Working in close collaboration with colleagues across academia, industry and government, within Australia and internationally, Professor Capon and his team address key areas of opportunity and need, based around specific diseases and therapeutic indications. With support from the Queensland Government, Professor Capon is also leading a research initiative that seeks to use knowledge of chemical ecology as a means to control invasive pests, with a particular emphasis on the cane toad. The Capon group has a strong multinational flavour with research collaborations into Spain, Denmark, New Zealand and the USA, and with members of the research team drawn from many countries across the Asia-Pacific region and Europe.

RESEARCH PROJECTS

- Detecting, isolating, characterising and elucidating the structure of novel bioactive metabolites from Australian marine and terrestrial biodiversity
- Biomimetically synthesising novel bioactive metabolites
- Bio-evaluating and SAR of novel bioactive metabolites against the indications of: **bacterial infection** *(non-cytotoxic control of virulence factors),* **fungal infection** (*synergists of azole antifungals),* **parasitic infection** *(gastrointestinal nematodes),* **viral infection** *(inhibiting infectivity),* **cancer** *(novel cytotoxins, plus selective inhibitors of K-Ras),* **diabetes** (*controlling beta and stem cell differentiation),* **pain** *(ion channel and opioid agonists and antagonists)* and **neurodegenerative diseases**
- Investigating cane toad chemical ecology, and developing innovative natural control solutions

KEY PUBLICATIONS

Capon, R.J., Hayes, R.A., and Grigg, G.C. In proceedings of the Cane Toad Workshop, *Cane toad chemical ecology: getting to know your enemy.*, Brisbane, **2006**; Invasive Animals Cooperative Research Centre: Brisbane, **2006**; 171-175.

Clark, B., Capon, R.J., Lacey, E., Tennant, S., and Gill, J.H. (2006). Citrinin Revisited: From Monomers to Dimers and Beyond. *Organic and Biomolecular Chemistry* **4**: 1520-1528.

Clark, B., Capon, R.J., Lacey, E., Tennant, S., and Gill, J.H. (2006). Polyenylpyrroles and polyenylfurans from an Australian isolate of the soil Ascomycete *Gymnoascus reessii. Organic Letters* **8**: 701-704.

Clark, B., Capon, R.J., Lacey, E., Tennant, S., and Gill, J.H. (2006). Quinolactacins Revisited: From Lactams to Imide and Beyond. *Organic and Biomolecular Chemistry* **4**: 1512-1519.

Ratnayake, R., Lacey, E., Tennant, S., Gill, J.H., and Capon, R.J. (2006). Isokibdelones: Novel heterocyclic polyketides from a *Kibdelosporangium* sp. *Organic Letters* **8**: 5267-5270.

Ratnayake, R., Lacey, E., Tennant, S., Gill, J.H., and Capon, R.J. (2006). Kibdelones: Novel anticancer polyketides from a rare Australian actinomycete. *Chemistry - A European Journal* **13**: 1610-1619.

HPLC installation.

LAB MEMBERS

Personal Assistant: Nadine Coleman

Research Officers: Dr Andrew Piggott, Dr Andrew Hayes, Dr Cedric Dooms, Dr Hua Zhang, Dr Frank Fontaine, Dr Kim Dastlik, Dr Xin Liu

PhD Students: Mohammed El-Nagger, Leith Fremlin, Walter Balansa, Raju Ritesh, Ranjala Ratnayake

Undergraduate Students: Caitlin Rudorfer, Kristian Dalle, Rachel Slade

Occupational Trainees: Monika Hermann, Christina Gosmann

Visiting Research Student: Kenneth Johansen

NMR & Protein Structure in Drug Design

David Craik

Our group uses NMR spectroscopy to determine the structures of proteins that are important in drug design programs and in agriculture. By elucidating the structures of biologically active proteins we are able to identify regions crucial for activity and can use this information to design new drugs. The proteins we study come from a range of animal and plant sources but are often involved in host defence. Examples include the conotoxins (venom components from marine snails) and the cyclotides (novel circular proteins from plants).

We have an interest in the discovery and structural characterisation of novel protein topologies. In particular we aim to determine the mechanisms of biosynthesis and evolutionary origin of circular proteins and to apply protein engineering principles to explore applications of circular proteins in drug design and agriculture.

We undertake protein engineering studies in which we modify protein frameworks either by "grafting" new biologically active epitopes onto them, or by stabilising them by cyclisation. We also study the protein-folding problem, i.e., how do proteins fold into the complex shapes that determine their functions?

The highlights of last year included our isolation and characterisation of a pair of key cyclic peptide-processing enzymes (asparaginyl endoprotease and peptide disulfide isomerase) and our identification of potential common processing mechanisms of circular proteins across divergent plant families.

Some of the other projects on which we are currently working are outlined below:

We use computer modelling and NMR spectroscopy to design novel proteins that are stabilised for drug design applications. We then synthesise them using solid-phase peptide synthesis or recombinant molecular biology methods. We currently have molecules under development for the treatment of multiple sclerosis, cardiovascular disease, cancer and chronic pain.

Our group discovered a family of proteins called cyclotides that are exceptionally stable and appear to be a natural combinatorial protein template. We undertake fieldwork in Australia and overseas for the collection of plant species so that we can explore the diversity and evolution of this novel protein family.

By unravelling the necessary elements for the processing and cyclisation of natural cyclic peptides we are working towards being able to transfer the precursors and processing machinery into a wide range of crop plants for pharming and crop protection initiatives.

We study the structures of a range of toxins from cone snails, spiders and snakes and use this information to understand their mode of action against ion-channels and other receptors.

With our collaborator, Professor Marilyn Anderson of La Trobe University, we are studying the structure-activity relationships of naturally occurring proteins involved in plant defense against insect attack.

Variations in the chemical composition of physiological fluids are being analysed by NMR spectroscopy to study the diagnosis and underlying causes of such diverse conditions as schizophrenia, growth defects and obesity.

RESEARCH PROJECTS

- Bioengineering circular proteins
- Discovering new circular proteins
- Pharming cyclic peptides
- Studying the structure-activity relationship of toxins
- Investigating plant proteinase inhibitors
- Conducting metabolomic screening

KEY PUBLICATIONS

Craik, D.J., and Adams, D.J. (2007). Chemical modifications of conotoxins to improve stability and activity. *ACS Chemical Biology* **2**: 457-468.

Craik, D.J., Cemazar, M., and Daly, N.L. (2007). The chemistry and biology of cyclotides. *Current Opinion in Drug Discovery and Development* **10**: 176-184.

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Gillon, A.D., Saska, I., Jennings, C.V., Renda, R.F., Craik, D.J., and Anderson, M.A. (2007). Biosynthesis of circular proteins in plants. *The Plant Journal* **53**: 505-515.

Greenwood, K.P., Daly, N.L., Brown, D.L., Stow, J.L., and Craik, D.J. (2007). The cyclic cystine knot miniprotein MCoTI-II is internalized into cells by macropinocytosis. *International Journal of Biochemistry and Cell Biology* **39**: 2252-2264.

Gruber, C.W., Cemazar, M., Anderson, M.A., and Craik, D.J. (2007). Insecticidal plant cyclotides and related cystine knot toxins. *Toxicon* **49**: 561-575.

Craik group photo 2007.

LAB MEMBERS

Research Officers: Dr Norelle Daly, Dr Richard Clark, Dr Horst Schirra, Dr Masa Cemazar, Dr Joshua Mylne, Dr Quenkin Kaas, Dr Jan Westerman, Dr. Ute Marx

Research Assistants: Dr Shane Simonsen, Jonas Jensen, Prascilla Tagore, Chia-Chia Tan, Emily McCallum, Jakov Kulis, Ernie Yulyaningsih

PhD Students: Laura Cascales, Philip Nguyencong, Sunithi Gunasekara, Christian Gruber, Crystal Yen-Hua Huang, David Ireland, Conan Wang, Reena Halai, Kathryn Greenwood, Ivana Saska

Masters Students: Natasha Chaduhary, Charlotta Alvarmo

Honours Students: Angeline Chan, James Lo, Shaffinaz Abdrahman, Alysha Elliot

Undergraduate Students: Andrew Kinghorn, Anzari Atic

Visitors: Dr Terry Qin, Dr Nina Tan

Chemistry & Human Therapeutics

David Fairlie

Our group works at the interface of chemistry, biology and disease. Some researchers study just chemistry, others just biology, and some work on both chemistry and biology to better understand the biology of life, ageing, disease and death.

Chemistry researchers in our group develop expertise in one or more of: computer-aided molecular and drug design; solid and solution phase organic synthesis; structure determination using NMR techniques; and interactions between small molecules, proteins, DNA and RNA. Outcomes include new chemical reactions/mechanisms/compounds, some compounds being enzyme inhibitors, protein agonists/antagonists, or structural mimics of protein surfaces.

Biology researchers in our group use our small molecules to interrogate specific protein functions on/in cells and unravel mechanisms of protein activation, biological/physiological processes, disease development, and drug action. Researchers gain insights to processes that are pivotal to human physiology or aberrant in disease, as well as interdisciplinary skills/knowledge/collaborations in enzymology, biochemistry, immunology, pharmacology, oncology, parasitology, virology and neurobiology.

RESEARCH PROJECTS

- Designing and Discovering Drugs (e.g. for GPCRs, proteases,etc)
- Synthetic Organic Chemistry (solution & solid phase)
- Determining Structure using NMR spectroscopy
- Enzymology & Molecular Pharmacology
- Investigating biological activities of small molecules that structurally mimic protein surfaces
- Studying mechanisms of disease development & drug action in human inflammatory disorders, viral or parasitic infections, cancers, neurodegenerative and cardiovascular diseases

KEY PUBLICATIONS

Blakeney, J.S., Reid, R.C., Le, G.T., and Fairlie, D.P. (2007). Nonpeptidic Ligands For Peptide-Activated GPCRs. *Chemical Reviews* **107**: 2960-3041.

Chappell, K.J., Stoermer, M.J., Fairlie, D.P., and Young, P.R. (2006). Insights to Substrate Binding and Processing by West Nile Virus NS3 Protease through Combined Modelling, Protease Mutagenesis, and Kinetic Studies. *Journal of Biological Chemistry* **281**: 38448-38458.

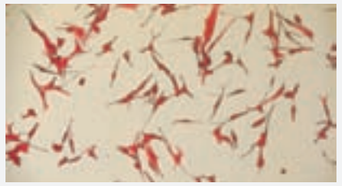
Kahnberg, P., Lucke, A.J., Glenn, M.P., Boyle, G.M., Tyndall, J.D.A., Parsons, P.G., and Fairlie, D. P. (2006). Design, Synthesis, Potency and Cytoselectivity Of Anticancer Agents Derived By Parallel Synthesis From Alpha-Aminosuberic Acid. *Journal of Medicinal Chemistry* **49**: 7611-7622.

Levick, S., Loch, D., Rolfe, B., Reid, R.C., Fairlie, D.P., Taylor, S.M., and Brown, L. (2006). Antifibrotic Activity of an Inhibitor of Group IIa Secretory Phospholipase A2 in Young Spontaneously Hypertensive Rats. *Journal of Immunology* **176**: 7000-7007.

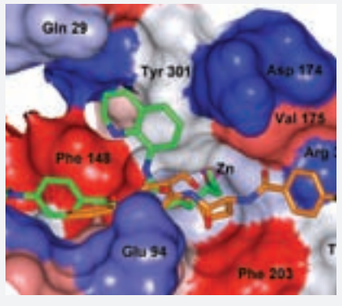
Shepherd, N.E., Hoang, H.N., Desai, V.S., Letouze, E., Young, P.R., and Fairlie D.P. (2006). Modular Alpha Helical Mimetics With Antiviral Activity Against Respiratory Syncitial Virus. *Journal of the American Chemical Society* **128**: 13284-13289.

Singh, Y., Stoermer, M.J., Lucke, A., Guthrie, T., and Fairlie, D.P. (2005). Structural Mimicry of Two Cytochrome b562 Interhelical Loops Using Macrocycles Constrained By Oxazoles and Thiazoles. *Journal of the American Chemical Society* **127**: 6563-6572.

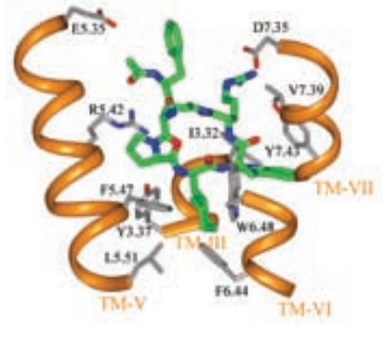
March, D.R., Proctor, L.M., Stoermer, M.J., Sbaglia, R., Abbenante, G., Reid, R.C., Wadi, K., Paczkowski, N., Tyndall, J.D.A., Taylor, S.M., and Fairlie, D.P. (2004). Potent Cyclic Antagonists Of The Complement C5a Receptor On Human Polymorphonuclear Leukocytes. Relationships Between Structures and Activity. *Molecular Pharmacology* **65**: 868-879.



Human MM96L melanoma cells treated with novel differentiating drug.



Human histone deacetylase bound to novel anticancer inhibitors.



Human GPCR receptor bound to novel anti-inflammatory antagonist.

LAB MEMBERS

Senior Research Officers: Dr John Abbenante, Dr Robert Reid, Dr Yogendra Singh, Dr Martin Stoermer

Research Officers: Dr Huy Hoang, Dr Giang Le, Dr Andrew Lucke, Dr Reik Löser, Dr Gloria Ruiz Gómez, Dr Conor Scully, Dr Nick Shepherd

PhD Students: Grant Barry, Jade Blakeney, Gavin Bryant, Renee Beyer, Russell Driver, Maria Halili, Dhiraj Hans, Rose Harrison, Praveen Madala, Ranee Singh, Jacky Suen

Masters Student: Praveer Gupta, Nicole Wheatley

Honours Students: Adam Crompton, Adam Cotterell

Undergraduate Students: Bruce Chau, Simon Chen, Ya-Mi Chuang, Kristian Dalle, Patricia Garcia

Structural Biology of Membrane Proteins, Macromolecular Assemblies & Viruses

Ben Hankamer

Determining the structures of membrane proteins, macromolecular assemblies and viruses is one of the great challenges of cell and structural biology. Using advanced high-resolution cryo-electron microscopes it is now possible to capture atomic-resolution information of biological macromolecules. However, as the captured images are inherently 'noisy', this information must be recovered by aligning many copies of the protein (10 000 – 1 000 000 individual molecules) either computationally (by single particle analysis), or biochemically (via crystallography).

As part of the IMB's Visible Cell™ project we have established a powerful single particle analysis pipeline, as well as new biotechnologies for template assisted 2D crystal production. The single particle process involves merging large numbers of 2D projection images of randomly oriented molecules to calculate 3D reconstructions. Our current benchmark resolution is ~10 Å at which individual α-helices are visualised, and we are actively developing processes to improve this further. In parallel we are developing detergent-resistant 2D templates that chelate Ni at the surface, to facilitate the systematic production of 2D crystals of tethered His-tagged membrane proteins. Using these twin approaches we are studying a wide range of important membrane proteins (e.g. photosynthetic membrane protein complexes, ATPases, mechanosensitive channels), macromolecular assemblies (AAA ATPases and related proteins, ferritin) and icosahedral viruses. These structures provide fundamental new insights into many fascinating molecular machines and feed into the Visible Cell™ project. These technologies are also being used to develop new bio-fuel production systems within the Solar Bio-fuels consortium.

The Solar Bio-fuels consortium (www.solarbiofuels.org), co-directed by Ben Hankamer, has brought together an international team of specialists to develop high-efficiency second-generation bio-fuel production systems using microalgae. This represents a rapidly expanding area of biotechnology of global significance. Our specialisation is the structural biology and biochemistry of the photosynthetic machinery, which drives the first step of converting solar energy into chemical energy (fuels). Consequently its optimisation offers significant downstream benefits for all bio-fuel production systems (bio-ethanol, bio-diesel, BTL diesel, bio-H_2 and bio-methane). With colleagues, we are now taking the 'Visible Cell' approach to develop a 3D atlas of the photosynthetic machinery within the cellular context. This 3D atlas will assist in the fine-tuning of the light capture and conversion processes of photosynthesis, just as a manual is required to tune the engine of a car.

RESEARCH PROJECTS

- High-Resolution Single Particle Analysis: Biology, Physics and software development
- The Visible Cell™ Project: Resolving the 3D structure of the macromolecular assemblies
- Template mediated 2D crystallisation: Towards streamlined membrane protein crystallisation
- Second-generation micro-algal bio-fuel systems: Development of bio-fuels systems for bio-H_2, bio-diesel and BTL-diesel production that are coupled to CO_2 sequestration

KEY PUBLICATIONS

Hankamer, B.D., Elderkin, S.L., Buck, M., and Nield, J. (2004). Organization of the AAA(+) adaptor protein PspA is an oligomeric ring. *Journal of Biological Chemistry* **279**: 8862-8866.

Iwata, M., Imamura, H., Stambouli, E., Ikeda, C., Tamakoshi, M., Nagata, K., Makyio, H., Hankamer, B., Barber, J., Yoshida, M., Yokoyama, K., and Iwata, S. (2004). Crystal structure of a central stalk subunit C and reversible association/dissociation of vacuole-type ATPase. *Proceedings of the National Academy of Science USA* **101**: 59-64.

Kruse, O., Rupprecht, J., Bader, K., Thomas-Hall, S., Schenk, P., Finazzi, G., and Hankamer, B. (2005). Improved photobiological H-2 production in engineered green algal cells. *Journal of Biological Chemistry* **280**: 34170-34177.

Mussgnug, J., Thomas-Hall, S., Rupprecht, J., Foo, A., Klassen, V., McDowall, A., Schenk, P., Kruse, O., and Hankamer, B. (2007). Engineering photosynthetic light capture: Impacts on improved solar energy to biomass conversion. *Plant Biotechnology Journal* **5**: 802-814.

Woolford, D., Ericksson, G., Rothnagel, R., Muller, D., Landsberg, M., Pantelic, R., McDowall, A., Pailthorpe, B., Young, P., Hankamer, B., and Banks, J. (2007). Swarm(PS): Rapid, semi-automated single particle selection software. *Journal of Structural Biology* **157**: 174-188.

Pantelic, R., Ericksson, G., Hamilton, N., and Hankamer, B. (2007). Bilateral Edge Filter: Photometrically weighted, discontinuity based edge detection. *Journal of Structural Biology* **160**: 93-102.

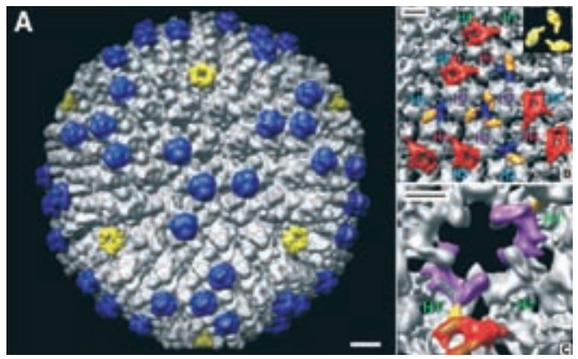
LAB MEMBERS

Research Officers: Dr Michael Landsberg, Rosalba Rothnagel

PhD Students: Radosav Pantelic, Evan Stephens, Matthew Timmins, Drew Ringsmuth, Erin Ahern, Winnie Waudo

MSc Students: Alizeé Malnoë

Honours Students: Emily Knauth, Lysha Lim, Robert Burnside, Anabelle Lindley, David Floyd (4th year biotech)



Bugs & Drugs: Rational Development of Novel Antibiotics & Environmentally Friendly Insecticides

Glenn King

Research in my laboratory is aimed at the development of novel pharmaceutical agents and environmentally friendly insecticides. Approximately half of the group is studying bacterial cytokinesis or signalling by bacterial histidine kinases in order to provide a molecular understanding of these key biological processes and to establish a platform for the development of novel antimicrobial agents. The remainder of the group is focused on developing novel antinociceptive agents and environmentally friendly insecticides by harnessing the remarkable chemical diversity encoded in the venoms of spiders. Most research projects are highly interdisciplinary and the experimental techniques employed range from molecular biology through protein chemistry to structure determination using NMR spectroscopy and X-ray crystallography. Research in the lab is currently funded by three ARC and four NHMRC research grants.

RESEARCH PROJECTS

- Developing novel antibiotics targeted against Gram-positive pathogens
- Investigating the architecture and function of the bacterial cell division machinery
- Using tarantula toxins to characterise ion channels involved in sensing pain
- Developing environmentally friendly insecticides based on spider-venom peptides

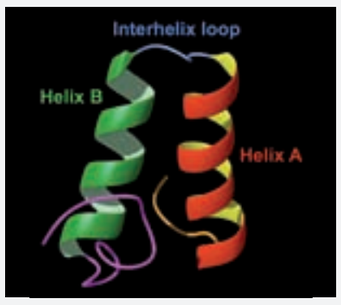
KEY PUBLICATIONS

Gorbatyuk, V.Y., Nosworthy, N.J., Robson, S.A., Bains, N.P.S., Maciejewski, M.W., dos Remedios, C.G., and King, G.F. (2006). Mapping the phosphoinositide-binding site on chick cofilin explains how PIP2 regulates the cofilin-actin interaction. *Molecular Cell* **24**: 511–522.

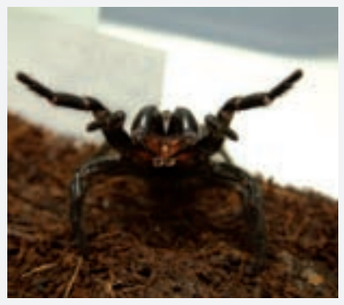
Robson, S.A., and King, G.F. (2006). Domain architecture and structure of the bacterial cell division protein DivIB. *Proceedings of the National Academy of Sciences USA* **103**: 6700–6705.

Rowland, S.L., Burkholder, W.F., Cunningham, K.A., Maciejewski, M.W., Grossman, A.D., and King, G.F. (2004). Structure and mechanism of Sda, an inhibitor of the histidine kinases that regulate initiation of sporulation in *Bacillus subtilis*. *Molecular Cell* **13**: 689–701.

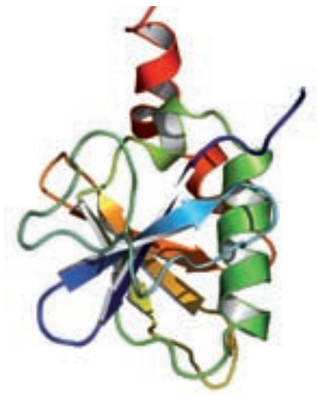
Szeto, T.H., Rowland, S.L., Rothfield, L.I., and King, G.F. (2002). Membrane localization of MinD is mediated by a C-terminal motif that is conserved across eubacteria, archaea, and chloroplasts. *Proceedings of the National Academy of Sciences USA* **99**: 15693–15698.



Structure of the Sda antikinase.



Australian funnel-web spider with venom dripping from fang tips.



Structure of the ß domain of the bacterial cell division protein DivIB.

LAB MEMBERS

Senior Research Officers: Dr Susan L. Rowland, Dr Mehdi Mobli

Research Officer: Dr David Wilson

Research Assistants: Lindsey Long, Natalie Saez

PhD students: Margaret Gentz, Kimberly Wadsworth

Undergraduate Interns: Elizabeth Bast, Tomas Miljenovic, Darshani Rapasinghe

Molecular Pharmacology of Venom Peptides

Richard Lewis

My research focuses on the discovery and characterisation of venom peptides, especially the conotoxins produced by the predatory cone snail. These highly structured peptides (mini-proteins) act at ion channels, G-protein coupled receptors and monoamine transporters found in the membranes of most cells, especially cells of the nervous system. Conopeptides make exquisite molecular tools, with some being developed as novel treatments for diseases including chronic pain. A major focus of the group is to discover new protein targets and develop peptides able to act at these targets to reduce pain sensation. This research involves the assay-guided isolation of venom peptides, peptide synthesis, tissue pharmacology, radioligand binding and electrophysiological studies, peptide structure elucidation by NMR, receptor mutagenesis, modelling, and finally co-crystal structures and docking simulations of the peptide target interaction. Xenome Ltd is developing an analogue (Xen2174) of χ-MrIA for chronic neuropathic, postsurgical and cancer pain. High-content screening approaches introduced into the lab in 2007 (using a BD Pathway 855) are expanding the array of targets through which venom peptides act. Finally, I am developing new methods for detection of the ciguatera toxins that contaminate Queensland seafood.

RESEARCH PROJECTS

- Discovering conopeptides that modify pain pathways (NHMRC)
- Determining sites of conotoxin action at the α_1-adrenoceptor and noradrenaline transporter (NHMRC)
- Studying interactions of conotoxins at nicotinic acetylcholine receptors, and calcium and sodium channels (NHMRC)
- Identifying novel anti-cancer agents from marine biodiversity (ARC)
- Identifying and characterising novel sodium channel toxins in squid and octopus (ARC)
- Discovering and characterising novel bioactives using high-content screening
- Developing venomic approaches to unravel the peptide diversity of cone snail venoms

KEY PUBLICATIONS

Dutertre, S., Ulens, C., Büttner, R., Fish, A., van Elk, R., Kendel, Y., Hopping, G., Alewood, P.F., Schroeder, C., Nicke, A., Smit, A.B., Sixma, T.K., and Lewis, R.J. (2007). AChBP-targeted α-conotoxin correlates distinct binding orientations with nAChR subtype selectivity. *EMBO Journal* **26**: 3858-3867.

Paczkowski, F.A., Sharpe, I.A., Dutertre, S., and Lewis, R.J. (2007). χ-Conopeptide and tricyclic antidepressant interactions at the norepinephrine transporter define a new transporter model. *Journal of Biological Chemistry* **282**: 17837-17844.

Ekberg, J., Jayamanne, A., Vaughan, C.W., Aslan, S., Thomas, L., Mould, J., Drinkwater, R., Baker, M.D., Abrahamsen, B., Wood, J.N., Adams, D.J., Christie, M.J., and Lewis, R.J. (2006). μO-conotoxin MrVIB selectively blocks Nav1.8 sensory neuron specific sodium channels and chronic pain without motor deficits. *Proceedings of the National Academy of Sciences USA* **103**: 17030-17035.

Nielsen, C.K., Lewis, R.J., Alewood, D., Drinkwater, R., Palant, E., Patterson, M., Yaksh, T.L., McCumber, D., and Smith, M.T. (2005). Anti-allodynic efficacy of the χ-conopeptide, Xen2174, in rats with neuropathic pain. *Pain* **118**: 112-124.

Lewis, R.J., and Garcia, M.L. (2003). Therapeutic potential of venom peptides. *Nature Reviews Drug Discovery* **2**: 790-802.

Sharpe, I.A., Gehrmann, J., Loughnan, M.L., Thomas, L., Adams, D.A., Atkins, A., Palant, E., Craik, D.J., Adams, D.F., Alewood, P.F., and Lewis, R.J. (2001). Two new classes of conopeptides inhibit the α_1 adrenoceptor and noradrenaline transporter. *Nature Neuroscience* **4**: 902-907.

*The novel analgesic χ-MrIA interacts with residues in the mouth of NET to non-competitively inhibit norepinephrine transport. NET modeled from the Leu transporter with residues affecting binding are labelled (from Paczkowski et al. J Biol Chem. **282**, 17837-17844 (2007)).*

LAB MEMBERS

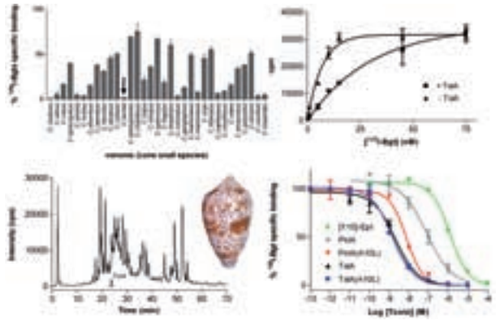
Research Officers: Dr Fil Paczkowski, Dr Lotten Ragnarsson-McGrath, Dr Marion Loughnan, Dr Aijun Yang, Dr Nira Gamage, Dr Natalie Lumsden

Research Assistants: Dianne Alewood, Jodie Major, Asa Anderson, Thea Monks, Alexis Barrett, Kim Hanchard, Jasmine Davis

PhD Students: Marco Inserra, Christine Yan, Claudia Zampata

MSc Student: Nausad Shaikh

Honours Student: Chau Phan



Isolation and characterization of α-conotoxin TxIA. (Top Left) AChBP screening for α-conotoxins in venoms of 30 species of Australian cone snails. (Bottom Left) LC-MS profile of the crude venom of Conus textile revealing TxIA. (Top Right) Saturation binding experiments revealed a competitive interaction of TxIA with Ls-AChBP. (Bottom Right) Displacement of 125I-Bgtx from Ls-AChBP by α-conotoxins TxIA, PnIA and analogues (from Dutertre et al., EMBO J 26:3858-3867 (2007)).

Protein Structure & Drug Design

Jenny Martin

Our group is driven by the need to understand the role of proteins in disease and to develop novel chemicals to modify the functions of disease-causing proteins. We use a range of biochemical and biophysical techniques to investigate the structure, function and interactions of proteins, with a particular emphasis on high-throughput protein crystallography and structure-based approaches for inhibitor design. Not surprisingly, our research this year has been enhanced enormously through the ARC LIEF-funded upgrade of the UQ ROCX Facility (see Deputy Director's report on page 7).

A major outcome over the past year or so has been the tremendous advance in our understanding of the regulation of SNARE proteins involved in insulin-stimulated trafficking of the GLUT4 glucose transporter. This process, which is critical to the regulation of blood glucose levels, is affected in Type II Diabetes. Our recent results, in collaboration with Professor David James (Garvan Institute), show that the Munc18c protein binds to a short N-terminal peptide of the SNARE syntaxin4 protein, and that this interaction stimulates SNARE ternary complex formation thereby promoting vesicle fusion (Latham et al., Traffic 2006). We then determined the structure of the Munc18c: Sx4 peptide complex showing that the N-peptide interaction is evolutionarily conserved in almost all SNARE systems (Hu et al., PNAS 2007). We are now addressing other SNARE systems and complexes to unravel the molecular mechanism(s) behind these complicated interactions.

Our long-running interest in bacterial redox folding factors led to a collaboration with Jim Bardwell (U Michigan) on the evolution of protein function in the lab, resulting in the conversion of DsbG into a DsbC-like protein by using single residue variations (Hiniker et al., PNAS 2007). We also determined the structure and evaluated the function of a DsbA enzyme from a Gram-positive organism, *S. aureus* DsbA (Heras et al., accepted in J Biol Chem) showing that *S. aureus* DsbA catalyses disulfide transfer in a manner different to that of *E. coli* DsbA. We are now focusing our attention on developing inhibitors of DsbA as potential antibacterial agents.

RESEARCH PROJECTS

- Studying the structure, function and interactions of SNARE proteins associated with insulin action
- Studying the structure, function and inhibition of redox folding factors involved in disease
- Investigating novel inflammation drug targets using high-throughput structure approaches
- Studying the structure, function and inhibition of transferase enzymes involved in disease

KEY PUBLICATIONS

Forwood, J.K., Thakur, A.S., Guncar, G., Marfori, M., Mouradov, D., Meng, W., Robinson, J., Huber, T., Kellie, S., Martin, J.L., Hume, D.A., and Kobe, B. (2007). Structural basis for recruitment of tandem hotdog domains in acyl-CoA thioesterase7 and its role in inflammation. *Proceedings of the National Academy of Sciences USA* **104**: 10382-10387.

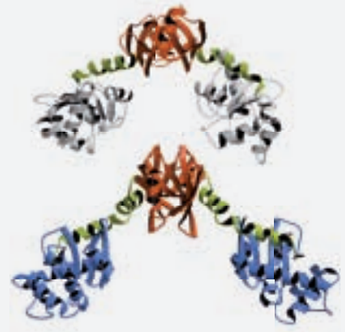
Heras, B., Kurz, M., Shouldice, S., and Martin, J.L. (2007). The Name's Bond ..... Disulfide Bond. *Current Opinion in Structural Biology* **17**: 691-698.

Hiniker, A., Ren, G., Heras, B., Zheng, Y., Laurinec, S., Jobson, R.W., Stuckey, J., Martin, J.L., and Bardwell, J.C.A. (2007). Laboratory evolution of one disulfide isomerase to resemble another. *Proceedings of the National Academy of Sciences USA* **104**: 11670-11675. (Open access)

Hu, S-H., Latham, C.F., Gee, C.L., James, D.E., and Martin, J.L. (2007). Structure of the Munc18c/Syntaxin4 N-peptide complex defines universal features of the N-peptide binding mode of SM proteins. *Proceedings of the National Academy of Sciences USA* **104**: 8773-8778.

Gruber, C., Cemazar, M., Heras, B., Martin, J.L., and Craik, D.J. (2006). Protein disulfide isomerase: The structure of oxidative folding. *Trends in Biochemical Sciences* **31**: 455-464.

Latham, C.F., Lopez, J.A., Gee, C.L., Hu, S-H., Westbury, E., Blair, D., Armishaw, C., Alewood, P.F., Bryant, N.J., James, D.E., and Martin, J.L. (2006). Molecular dissection of the Munc18c/Syntaxin4 interaction: Implications for regulation of membrane trafficking. *Traffic* **7**: 1408-1419.



LAB MEMBERS

Senior Research Officers: Dr Begoña Heras, Dr Shu-Hong Hu

Research Officers: Dr Nathan Cowieson (Australian Synchrotron Research Fellow), Dr Gordon King (SRC Crystallisation Officer), Dr Gautier Robin, Dr Stephen Shouldice (UQ Postdoctoral Fellow)

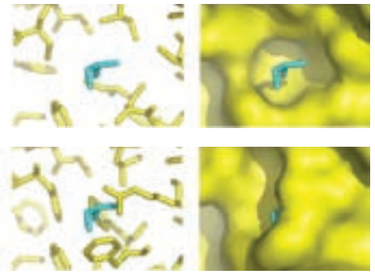
UQ ROCX X-ray Lab Manager: Karl Byriel

Research Assistants: Kevin Chen, Russell Jarrott, Patricia Walden

PhD Students: Mareike Kurz, Nyssa Drinkwater, Michelle Christie

Honours Student: Natalie Saez

Undergraduate Student: Rachel Effeney



Combinatorial Chemistry & Molecular Design

Mark Smythe

Our research focuses on advancing drug design and synthetic organic chemistry to discover novel biologically active molecules. We apply these new drug design and discovery methodologies to discover drugs to treat unmet medical needs.

Using a combination of mathematics, software development, drug design and combinatorial chemistry, we are developing new approaches to identify biologically active molecules. Such arrays of molecules are focused towards modulating therapeutic targets. Thus, projects are multidisciplinary and focused on achieving medical outcomes.

RESEARCH PROJECTS

- Modulating hematopoietic prostaglandin D2 synthase for allergic disease
- Studying antagonists of Myb for treatment of leukaemia
- Designing SHP-1 inhibitors to boost haematopoiesis
- Developing antipathogenic compounds to treat microbial infections
- Exploiting biologically relevant scaffolds
- Developing new computational algorithms and strategies for sampling biologically relevant chemistries
- Developing a synthetic process for the combinatorial synthesis of biologically relevant compounds
- Developing in vitro and cell-based assays for screening arrays of compounds

KEY PUBLICATIONS

Horton, D.A., Severinsen, R., Kofod-Hansen, M., Bourne, G.T., and Smythe, M.L. (2005). A versatile synthetic approach to peptidyl privileged structures using a safety catch linker. *Journal of Combinatorial Chemistry* **7**: 421-435.

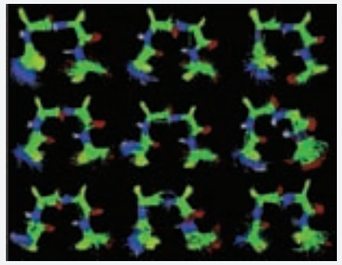
Horton, D.A., Bourne, G.T., and Smythe, M.L. (2003). The Combinatorial Synthesis of Bicyclic Privileged Structures or Privileged Substructures. *Chemical Reviews* **103**: 893-930.

Meutermans, W.D.F., Bourne, G.T., Golding, S.W., Horton, D.A., Campitelli, M.R., Craik, D., Scanlon, M., and Smythe, M.L. (2003). Difficult Macrocyclisations: New Strategies for Synthesising Highly Strained Cyclic Tetrapeptides. *Organic Letters* **5**: 2711-2714.

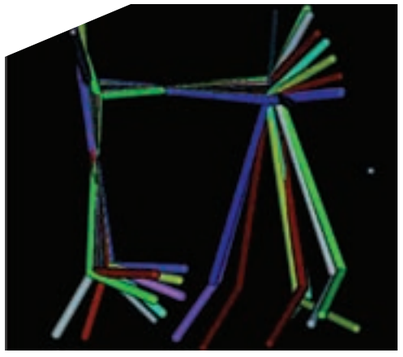
Bourne, G.T., Golding, S.W., McGeary, R.P., Meutermans, W.D.F., Jones, A., Marshall, G.R., Alewood, P.F., and Smythe, M.L. (2001). The Development and Application of a Novel Safety-Catch Linker for BOC-Based Assembly of Libraries of Cyclic Peptides. *Journal of Organic Chemistry* **66**: 7706-7713.

Meutermans, W.D.F., Golding, S. W., Bourne, G.T., Miranda, L.P., Dooley, M.J., Alewood, P.F., and Smythe, M.L. (1999). Synthesis of difficult cyclic peptides by inclusion of a novel photolabile auxiliary in a ring contraction strategy. *Journal of the American Chemical Society* **121**: 9790-9796.

ß-turns are important topological motifs for biological recognition of proteins and peptides. Nine clusters represent the topology of the side chain scaffold architecture of the vast majority of ß-turns.



The ß-turns within each of the nine clusters are superimposed onto the cluster's mean structure. The colouring schemes are: N: blue, O: red, H: white, C: green and Cß: yellow.



Superimposition of the mean structures of the nine clusters. The superimposition is based on the three atoms Ca1, Ca2 and Ca3. The colour code for each cluster is: 1-magenta, 2-red, 3-yellow, 4-green, 5-orange, 6-dark blue, 7-white, 8-light blue and 9-grey.

LAB MEMBERS

Senior Research Officers: Dr Craig Murphy, Dr Greg Bourne

Research Officer: Dr Rena Hirani, Dr Peter Bain, Dr Gerald Hartig

Research Assistants: Jill Turner, Jaimee Duncan, Angelika Christ, Christie Bentley

PhD Students: Christina Kulis, Matt Daley

Modelling & Visualising Cellular Processes

Kevin Burrage

This group works on developing simulations and visualisation methodologies for understanding the behaviour of complex cellular processes both on the plasma membrane and at the genetic regulatory level. The simulation models take into account stochastic effects, while the visualisation focuses on two or three-dimensional display.

In microscopic systems formed by living cells, the small numbers of reactant molecules can result in dynamic behaviour that is discrete and stochastic rather than continuous and deterministic. Our research introduces new classes of discrete stochastic methods that more accurately and effectively reflect the underlying cellular models.

We are also focusing on some new methods for both large-scale kinetics and spatial methods that more faithfully capture complex kinetics within the cell.

RESEARCH PROJECTS

- Developing new Monte-Carlo Simulation techniques in conjunction with the group of John Hancock and researchers at Oxford University (Dan Nicolau Jr.) that allow us to model the behaviour of lipid rafts and to investigate the effects of anomalous diffusion
- Modelling the effects of transcriptional and translational delays in a variety of genetic regulatory settings including Hes1 in mouse, and Her1/7 in somite formation in zebrafish
- Developing models for quorum sensing that describe bi-modal populations effects better than previous deterministic models
- Developing spatial models that capture complex chemical kinetics within the cell

KEY PUBLICATIONS

MacNamara, S., Burrage, K., and Sidje, R.B. (2008). Multiscale modeling of chemical kinetics via the master equation. *SIAM Journal: Multiscale Modelling and Simulation* **6**: 1146-1168.

Burrage, K., Hancock, J., Leier, A., and Nicolau Jr., D.V. (2007). Modelling and simulation techniques for Membrane Biology. *Briefings in Bioinformatics* **8**: 234-244.

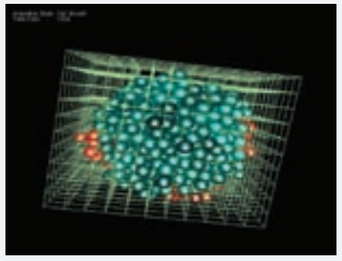
MacNamara, S., Burrage, K., and Sidje, R.B. (2007). An improved finite state projection algorithm for the numerical solution of the chemical master equation with applications. *ANZIAM Journal* **48**: C413–C435.

MacNamara, S., Burrage, K., and Sidje, R.B. (2007). Numerical methods for the chemical master equation and applications to stochastic models or receptor oligomerisation, Proceedings of the 6th International Congress on Industrial and Applied Mathematics, Zürich, 2007.

MacNamara, S., Burrage, K., and Sidje, R.B. (2007). Stochastic analysis of the VEGF receptor response curve, in T.D. Pham and X. Zhou, editors, COMPUTATIONAL MODELS FOR LIFE SCIENCES–CMLS '07: 2007 International Symposium on Computational Models of Life Sciences, pp. 238-247, AIP Conference Proceedings Volume 952, 2007. ISBN 978-0-7354-0466-3.

Marquez-Lago, T., and Burrage, K. (2007). Binomial tau-leap spatial stochastic simulation algorithm for applications in chemical kinetics. *Journal of Chemical Physics* **127**: 1.

Nicolau Jr., D.V., Burrage, K., Nicolau, D.V., and Maini, P.K. (2007). Pomitaxis: computing with Bacterial Chemotaxis. *Biosystems* In print.



A rectangular discretisation of the space occupied by the cell colony. This discretisation is used to efficiently locate nearest neighbours, done by querying neighbouring volumes as opposed to querying the entire colony itself. In collaboration with Mr David Woolford.

SGI Origin supercomputer.

LAB MEMBERS

Senior Research Officer: Dr Roger Sidje

Research Officers: Dr Andre Leier, Dr Tatiana Marquez Lago, Dr Jiangning Song, Dr Shoaib Sehgal

PhD Students: Shev MacNamara, Alhadi Bustamam, Farah Abdullah, Duncan Mortimer

Computational Neuroscience

Geoff Goodhill

Understanding how trillions of nerve cells form networks that allow us to sense, interact with and think about the world around us is one of the major scientific challenges of the 21st century. Quantitative models of brain development and function will give us a better understanding of how to treat brain disorders, recover after brain injury, and build smarter computers. Ultimately such models will inform the centuries-old question of how our genes and our environment interact to make each of us a unique individual.

We use theoretical, computational and experimental techniques to investigate the specific problem of how biological nervous systems become wired up during development. A question we are particularly interested in is how growing axons find their targets by detecting molecular gradients. Using a combination of novel experimental assays and theoretical models based on Bayes-optimal signal processing, we are probing the astonishing abilities of axons to extract directional information from noisy receptor binding signals.

Another main question we are interested in is how the statistical structure of our visual environment influences the development of the mammalian visual system. Using computational models for how neural activity affects connection strengths between neurons, we are examining how the map-like representations of visual features, such as orientation selectivity, are formed in the developing visual cortex. The lab is also involved in collaborative projects investigating sensorimotor feedback and control, and mechanisms of spatial navigation in bees, rats and robots.

RESEARCH PROJECTS

- Using in vitro assays to examine the response of nerve fibres to molecular gradients
- Building theoretical/computational models for the chemotaxis of nerve fibres, particularly those based on Bayes-optimality principles
- Building theoretical/computational models to understand how genetic and environmental factors combine to shape brain structure, particularly in the visual system
- Modelling sensorimotor control and mechanisms of spatial navigation

KEY PUBLICATIONS

Mortimer, D., Fothergill, T., Pujic, Z., Richards, L.J., and Goodhill, G.J. (2008). Growth Cone Chemotaxis. *Trends in Neuroscience* **56**: 301-311.

Giacomantonio, C.E., and Goodhill, G.J. (2007). The effect of angioscotomas on map structure in primary visual cortex. *Journal of Neuroscience* **27**: 4935-4946.

Goodhill, G.J. (2007). Contributions of theoretical modelling to the understanding of neural map development. *Neuron* **56**: 301-311.

Carreira-Perpinan, M.A., Lister, R., and Goodhill, G.J. (2005). A computational model for the development of multiple maps in primary visual cortex. *Cerebral Cortex* **15**: 1222-1233.

Goodhill, G.J., and Xu, J. (2005). The development of retinotectal maps: a review of models based on molecular gradients. *Network: Computation in Neural Systems* **16**: 5-34.

Rosoff, W.J., McAllister, R.G., Esrick, M.A., Goodhill, G.J., and Urbach, J.S. (2005). Generating controlled molecular gradients in 3D gels. *Biotechnology and Bioengineering* **91**: 754-759.

Xu, J., Rosoff, W.J., Urbach, J.S., and Goodhill, G.J. (2005). Adaptation is not required to explain the long-term response of axons to molecular gradients. *Development* **132**: 4545-4552.

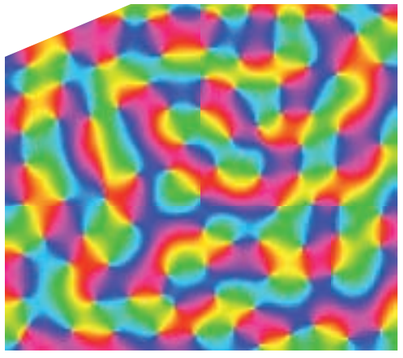
Carreira-Perpinan, M.A., and Goodhill, G.J. (2004). The influence of lateral connections on the structure of cortical maps. *Journal of Neurophysiology* **92**: 2947-2959.

Goodhill, G.J., Gu, M., and Urbach, J.S. (2004). Predicting axonal response to molecular gradients with a computational model of filopodial dynamics. *Neural Computation* **16**: 2221-2243.

Rosoff, W.J., Urbach, J.S., Esrick, M., McAllister, R.G., Richards, L.J., and Goodhill, G.J. (2004). A new chemotaxis assay shows the extreme sensitivity of axons to molecular gradients. *Nature Neuroscience* **7**: 678-682.

Goodhill, G.J. (2003). A theoretical model of axon guidance by the Robo code. *Neural Computation* **15**: 549-564.

Carreira-Perpinan, M.A., and Goodhill, G.J. (2002). Are visual cortex maps optimized for coverage? *Neural Computation* **14**: 1545-1560.



Orientation preferences of a small patch of visual cortex simulated using a self-organising algorithm based on Hebbian learning.

LAB MEMBERS

Senior Research Officer: Dr William Rosoff

Research Officers: Dr Zuc Pujic, Dr David Smith, Dr Julia Feldner

Research Assistant: Clare Giacomantonio

PhD Students: Duncan Mortimer, Jonathan Hunt

Molecular Dynamics of Biomolecular Systems

Alan Mark

The group, with members based both at The University of Queensland (UQ) and the University of Groningen, The Netherlands, (RUG), concentrates on modelling the structural and dynamic properties of biopolymers such as proteins, nucleic acids and lipid aggregates. In particular, we use computer simulations to understand and predict the macroscopic (experimentally observable) behaviour of complex biomolecular systems based on the interactions between atoms. We develop the software, atomic force fields and theoretical models needed to address a range of fundamental questions, such as: How do proteins fold? Why, in Alzheimer's Disease, BSE and some forms of Type II diabetes do specific proteins misfold, forming destructive amyloid aggregates? How do cell surface receptors transmit a signal through the cell membrane? Why does one drug molecule bind better than another?

1. Protein and peptide folding: Understanding how proteins fold is one of the grand challenges of modern biology. It is also a critical test of our ability to accurately predict interactions in protein systems. Currently, it is not possible to directly simulate the folding of proteins in atomic detail. Dramatic progress has, however, been made in the de novo folding of small peptides and the refinement of some proteins. Research on folding is conducted at multiple levels. Small model systems are used to refine force fields and simulation techniques. Designed peptides are used to help understand how peptides switch between soluble and amyloidogenic forms.

2. Cell surface receptors: These receptors play a vital role in cellular communication, and trafficking, but little is known in regard to the mechanism by which the binding of a molecule to an extracellular receptor transfers a signal across the cell membrane or how changes in the environment can activate certain surface receptors. We are, for example, investigating the mechanism by which low pH triggers the activation of the Dengue E protein, which plays a critical role in the entry of the virus into cells.

3. Lipid aggregates and membrane-protein interactions: Cell membranes are the archetypal self-organised supramolecular structure. Membrane protein complexes also represent a new frontier in structural biology. Using simulations, we are able to directly investigate how bilayers and vesicles form. We are also investigating the assembly of functional structures such as the assembly of anti-microbial peptides into transmembrane pores. This in turn is being used to understand the mechanism by which larger complexes form in heterogeneous environments.

RESEARCH PROJECTS

- Understanding protein and peptide folding
- Simulating membrane-protein interactions
- Modelling the nucleation and growth of amyloid fibrils
- Atomically simulating self-organisation in biomolecular systems

KEY PUBLICATIONS

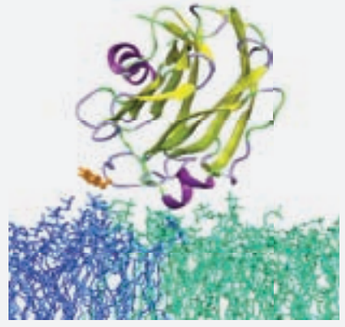
Periole, X., and Mark, A.E. (2007). Convergence and sampling efficiency in replica exchange simulations of peptide folding in explicit solvent. *Journal of Chemical Physics* **126**: 014903.

Leontiadou, H., Mark, A.E., and Marrink, S.J. (2006). Antimicrobial peptides in action. *Journal of the American Chemical Society* **128**: 12156-12161.

Fan, H., Mark, A.E., Zhu, J., and Honig, B. (2005). Comparative study of generalized Born models: Protein dynamics. *Proceedings of the National Academy of Sciences USA* **102**: 6760-6764.

Marrink, S.J., de Vries, A.H., and Mark, A.E. (2004). Coarse grained model for semiquantitative lipid simulations. *Journal of Physical Chemistry B* **108**: 750-760.

Oostenbrink, C., Villa, A., Mark, A.E., and van Gunsteren, W.F. (2004). A biomolecular force field based on the free enthalpy of hydration and solvation: The GROMOS force-field parameter sets 53A5 and 53A6. *Journal of Computational Chemistry* **25**: 1656-1676.



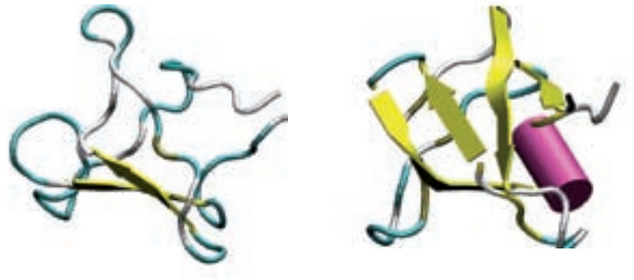
A simulation of the spontaneous binding of Equinatoxin II (a pore forming toxin from the European sea anemone, Actinia equina, L) to the interface between raft forming sphingomyeline and DPPC phospholipids.

LAB MEMBERS

Research Officers: Dr David Poger(UQ), Dr Itamar Kass (UQ), Dr Aldo Rampioni (RUG), Dr Semen Yesylevskyy (RUG), Dr Alpesh Malde (UQ), Dr Maria Ratajczak (UQ)

Administration: Chantel Potter (UQ)

PhD Students: Matthew Breeze (UQ), Ajinkya Joshi (UQ), Daniela Mueller (RUG), Ying Xue (RUG), Magdelena Siwko (RUG), Jelger Risselada (RUG)



The initial and finial configurations from a 200 ns simulation of the folding of an SH3 domain from a proposed folding intermediate. The finial structure differs from the experimental structure by only 0.18 nm backbone RMSD within experimental uncertainty.

Applied Statistics & Bioinformatics

Geoffrey McLachlan

My research in applied statistics is in the related fields of classification, cluster and discriminant analyses, data mining, image analysis, intelligent systems, machine learning, neural networks, and pattern recognition, and in the field of statistical inference. The focus in the latter field has been on the theory and applications of finite mixture models and on estimation via the E(expectation)-M(maximization) algorithm.

I am also actively involved in the field of bioinformatics with the focus on the development of methods and software for the analysis of data from high-throughput genomics projects, with particular emphasis on gene-expression profiles. The limitations of conventional methods of cancer classification and diagnosis based on the site and appearance of the tumour or organ are well-known. With microarrays allowing genome-scale measures of gene expression, attention has turned to using differences in the activity of the gene expressions (gene profiling) to classify and diagnose tumours. However, the complexity of tumours makes it likely that a diagnostic test will be based on marker profiles rather than individual markers. But the identification of relevant subsets of the genes has its challenges, because typically thousands of gene expression levels are available from only tens of patients. It means that off-the-shelf methods of statistical analysis cannot be implemented, at least not without serious modifications. Thus, there is a need for new methodologies to be able to process thousands of genes with the aim of finding those genes that are biologically heterogeneous and therefore potential markers for cancer type, treatment therapies, or clinical outcomes.

RESEARCH PROJECTS

- Statistical modelling via finite mixture models, including methods for the detection of differentially expressed genes in different treatment classes or in time-course studies
- Analysing the statistics of microarray gene-expression data for the development of disease diagnostics
- Developing diagnostic methods for cancer, using multiple molecular indices in conjunction with clinical factors

KEY PUBLICATIONS

Baek, J., Son, Y.S., and McLachlan, G.J. (2007). Segmentation and intensity estimation of microarray images using a gamma-t mixture model. *Bioinformatics* **23**: 458-465.

Do, K.-A., McLachlan, G.J., Bean, R.W., and Wen, S. (2007). Application of gene shaving and mixture models to cluster microarray gene expression data. *Cancer Informatics* **2**: 1-19.

McLachlan, G.J., Chevelu, J., and Zhu, J. (2007). Correcting for selection bias via cross-validation in the classification of microarray data. In Beyond Parametrics in Interdisciplinary Research: A Festschrift to P.K. Sen, N. Balakrishnan, E. Pena, and M.J. Silvapulle (Eds.). IMS Lecture Notes-Monograph Series, Hayward, California, pp. 383-395.

McLachlan, G.J., Bean, R.W., and Ben-Tovim Jones, L. (2006). A simple implementation of a normal mixture approach to differential gene expression in multiclass microarrays. *Bioinformatics* **22**: 1608-1615.

Ng, S.K., McLachlan, G.J., Wang, K., Ben-Tovim, L., and Ng, S.W. (2006). A mixture model with random-effects components for clustering correlated gene-expression profiles. *Bioinformatics* **22**: 1745-1752

Ben-Tovim Jones, L., Ng, S.K., Ambroise, C., Monico, K., Khan, N., and McLachlan, G.J. (2005). Use of microarray data via model-based classification in the study and prediction of survival from lung cancer. In Methods of Microarray Data Analysis IV JS Shoemaker & SM Lin (Eds.) New York: Springer, pp. 163-173.

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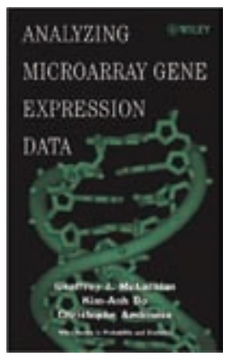
McLachlan, G.J., Bean, R.W., and Peel, D. (2002). A mixture model-based approach to the clustering of microarray expression data. *Bioinformatics* **18**: 413-422.

LAB MEMBERS

Research Officers: Dr Ian Wood, Lloyd Flack

PhD Students: Justin Zhu, Katrina Monico



Books that Professor McLachlan has edited or to which he has contributed.

AFFILIATE APPOINTMENTS

The purpose of affiliate appointments is to foster collaborations in teaching, research and related activities between the Institute for Molecular Bioscience (IMB) and Schools at The University of Queensland. Affiliate appointees to the IMB contribute through active involvement with relevant IMB Groups, facilities or research programs and through joint supervision of research higher degree students. Affiliate appointees contribute to the intellectual life of the Institute through attendance at IMB seminars, Divisional meetings and IMB Group Leader retreats. Salary for affiliate appointees is paid by the relevant University of Queensland School.

ASSOCIATE PROFESSOR STEVE BARKER
School of Molecular and Microbial Sciences

PROFESSOR MATT BROWN
Diamantina Institute for Cancer, Immunology and Metabolic Medicine

PROFESSOR IAN FRAZER
Diamantina Institute for Cancer, Immunology and Metabolic Medicine

PROFESSOR TOM GONDA
Diamantina Institute for Cancer, Immunology and Metabolic Medicine

PROFESSOR PETER GRESSHOFF
Centre for Integrative Legume Research

PROFESSOR WAYNE HALL
School of Population Health

PROFESSOR JANE HUNTER
School of Information Technology and Electrical Engineering

ASSOCIATE PROFESSOR STUART KELLIE
School of Molecular and Microbial Sciences

PROFESSOR BOSTJAN KOBE
School of Molecular and Microbial Sciences

ASSOCIATE PROFESSOR FRED MEUNIER
Queensland Brain Institute

ASSOCIATE PROFESSOR JOE ROTHNAGEL
School of Molecular and Microbial Sciences

PROFESSOR ISTVAN TOTH
School of Molecular and Microbial Sciences

ASSOCIATE PROFESSOR PAUL YOUNG
School of Molecular and Microbial Sciences

(Top Row) Associate Professor Steve Barker, Professor Matt Brown, Professor Ian Frazer, Professor Tom Gonda, Professor Peter Gresshoff, Professor Wayne Hall and Professor Jane Hunter.
(Bottom Row) Associate Professor Stuart Kellie, Professor Bostjan Kobe, Associate Professor Fred Meunier, Associate Professor Joe Rothnagel, Professor Istvan Toth and Associate Professor Paul Young.

IMBcom

IMBcom Pty Ltd is The University of Queensland's company for commercialisation of the IP arising from the research of the IMB. It is responsible for protection and development of the IMB's intellectual property portfolio. Established in 2000, IMBcom has a skilled, independent Board of Directors and operates as a separate commercial entity, but with a charter of service to the University's commercialisation objectives. The company has nineteen employees who provide the necessary skills and support to IMB researchers in commercialising the results of their discoveries.

IMBcom uses a model of cooperative integration with the discovery activities of the research labs. IMBcom staff are involved from the early stages with the planning and delivery of ways to add value to the emergent innovations. The company manages the IMB's Intellectual Property as custodians, developers, and drivers, resulting in licences, contracts and the formation of start-up companies to take discovery to products and services into markets.

IMBcom has had a historical strategic focus on developing new companies. During the first five years, IMBcom has seen the establishment of 11 new biotechnology companies, two in conjunction with UniQuest. These companies have raised more than $40 million through private sector investment, $16 million in federal and state government commercial grants and currently employ or contract over 60 individuals in R&D and commercialisation. These spinouts have gone on to develop strategic relationships in their own right with many other Australian and international biotechnology and pharmaceutical companies, and have encouraged the growth and establishment of service providers, adding to the fabric and critical mass of the industry in Queensland. The companies continue to mature under their own management once substantial first round investment is raised. One of the companies developed in partnership with Uniquest, Xenome, has now moved to become completely independent of the University, and the funds generated for the IMB and IMBcom are being used to provide the "proof-of-concept" funds for future IP and product development.

The IMB has a commitment to the training of high-quality graduate students in the molecular biosciences and aspires to provide a more holistic training with the inclusion of commercial and ethical dimensions. IMBcom has supported this objective through the provision of workshops throughout the training period. These "bootcamps", or BioBusiness Retreats, incorporate elements of career preparation, understanding and working in a commercial environment, and working in teams to produce outcomes. The training engages experienced professionals from the pharmaceutical, biotechnology, investment and research industries. The training has provided one of the building blocks of the commercial culture emerging in the IMB. These programs have provided commercial, project and team management skills to over 240 individuals to date, some of whom have adopted careers in the industry, being placed in Queensland biotechnology companies and IMBcom itself. The IMBcom model is now widely imitated by other organisations that recognise that the preservation of value in intellectual property is the key to building assets upon which industry develops.

IMBcom provides assistance to Queensland and Commonwealth government departments and agencies with respect to biotechnology industry development, and is well regarded as an effective advocate for Queensland's consistent promotion of the Smart Queensland agenda. IMBcom showcases not only the IMB and the University to industry and investment, but Queensland as an industry destination.

POSTGRADUATE RESEARCH

It has been yet another exciting year for the IMB Postgraduate Program, with 37 new students joining the program throughout the year. Nearly one third of these were from overseas (from countries as diverse as Germany, USA, UK, Brazil, Singapore, Indonesia, Thailand and Malaysia) and, interestingly, slightly over one third commenced their degree in the middle of the year, rather than at the more traditional January – March start date. We also had another solid year for completions, with more than 20 IMB students receiving their PhD degrees (for a full list see Table 1 page 56) and a further seven submitting their theses for examination in 2007. We currently have approximately 130 research higher degree (RHD) students enrolled through the IMB and are hoping this number will grow slightly throughout 2008.

Not only are our students growing in numbers, they are continuing to produce high-quality research outcomes. Half of our 2006 graduates, or 12 of 24, were nominated for consideration for the Dean's List for 2006, with Ben Clark (Capon lab), Alistair Forrest (Grimmond lab), Markus Kerr (Teasdale lab) and Matthew Kirkham (Parton lab) being successful. A snapshot of some of our students' other achievements can be seen in Table 2 (page 56).

This year saw the continuation of two specialist awards, initiated in 2006 for our IMB RHD students, through generous sponsorship by leading companies in the field of life science.

- The Roche Award for Postgraduate Career Development (RAPCD) yet again attracted a very high standard of entries for the selection panel to consider. The three finalists, Andrew Noske (Marsh lab), Michael Tallack (Perkins lab) and Rehani Villani (Wainwright lab), gave a 15-minute oral presentation to a second selection panel, which included Dr Andreas Goertz and Ms Susan Matthews from Roche. The presentations were wonderful, reflecting both the talent of our students and the diversity of the IMB's research approaches, and the judging panel spent much time deliberating. The ultimate winner, announced by Dr Goertz at the Institute-wide Friday Seminar Series, was Rehan Villani with her presentation, "Hedgehog Signalling: Balancing Skin Turnover and Skin Cancer". Rehan has not yet had the opportunity to use her $1500 prize but is intending to put it to good use in the first half of 2008.
- The Olympus Life Science Research Postgraduate Travel Award, as per last year, attracted a number of visually as well as scientifically stunning entries, which took the form of still images or videos. Unlike last year however, where an IMB-based team narrowed the entries to the three finalists, this year the Olympus selection team saw all entries and selected a winner and two runners-up from the total pool. The winner was Samantha Murphy (Parton lab), with her video titled "Characterisation of lipid droplet metabolism in adipocyte cells (Phat and Fusogenic)", while the runners-up were Natalie Butterfield (Wicking lab) and Andrew Noske (Marsh lab), who both received gifts from Olympus. Interestingly, Natalie was runner-up last year too, suggesting not only that Natalie continues to produce great work but also that the selection procedures are robust. Sam intends to use her $1000 travel money to attend a conference in 2008. All recipients were presented with their awards by Mr Kieren McHugh and Mr Paul Pearce from Olympus at the IMB Molecular Genetics and Development Divisional Forum.

Once again, we greatly appreciate the generous support of the IMB graduate program by both Olympus and Roche and hope these awards continue. For more information regarding the instigation of these awards, please see the 2006 annual report.

Our honours cohort was smaller than usual for 2007 and, as with our RHD students, was distributed such that nearly half the students commenced their honours study mid-year. We had 19 students commencing in February, seven students who carried over from July 2006 and seven others who commenced in July 2007. The Amgen Award for the most outstanding honours student at the IMB in 2006 was presented in August by Ms Bronwyn Shanahan and Ms Jo McNaughton from AMGEN Australia Pty Ltd to Emma Redhead from Dr Tim Bailey's group. Emma, whose honours project focused on developing a discriminative algorithm for detecting motifs in DNA and protein sequences, continued in the Bailey lab as a research assistant for much of 2007 before travelling overseas. Amgen Australia has been presenting our honours students with this award for over a decade and we are thrilled by their continued support of our young researchers.

IMB also continued the Undergraduate Research Scholarship Scheme (URSS) in 2007, giving 21 third-year students the opportunity to work in a laboratory within one of our divisions for eight hours per week during semester. Additionally, more than a dozen third-year students completed mini-research projects as part of the "Introduction to Research" module of their respective degrees, 14 summer students undertook projects in 2007/2008 and several Advanced Studies students completed research projects as part of their program. We also continued our involvement with the Advanced Studies Program lunchtime seminar series coordinated by Ms Robyn Evans from the BACS Faculty at UQ. Once again, we hosted many international students, primarily from Germany, Sweden and France but also from India, Singapore, Denmark, USA and the Netherlands, who joined IMB for several months as occupational trainees, undertaking overseas research placements as part of their degree requirements within their home institutions. We also welcomed a number of year 10, 11 and 12 students from schools throughout Queensland to undertake a brief period of work experience within research laboratories.

Our IMB student association (SIMBA) had yet another very productive year, ushering in a new Executive in May comprising Adam Costin (President), Josefine Sprenger (Vice President), Andrew Noske (Secretary) Elaine Haase (Treasurer), Alex Combes (SIMBAlize editor-in-chief) and Tom Whitington (Webmaster). This Executive continued with the vibrancy of the last, better promoting the SIMBA website among the general IMB community, continuing the fine tradition of the bimonthly electronic student journal, SIMBAlize,

and organising a host of social events and bonding exercises. This included the inaugural IMB/AIBN combined trivia night, which proved very successful in bringing students and staff from the two research institutes together. Throughout the year, the IMB Early Career Researcher (ECR) Committee also provided useful information sessions and a mentoring breakfast, as well as continuing to coordinate the Institute-wide Monday Midday Meetings, which provided an ideal venue for some of our postdocs and more senior PhD students to present their research to the Institute. During 2007 the members of the ECR committee included postdocs Dr Terje Svingen, Dr Dagmar Wilhelm, Dr Karen McCue, Dr Michael Hanzal-Bayer, Dr Mathias Francois, Dr Andrew Brooks, Dr Allison Pettit, and PhD students Evan Stephens and Simon Wilkins.

The ECR committee ran several information sessions in conjunction with the Graduate Program this year, including a set of two one-hour scientific writing workshops in March, conducted by Dr Joan Leach, who is part of the science communication program at UQ. These sessions were very well received and will be expanded in the future. Another information session in October, (coordinated largely by Evan Stephens from the ECR committee and funded by the Postgraduate Program), was conducted by Dr Hugh Kearns from Flinders University. The morning session, covering, "The 7 Secrets of Highly Successful PhD Students", was complemented by an afternoon session discussing, "Defeating self-sabotage", both of which were well received and provided food for thought for our student body.

In addition to these information sessions, the Postgraduate Program continued to run its regular set of workshops designed to assist students in overall career development. These included IMBcom's "Biobusiness Day Out" in November, which was compulsory for first-years (as it replaced the "Introduction to Bio-Business" Workshop) and IMBcom's three-day "BioBusiness Retreat" for the third-years, which was held in June at the Grand Pacific, Caloundra. Once again, feedback from the retreat was extremely positive, with students really enjoying the mentoring sessions, the networking opportunities and career advice. We reinitiated our basic statistics course with Carl Sherwood, the eight-week sessions proving so popular that we ran them in both semesters, as well as conducting a three-day specialist workshop on the program R, conducted by Professor John Maindonald from the Australian National University.

The year has also been a time of change for the UQ Graduate School, with the RHD offices initiating a number of changes in practice that are set to continue in 2008 and 2009. The most important change for this year was the deregulation of the Australian Postgraduate Award and UQ Research Scholarships schemes such that, as of October 2007, domestic students have been able to apply for a scholarship at any time throughout the year, with their scholarship application being linked to the application for enrolment into the RHD program. This has proved beneficial for a number of our potential students, who, until this year, were tied to an October deadline, requiring many to establish PhD projects while trying to complete their honours thesis. For a full list of scholarship outcomes for 2007/2008, please see Table 3. There has also been a change to the way the University handles international student costs, which may have implications for fee-waiver opportunities in the future.

The IMB has been very fortunate to have Professor Rob Capon continue in his role as the IMB Postgraduate Coordinator and once again serve as the IMB representative on the UQ Postgraduate Committee of the Academic Board throughout the year. Through his ongoing dedication and vigilance to all aspects of the Graduate Program, Rob is continuing to drive the IMB Postgraduate Program forward in a proactive and positive way to help deliver to our students the best overall research training possible.

TABLE 1: PhD CONFERRALS FOR 2007

Last Name	First Name	Group	Degree	Thesis Title	Where are they now?
Allen	**Tamara**	Muscat	PhD	Regulation of PPARg Activity by Novel Modulators	Baker Heart Research Institute, Melbourne, Australia
Barry	**Daniel**	Craik	PhD	Structural and Dynamic Studies of Cyclotides and their Precursors	Queensland Institute of Medical Research, Brisbane, Australia
Constantin	**Myrna**	Hume	PhD	Transcriptional Regulation of the c-fms Promotor by the ETS Family of transcription Factors	Travelling
Dave	**Richa**	Sweet	PhD	Functional Characterisation of the Role of Protein Tyrosine Phosphatase CD148 in Macrophages	Institute for Molecular Bioscience (Wainwright group), Brisbane, Australia
Davis	**Melissa**	Teasdale	PhD	Defining the Membrane Organisation of Eukaryotic Proteins	Institute for Molecular Bioscience (Ragan group), Brisbane, Australia
Garcia Castro	**Alexander**	Ragan	PhD	Developing Ontologies in the Biological Domain	Institute for Infocomm Research, Singapore
Gardiner	**Melissa**	Perkins	PhD	Determining the role of klf4 in zebrafish development	Queensland Brain Institute, Brisbane, Australia
Gruber	**Christian**	Craik	PhD	Plant Cyclotides: Evolution, Biosynthesis and Application of Circular Cystine Knot Mini-Proteins Cystine Knot Mini-Proteins	Vienna Medical University, Austria
Hamwood	**Tamarind**	Hume	PhD	The Structural Basis of CSF-1:CSF-1R Interactions	CBio Pty Ltd, Brisbane, Australia
Helwani	**Falak**	Yap	PhD	Cortactin regulates actin cytoskeletal dynamics at E-cadherin Adhesive Contacts	Mater Medical Research Institute, Brisbane, Australia
Imperial	**Julita**	Alewood	PhD	Novel peptides from Conus planorbis, Terebra subulata, and Hastula hectica	University of Utah, Salt Lake City, Utah, USA
Ireland	**David**	Craik	PhD	Structure-Activity Relationships in Biotechnology: Scientific and Business Perspectives	UniQuest Pty Ltd., The University of Queensland, Brisbane, Australia
Joseph	**Shannon**	Stow	PhD	The Exocytic and Endocytic Trafficking of E-cadherin in Epithelial Cells	Patient Safety Officer, Emerald Hospital, Queensland, Australia
Kay	**Jason**	Stow	PhD	Intracellular Cytokine trafficking and Phagocytosis in Macrophages	Hospital for Sick Children, Toronto, Canada
Loughnan	**Marion**	Lewis/ Alewood	PhD	Discovery and Characterisation of Conopeptide antagonists of nAChRs	Institute for Molecular Bioscience (Lewis group), Brisbane, Australia
Lovelace	**Erica**	Craik	PhD	The Structure, Activity and Engineering of Two Disulfide-bonded Conotoxins	Fred Hutchinson Cancer Research Center, Seattle, USA
Palmer	**James**	Wainwright	PhD	Characterisation of the Host Immune response in Cystic Fibrosis Mice	Institute for Molecular Bioscience (Wainwright lab), Brisbane, Australia
Pippal	**Jyotsna**	Muscat	PhD	The Role of PPAR-alpha In Lipid and Carbohydrate Metabolism of Skeletal Muscle Cells	Prince Henry's Institute of Medical Research, Melbourne, Australia
Ratnayake	**Ranjala**	Capon	PhD	Chemistry and Bioactivity Studies of Australian Microorganisms	National Cancer Institute, Frederick, USA
Ren	**Gang (Albert)**	Munn	PhD	Interactions between PCH proteins Hof1p and Vrp1p in regulation of cell division and membrane transport	Institute for Molecular Bioscience (Yap lab), Brisbane, Australia
Saska	**Ivana**	Craik	PhD	Biosynthesis of Circular Proteins in Plants	Institute for Molecular Bioscience (Craik lab), Brisbane, Australia
Woolford	**David**	Hankamer	PhD	Advanced Algorithms, Software and Applications in Single Particle Analysis	Baylor College of Medicine, Houston, USA
Wu	**Andy Chiu Ku**	Cassady	PhD	Invitro and In vivo Characterisation of Celllular Responses to PHBV and Hydroxyapatite/PHBV Composites as Bone Biomaterials.	School of Biomedical Sciences, The University of Queensland, Brisbane, Australia

Table 2: Non-IMB Awards received by PhD Students in 2007

Recipient	Award
Natalie Butterfield (Wicking lab)	Finalist, Oral Abstract presentation, Australian Society of Medical Research Postgraduate Student Conference
Ming Kang Chang (Sweet lab)	Third Prize, Oral Abstract presentation, Australian Society of Medical Research Postgraduate Student Conference
Alex Combes (Koopman lab)	Winner, Invitrogen Molecular Probes Photo Competition Most Outstanding Individual Presenter, GSK Biopitch, IMBcom Biobusiness Retreat
Melissa Gardiner (Perkins lab)	UQ Graduate School Research Travel Award
Dhiraj Hans (Fairlie lab)	Gates Foundation Global Health Series Travel Award
Jason Kay (Stow lab)	$1000 Travel Grant, Keystone Symposia macrophage conference
Tim Mercer (Mattick lab)	UQ Graduate School Research Travel Award
Philip Nguyencong (Craik lab)	UQ Graduate School Research Travel Award
Amber Stephens (Munn lab)	UQ Graduate School Research Travel Award
Rehan Villani (Wainwright lab)	Poster Prize, Australian Society of Medical Research Postgraduate Student Conference
Simon Wilkins (Perkins lab)	UQ Graduate School Research Travel Award

TABLE 3: Scholarships Obtained in 2007 for Funding in 2008

7	Australian Postgraduate Awards/UQRS (2 additional scholarships obtained early 2008)
1	Endeavour International Postgraduate Research Scholarships/UQRS
3	UQ International Research Awards/UQRS
1	Endeavour Postgraduate Research Scholarship
1	Endeavour Turkey Postgraduate Award
2	ANZ Trustees PhD Scholarships in Medical Research
1	The Cancer Council Queensland ('John Earnshaw Scholar')
3	AusAID Scholarships (2 from transferred students)
2	Home Government scholarships

VISITING SPEAKERS

DR KIRILL ALEXANDROV

Department of Physical Biochemistry, Max-Planck-Institute for Molecular Physiology, Germany

"Development of new tools and approaches for the analysis of GTPase controlled molecular machines"

PROFESSOR ALAN W. BELL

Chairman, Department of Animal Science, Cornell University, New York, USA

"The fetal origins hypothesis: evidence and implications for performance and health of livestock species"

PROFESSOR MAXWELL R. BENNETT AO

Director, Brain & Mind Research Institute, University of Sydney

"Astrocyte and microglia signalling in the brain"

PROFESSOR MARGARET BRIMBLE

Department of Chemistry and Maurice Wilkins Centre for Molecular Biodiscovery, University of Auckland, New Zealand

"Medicinal Chemistry: An Academic Discipline or a Commercial Reality?"

PROFESSOR KEVIN BURRAGE

Director, Advanced Computational Modelling Centre, The University of Queensland

"Is mathematical modelling and simulation of any practical use in the life sciences?"

DR ANTONY COOPER

Garvan Institute

"Misfolded proteins and disease: Insights into Parkinson's Disease and ALS from model systems"

ASSOCIATE PROFESSOR PETER CURRIE

Developmental Biology Laboratory Head, Victor Chang Cardiac Research Institute

"Zebrafish models of skeletal muscle development and regeneration"

ASSOCIATE PROFESSOR SAM EL-OSTA

Baker Heart Research Institute

"Transient hyperglycemia induces vascular epigenetic changes that cause persistent increased gene expression during subsequent normoglycemia"

DR MATTHIAS ERNST

Ludwig Institute for Cancer Research, Royal Melbourne Hospital

"Using reverse genetics to dissect mechanisms maintaining epithelial homeostasis in the gut"

DR ALEX FRANZUSOFF

GlobeImmune, Colorado, USA

"Sheep in wolf's clothing – engineering yeast for use in cancer and viral immunotherapy"

PROFESSOR RUDI GLOCKSHUBER

Institute of Molecular Biology and Biophysics, Zurich, Switzerland

"Assembly of type 1 pili in *Escherichia coli*"

DR ERICA A. GOLEMIS

Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA

"HEF1/NEDD9, a scaffold for metastasis"

PROFESSOR THOMAS GOODWIN

Department of Chemistry, Hendrix College, Arkansas, USA

"Utilisation of green extraction techniques for pheromones in elephants, maned wolves and ring-tailed lemurs"

PROFESSOR JENNY GRAVES

Research School of Biological Sciences, Australian National University

"Weird animal genomes and the evolution of sex"

PROFESSOR JEAN GRUENBERG

Department of Biochemistry, University of Geneva, Switzerland

"Membrane dynamics in the endosomal pathway"

PROFESSOR GARY HALLIDAY

Melanoma and Skin Cancer Research Institute, University of Sydney

"Ultraviolet radiation-induced skin cancer: the outcome of immunosuppression and gene mutations"

ASSOCIATE PROFESSOR STUART HOOPER

Monash University

"Imaging Lung Aeration at Birth"

PROFESSOR JONATHON HOWARD

Max Planck Institute of Molecular Cell Biology, Dresden, Germany

"From single motor proteins to cellular motility"

DR MICHAEL HUCKA

Co-director, Biological Network Modelling Center, The Beckmann Institute, California Institute of Technology, USA

"SBML, BioModels Database, MIRIAM and SBO: infrastructure for computational systems biology"

PROFESSOR DAVID HUME

Edinburgh Bioscience Research Centre, Scotland

"The Biology of Macrophages"

PROFESSOR PETER HUNTER

Director, Bioengineering Institute, University of Auckland, New Zealand and Professor, Oxford University

"Cardiac modelling: From ion channels and protein pathways to integrative cell, tissue and organ function"

PROFESSOR NANCY JENKINS

Institute of Molecular and Cell Biology, Singapore

"Harnessing transposons for cancer gene discovery"

HUGH KEARNS

Flinders University

"The Seven Secrets of Highly Successful PhD Students" and "Defeating Self-Sabotage"

DR PHILIP KIM

Department of Molecular Biophysics and Biochemistry, Yale University, USA

"Jumping Scales: How 3D structures and Molecular Genetics Meet in Protein Networks"

PROFESSOR MARTIN LAVIN

Queensland Institute of Medical Research

"ATM activation and downstream signalling protection against cancer and neurodegeneration"

DR LARS LEICHERT

Department of Molecular, Cellular and Developmental Biology, University of Michigan, USA

"Global Identification of Redox-Regulated Proteins"

DR GREG MUNDY

Director, Center for Bone Biology, Vanderbilt University Medical Centre, Nashville, Tennessee, USA

"New Concepts of the Vicious Cycle of Breast Cancer Metastasis to Bone"

ASSOCIATE PROFESSOR OSAMU MARUYAMA

Kyushu University, Japan

"ParScope: Predicting Transcription Factor Binding Sites through Parsimonious Composite Patterns"

PROFESSOR ROBERT MURPHY

Carnegie Mellon University, USA

"Automated Interpretation of Subcellular Patterns in Microscopic Images: Bioimage Informatics for Systems Biology"

DR MANDAR NAIK

Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan

"Roles of structure and structural dynamics in antibody recognition of allergen proteins"

PROFESSOR BRENT REYNOLDS

Queensland Brain Institute

"Targeting CNS cancer cell lines"

PROFESSOR DAGMAR RINGE

Rosenstiel Basic Medical Sciences Research Center, Braindeis University, Massachusetts, USA

"Mechanism of control of gene expression: the diphtheria toxin repressor"

PROFESSOR JEFF ROSEN

Baylor College of Medicine, Houston, Texas, USA

"Stem/progenitor cells in the etiology and treatment of breast cancer"

PROFESSOR ROB SAINT

Director, ARC Special Research Centre for the Molecular Genetics of Development, Australian National University

"A versatile Rho GPTase signalling pathway in cell division and migration"

PROFESSOR RICK SHINE

School of Biological Sciences, University of Sydney

"Mr Toad comes to Darwin: an evolutionary perspective on the cane toad invasion"

PROFESSOR EVAN SIMPSON

Director, Prince Henry's Institute of Medical Research

"Sex, fat and cancer"

PROFESSOR MANDYAM SRINIVASAN

Queensland Brain Institute

"Smart computers in small brains: vision, navigation, perception and cognition in honey bees"

DR DANIELA STOCK

Victor Chang Cardiac Research Institute

"Structure and function of proton translocating ATPases"

PROFESSOR BRIAN STORRIE

University of Arkansas for Medical Sciences, Little Rock, USA

"Rab6 regulates both ZW10/RINT-1- and conserved oligomeric Golgi complex-dependent Golgi trafficking and homeostasis"

PROFESSOR JILL TREWHELLA

School of Molecular and Microbial Sciences, University of Sydney

"Protein-protein interactions in signalling pathways: what we can learn from solution scattering methods"

PROFESSOR GISOU VAN DER GOOT

Global Health Institute, Ecole Polytechnique Federale de Lausanne, Switzerland

"Anthrax toxin: from entry to cell death"

PROFESSOR GREG VERDINE

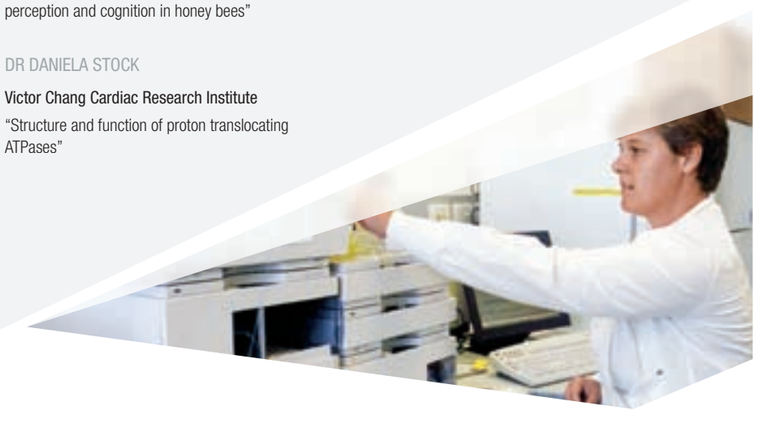
Department of Chemistry and Chemical Biology and Department of Molecular and Cellular Biology, Harvard University, USA

"The search for damaged bases in the genome"

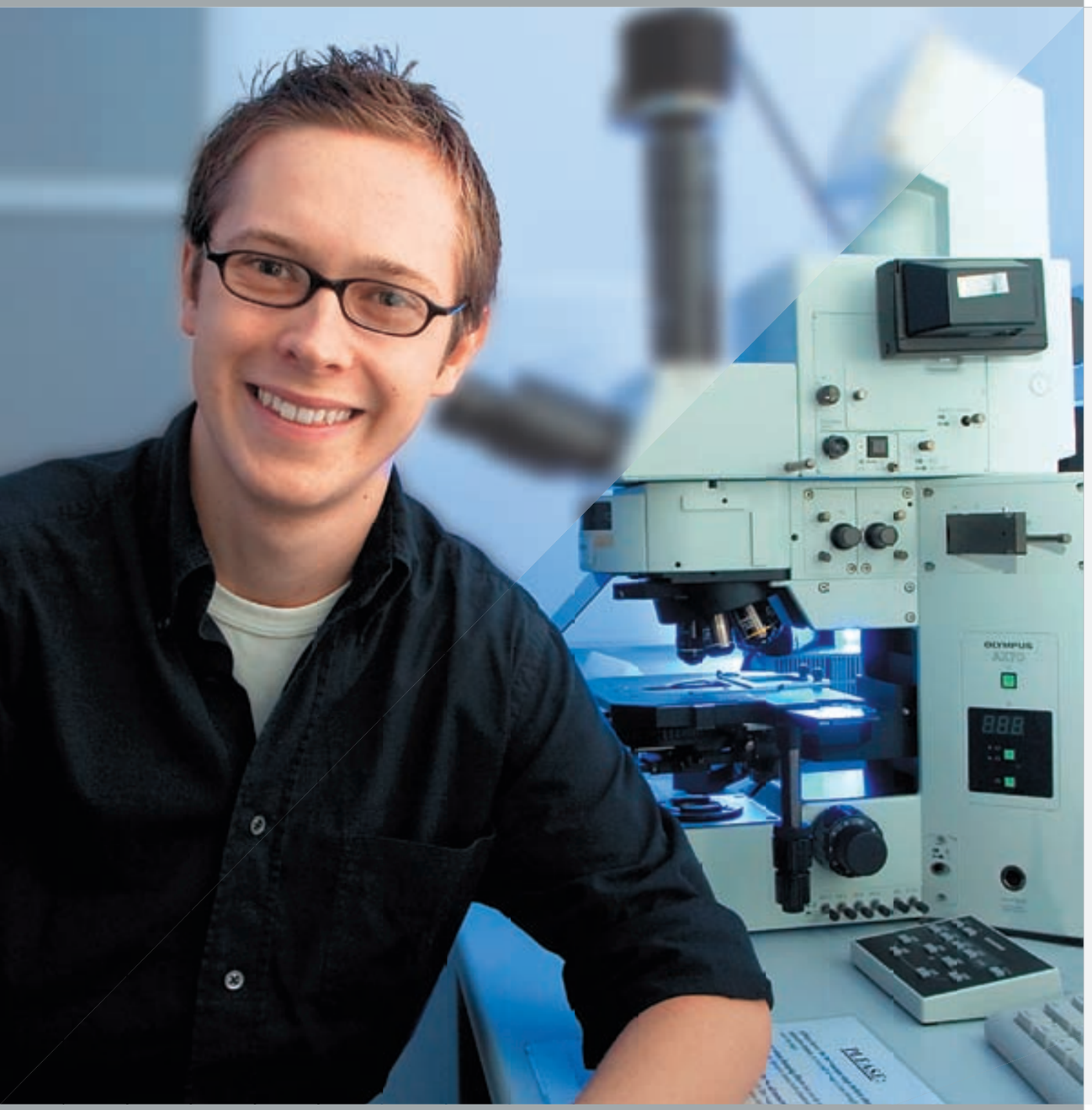
DR CHRIS L. WALLER

Director, World Wide Chemistry Informatics, Pfizer Global Research and Development, USA

"Challenges, strategies and solutions for drug discovery data integration at Pfizer"



COLLABORATIVE RESEARCH PARTNERSHIPS



Further underlining the Institute's commitment to research excellence, IMB Group Leaders collaborate extensively with partners both within Australia and internationally. The IMB is a core partner and participant in many research centres around the country, including three Major National Research Facilities (MNRFs) and two Cooperative Research Centres (CRCs).

These programs are integral to building Australia's national and international research capabilities. They aim to create the scale and focus necessary to maintain and develop Australia's world-class standing in priority areas through highly innovative research that addresses challenging and significant problems. CRCs and COEs make vital contributions to Australia's research landscape and produce outcomes with economic, social and cultural benefits to the country. Involvement in these ventures reflects very highly on the participating researchers, indicating the immense value of their work in both scientific and commercial terms.

ARC SPECIAL RESEARCH CENTRE FOR FUNCTIONAL AND APPLIED GENOMICS

The ARC Special Research Centre for Functional and Applied Genomics provides and develops rate-limiting technologies that enable world-class research in the field of genomics. An integrated network of core technologies, including computational biology, structural biology, proteomics, an animal transgenics service, as well as a microarray facility, have been established. The future of the SRC will see the coordinated application of these technologies to provide meaningful description of biological systems such as mammalian cells, from the structure, location and function of individual proteins to the control networks that allow the system to respond to its environment in development, differentiation and disease.

AUSTRALIAN PHENOMICS FACILITY

The Australian Phenomics Facility (APF) is based at the John Curtin School for Medical Research and is a Major National Research Facility (MNRF) formed by support from the IMB, the Australian National University and the Garvan Institute for Medical Research. The APF is based around the use of mouse genetics to discover novel genes that influence traits of medical relevance. Large populations of mice are exposed to a mutagen, traits are identified and selected and then genetic mapping is used to locate the general regions where the genes reside. The mutagen used to create the mutants leaves a particular genetic fingerprint that can be discerned by sequencing candidate genes, thus identifying the gene responsible for the trait under consideration. This is a very powerful approach to biology which enables gene function to be elucidated based upon the high-throughput analysis of phenotypes ("phenomics").

ARC CENTRE OF EXCELLENCE IN BIOTECHNOLOGY AND DEVELOPMENT

The ARC Centre of Excellence in Biotechnology and Development (CBD) was established in 2003 to focus on the biology of male germ cells – embryonic stem cells that eventually produce sperm cells in men. A review of the Centre in 2007 confirmed its status as a Centre of Excellence, and extended its funding for a further three years. The Centre will receive $6.42 million from 2008. Collaborating institutions include the IMB, the Universities of Queensland, Melbourne, and Newcastle, Monash University and the Australian National University. Unlike many other types of stem cells, germ cells represent a truly "blank slate" that can develop into any tissue in the body. Understanding their specification and programming is central to contemporary efforts to harness stem cell technologies. Since male fertility depends on generating sperm cells in vast numbers, and since genetic and environmental factors commonly disturb the quantity and quality of sperm produced, the research will further impact on understanding and possible treatment of infertility, a distressing condition that represents a massive healthcare burden in Australia and worldwide. Disorders of germ cells are often accompanied by testicular cancer, and so the potential medical significance of this research is twofold. It has become increasingly clear that manipulating the quantity and/or quality of germ cells, particularly male germ cells, presents powerful opportunities in the pest management arena, and in other biotechnological pursuits such as the management of endangered wildlife species.

ARC CENTRE OF EXCELLENCE IN BIOINFORMATICS

The ARC Centre in Bioinformatics, with headquarters at IMB, brings Australian and overseas researchers together into interdisciplinary programs designed to explore how information in the genome is transformed into structure and function in the mammalian cell. Perspectives and technologies of mathematics, statistics, high-performance computation, information technology, genomics and high-throughput experimental phenomic biology are focused on representing the mammalian cell as a complex system of molecular networks, and building a common modeling and visualisation environment to simulate its development and behaviour. Although directed in the first instance towards understanding human health and development, the Centre's technologies and output are generally applicable to biotechnology, while building critical mass in advanced bioinformatics is vital to Australia's international competitiveness in bio-based industries. In 2007, the Centre was upgraded to a Centre of Excellence, which will result in a further $3.3 million in funding from 2008.

CRC FOR CHRONIC INFLAMMATORY DISEASES

The IMB is a core participant in the CRC for Chronic Inflammatory Diseases (CRC-CID), whose partners are Monash University, The University of Melbourne and AstraZeneca. The major objective of the CRC is to discover new molecular targets involved in the pathogenesis of chronic inflammatory lung and joint disease and use this information to develop novel treatments for these disorders. The CRC is using gene microarrays, proteomics, cell-based assays and genetically modified animal models of disease to understand how macrophages cause chronic inflammation. The CRC is structured to facilitate the entire drug discovery cycle: primary target identification using functional genomic and proteomic approaches, target validation in disease models and human tissues, high-throughput cell-based assay development, lead target screening, generation of therapeutic and research antibodies, and the development of macrophage-targeted drug delivery strategies.

COLLABORATIVE RESEARCH PARTNERSHIPS

AUSTRALASIAN INVASIVE ANIMALS CRC

Australasian Invasive Animals CRC is a venture aiming to counteract the impact of invasive animals through the development and application of new technologies and integrating approaches across agencies and jurisdictions. It is the first time that research, industry, environmental, commercial and government agencies have combined to create and apply solutions for invasive animal threats, which cost Australasia at least $720 million per annum. This unique partnership will deliver the means to deal with existing high-profile invasive animal pests as well as those that have the potential to cause catastrophic impacts in the future. Professor Peter Koopman from the IMB currently serves on the advisory board for the Daughterless Carp Program of the AIACRC. This program, based at CSIRO fisheries in Hobart, uses innovative technologies with a view to skewing the sex ratios of wild populations of the common carp, one of the most widespread threats to indigenous fish species in our larger waterways. Professor Koopman's laboratory is also expanding this program, under the auspices of the CRC, to develop a similar management strategy for the cane toad, currently ecological public enemy number one in Queensland.

AUSTRALIAN MICROSCOPY & MICROANALYSIS RESEARCH FACILITY

The Advanced Cryo-Electron Microscopy Laboratory – the Queensland node of the Australian Microscopy & Microanalysis Research Facility – is housed in a purpose-built facility at IMB. This MNRF was formed as a collaboration between the Universities of Queensland, Western Australia, Melbourne, New South Wales and Sydney. The facility, which includes a 300kV Technai microscope, is currently the only one in Australia or New Zealand capable of collecting and processing atomic resolution images at low temperature, as well as undertaking a 3D electron microscope (EM) tomography of organelles, cells and tissues at both ambient and low temperature. Only a handful of international (and no other Australian) laboratories can offer researchers equivalent state-of-the-art research tools for high-resolution 3D structure studies of cells and molecules. The AMMRF is a successor to the Nanostructural Analysis Network Organisation (NANO).

AUSTRALIAN STEM CELL CENTRE

The Australian Stem Cell Centre (ASCC) is a national research and funding facility set up by the ARC, The Victorian Department of Industry, Innovation and Regional Development, and the Federal Department of Education, Science and Training through a linked MNRF. The ASCC is primarily based at Monash University, but through the guidance of the Scientific Management Advisory Committee (SMAC) and a process of due diligence, the ASCC funds research which falls within its core expertise platform areas or its therapeutic focus areas. The IMB has very close links with the ASCC. Professor Melissa Little was seconded to the Centre in 2007 as its Chief Scientific Officer, where she will be responsible for developing strategy, scientific review and management. She will also develop a Queensland division of the ASCC based at UQ. Associate Professor Andrew Perkins, Dr Sean Grimmond and Dr Rohan Teasdale hold a joint grant in the therapeutic platform of "haematological disorders". The aim of this project is to harvest the immense potential of embryonic stem cells to provide a novel supply of haematopoietic stem cells (HSCs) for bone marrow transplantation, as well as other blood products. Dr Sean Grimmond also holds a joint project grant with Professor Martin Pera of the ASCC in the core platform technology of "embryonic stem cell technology". Dr Grimmond's international expertise in expression profiling is employed to try to dissect the genetic hierarchies involved in human ES cell differentiation. In addition, the Renal Regeneration Consortium and Nephrogenix, which are both based at two hubs – the IMB and Monash University – have very close links with the ASCC through a research memorandum of understanding. An eventual core aim of the RRC is to employ embryonic and adult stem cell technologies to deliver cells with therapeutic potential to patients with end-stage renal failure.

AUSTRALIAN GENOME RESEARCH FACILITY

The Australian Genome Research Facility (AGRF) is an MNRF of the Commonwealth Government and was established in 1996 through an MNRF application led by Professor John Mattick, who served as the inaugural director until 2002, and Board Member until 2004. Professor Brandon Wainwright currently serves on the AGRF Board. The AGRF is a state-of-the-art facility for the collection of molecular genetic information covering large-scale DNA sequencing, genotyping, microarraying, agricultural genomic services and other resources for the genetic and physical mapping of chromosomes, mutation detection and associated bioinformatic analysis. It serves several hundred research groups across all states and territories of Australia from nodes at The University of Queensland, the Walter and Eliza Hall Institute of Medical Research in Melbourne, and the Waite Campus of the University of Adelaide.

ACRF DYNAMIC IMAGING FACILITY FOR CANCER BIOLOGY

This facility was launched in August 2005 with the aid of a grant from the Australian Cancer Research Foundation (ACRF). It is the only one of its kind in Australia and the laboratory at the IMB houses two technologically advanced microscope systems that will enable cutting-edge research into cancer biology. IMB researchers are now able to make live movies and track the movements and behaviour of breast cancer cells with a higher resolution, greater capability and more quickly than ever before. The new facility also allows researchers to optically dissect cancerous and non-cancerous cells and reconstruct them in 3D, revealing much greater detail about their inner workings. Researchers can also now examine a vast range of proteins at the same time and examine their dynamics in live cells over time.

RIKEN

RIKEN is the Institute for Physical and Chemical Sciences of the Japanese Science and Technology Agency, and a major site of genomics research in Japan. Professor John Mattick has a visiting scientist appointment at RIKEN. The RIKEN Genome Sciences Centre is based at Yokohama and Wako, in the Tokyo area. In the late 1990s, RIKEN established a program aimed at elucidating the complete transcriptional output of the mouse. More recently, the program has shifted focus towards the elucidation of transcriptional control networks. Both activities have involved the establishment of large international consortia, firstly the FANTOM consortium (Functional Annotation of Mouse), and more recently the Genome Network consortium. The consortium has previously published a comprehensive analysis of the human and mouse transcriptomes, resulting in a series of papers in *Nature Genetics, PLoS Genetics, PLoS Computational Biology, Genome Biology* and *Genomics.*

QUEENSLAND FACILITY FOR ADVANCED BIOINFORMATICS (QFAB)

QFAB was established in 2006 with a $1.9 million Queensland State Government grant and is based at the IMB. It is rapidly becoming a leader in supporting the bioinformatics requirements of research-intensive universities, institutions and companies, beyond the capability of any single organisation in Australia or the Asia-Pacific region. It provides the bioinformatics, ICT, research biology and clinical community with secure access to data and the tools to efficiently deliver relevant solutions. Its projects cover: programmatic access to large data sets and tools, data integration and workflow technology for biological and health data, mirror site for genome browsers, annotation pipelines and workflows for biological and health data, genotype/phenotype linkages, analysis and visualisation of biological data and building and using web-based tools.

NETWORK FOR PANCREATIC ORGAN DONORS WITH DIABETES (NPOD)

nPod is an initiative of the Juvenile Diabetes Research Foundation (JDRF) and brings together Organ Procurement Organisations, academic institutions and leading diabetes researchers from across Europe and America. The only Australian node is at the IMB in the laboratory of Dr Brad Marsh, who in addition to his research also chairs the Communications & Awareness Subcommittee. nPod aims to improve the procurement of pancreatic tissue specifically from patients and donors at high risk of developing type 1 diabetes. It is the first trial of its kind anywhere in the world and it is hoped that it will improve our understanding of the onset and progress of type 1 diabetes.

COMMUNITY ENGAGEMENT

The IMB has a mission not just to perform excellent research, but also to engage with the community and make them aware of us and what we do. We achieve this through a number of avenues.

IMB WEBSITE www.imb.uq.edu.au

The IMB website is the main source of detailed information for community members interested in the IMB. It describes the research of each group, employment and postgraduate opportunities, commercialisation, news, conferences and more. It also houses all of the publications of the IMB in electronic form, so these can be accessed from anywhere in the world. It is the top site for people searching the term 'molecular bioscience' in Google, indicating that it is a valuable resource for those interested in this area of research.

IMB TOURS

The Institute welcomes enquiries from interested parties who would like to tour the facility. A tour allows people to view some of our world-leading equipment and laboratories, and hear about our research, postgraduate and commercialisation activities. In 2007, the IMB played host to groups of school students, international university students and staff, politicians, dignitaries and researchers.

SCIENTISTS IN SCHOOLS

Just as school groups visit the IMB, so too do IMB researchers visit schools, in the form of the Scientists in Schools program. This allows individual researchers with a passion for communication and education to be paired with a school teacher. The program is flexible, allowing the scientist and teacher to decide on the interaction that best suits both their needs. Three IMB scientists – Dr Brad Marsh, Karin Kassahn and Adi Idris – participated in the program in 2007, lending their expertise to four schools.

PUBLIC EVENTS

The IMB played a role in several public events in Brisbane during 2007. The Bridge Fun Day, held in February, celebrated the opening of the Eleanor Schonell Bridge linking the University's St Lucia campus with the southern side of the Brisbane River. The Fun Day was held on the banks of the river, and the IMB stall offered information about the Institute as well as an activity in the form of extracting DNA from strawberries. Over 100 people participated in the extraction.

The DNA extraction also took a starring role at a much larger public event: the Royal Brisbane Show, or the 'Ekka', as it is colloquially known. The IMB was part of a larger UQ display, and again, the strawberry DNA extraction was well received with around 2000 people taking part over three days. This was also an opportunity to disseminate information about the Institute to those who were interested.

UQ held its Open Day in August, with nearly 15 000 people attending. The day was not just for prospective students, but also for any community member who wanted to take a closer look at the university. Within the IMB, PhD students hosted tours of the Institute and there were displays from individual research groups.

IMB OUTPUT

The IMB's quarterly newsletter allows community members to receive regular updates on the research of the IMB. It is written so non-scientists can understand it, and is available on the IMB website under "About the IMB". To subscribe to IMB output and receive either a hard or an electronic copy every three months, please visit the IMB website and follow the "Subscribe to IMB News" link on the front page.

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Mary Wang
Research Officer

Shivangi Wani
Research Assistant

Mike Waters
Group Leader

Winnie Waudo
PhD Student

Jane Weber
Research Assistant

Jan Westerman
Research Officer

Nicole Wheatley
Masters Student

Tom Whitington
PhD Student

Carol Wicking
Group Leader

Dagmar Wilhelm
Research Officer

Lorine Wilkinson
Research Officer

Ben Wilson
Research Officer

Danielle Wilson
PhD Student

David Wilson
Research Officer

Lanna Wong
Manager, ARC Centre of Excellence in Bioinformatics

Simon Wong
Research Officer

David Wood
Computer Systems Officer

Andy Wu
PhD Student

Fiona Wylie
Research Officer

Christine Yan
PhD Student

Aijun Yang
Research Officer

Alpha Yap
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Greg Young
Lab Manager

Tiffany Young
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Zheng Yuan
Senior Research Officer

Poh Yuen Chin
Undergraduate Student

Ernie Yulyaningsih
Research Assistant

Claudia Zampata
PhD Student

Boris Zhang
Research Officer

Hua Zhang
Research Officer

Shane Zhang
Research Assistant

IMBcom STAFF

Catherine Benham
Administrative Assistant

Lisa Black
Team Assistant

Kellie Broderick
Manager, Infrastructure & Education

Leah Creed
Legal Counsel & Company Secretary

Noi Inthasan
IP & Operations Support

Peter Isdale
Chief Executive Officer

Zachary King
Commercialisation Assessment Officer

Christine Lane
Grants Consultant

Andrew Leech
IP Associate

Bridget Maher
Commercialisation Assessment Officer

Emma McComb
IP Associate

Jodie McNab
Company Accountant

Chris Price
VP of Commercial Development

Lyn Rosen
Executive Assistant

Amanda Smith
Manager, Intellectual Property

Karen Soxsmith
Systems Support

Olivia Teed
IP Support and Marketing

Erin Wansbrough
Business Development Manager

Simon Wilkins
Commercial Intelligence Analyst

FINANCIAL STATEMENTS

STATEMENT OF OPERATING INCOME & EXPENDITURE
Year Ended 31 December 2007

INCOME:	NOTE	2003	2004	2005	2006	2007
University of Queensland (Operating Grant)	1	8,122,858	6,877,099	7,225,765	10,767,311	11,087,942
University of Queensland Research Grants		277,337	228,999	334,500	252,252	300,436
State Government		8,500,000	10,000,000	10,425,000	10,175,000	11,127,168
SRC Grant (Australian Research Council)		1,005,151	1,117,038	1,137,436	1,159,047	1,182,516
Australian Research Council	2	3,218,103	4,261,849	4,744,519	5,218,279	6,010,239
Arthritis Foundation of Australia		0	0	14,950	0	0
Australian Cancer Research Foundation		0	600,000	600,000	0	0
Australian Nuclear Science & Technology Organisation		0	0	85,355	78,757	230,492
Australian Stem Cell Centre		0	306,219	161,691	159,780	467,335
Cancer Council South Australia		30,500	30,500	0	0	0
Clive and Vera Ramaciotti Foundation		0	0	0	0	60,000
Community Health + Tuberculosis Australia		0	0	0	49,000	0
CRC for Discovery of Genes for Common Human Diseases		48,946	0	0	0	0
CRC for Chronic Inflammatory Diseases		968,800	1,261,017	1,367,457	1,326,058	1,462,776
CRC for Pest Animal Control		0	0	0	122,210	0
Dairy Australia		0	338,779	203,765	167,644	700,321
Department Industry Science & Resources		0	0	0	0	200,000
Department of Primary Industries		0	0	0	0	50,000
Diabetes Australia Research Trust		0	0	0	45,000	0
Human Frontiers Science Program		146,291	138,057	0	0	81,783
The John Trivett Foundation		0	0	0	0	267,817
Juvenile Diabetes Foundation International		0	151,732	177,814	178,634	147,708
The Murdoch Institute		0	0	0	0	347,527
National Institute of Health (US)		1,049,548	1,475,684	1,132,358	1,176,642	969,415
National Health and Medical Research Council	2	6,761,404	6,438,350	9,819,880	7,888,967	11,054,142
National Heart Foundation		42,735	50,000	50,000	0	0
New Zealand Dept Science & Technology		0	0	0	0	81,392
Novartis		641,790	0	0	0	0
Post Graduate Scholarships		73,467	91,968	140,237	261,263	305,255
QIMR		60,575	0	0	0	0
Queensland Cancer Fund		72,590	140,000	215,100	148,700	312,000
Wellcome Trust		204,763	180,706	150,311	0	0
Commercial Income		1,517,449	1,473,905	1,856,012	2,018,054	4,880,234
Cross-Institutional contributions to LIEF or Facilities		122,500	192,800	60,000	509,472	188,000
University of Newcastle (re ARC Centre)		127,727	127,893	47,727	252,562	128,218
QBP recoveries		331,594	312,979	316,211	386,092	371,257
Shared Grants		105,845	128,764	262,062	234,685	4,000
Conference Income		55,275	25,501	73,032	66,615	184,340
QBPStore		0	44,021	247,890	276,819	314,057
Wesley Research Institute		0	0	0	20,000	93,645
Miscellaneous Income		392,822	355,652	416,707	399,887	357,293
TOTAL INCOME:		**33,878,069**	**36,349,512**	**41,265,778**	**43,338,729**	**52,967,307**
Funds brought forward from previous year	3	7,545,101	6,746,999	6,557,150	9,050,612	11,441,270
TOTAL FUNDS AVAILABLE		**41,423,170**	**43,096,511**	**47,822,929**	**52,389,341**	**64,408,577**
EXPENDITURE:						
Salaries – Research		12,238,779	16,195,354	18,430,158	20,110,376	22,878,237
– Administration		1,365,120	1,243,375	1,343,782	1,205,466	1,349,056
– Infrastructure		1,735,158	2,131,608	2,383,622	2,673,620	2,368,795
Research Services		6,938,972	7,667,863	9,976,365	10,995,871	13,099,865
Education Programs	4	484,360	418,784	375,177	358,445	332,919
Administration	5	519,046	383,224	379,317	529,612	521,743
Infrastructure	6	1,568,251	1,772,942	1,287,442	1,295,139	1,862,212
Capital Equipment	7	8,649,700	5,521,066	3,389,715	2,569,801	5,156,825
IMBcom		1,176,785	1,205,144	1,206,738	1,209,741	1,197,920
TOTAL EXPENDITURE:		**34,676,171**	**36,539,360**	**38,772,316**	**40,948,071**	**48,767,573**
Funds carried forward:	**8**	**6,746,999**	**6,557,150**	**9,050,612**	**11,441,270**	**15,641,004**

EXPLANATORY NOTES TO STATEMENT OF INCOME & EXPENDITURE

1/ A) IN-KIND CONTRIBUTIONS

Figure does not include the following salaries for joint appointments paid by other departments:

	Department	Percentage
K. Burrage	Mathematics	80
G. McLachlan	Mathematics	80
G. Goodhill	QBI/Maths	80
A. Mark	SMMS	80

B) GROSS INCOME & CORPORATE SERVICES CHARGE

The 2006 Annual Report, for the first time, showed University of Queensland Operating Grant Income as a gross amount and Corporate Services charge shown separately under expenditure. For 2007 we have reverted back to the previous method for better direct comparison. 2006 figures have been adjusted accordingly and now show the nett.

2/ FELLOWSHIP/PROJECTS FROM GOVERNMENT AGENCIES

Australian Research Council	
Projects	3,240,483
Fellowships	1,254,964
	4,495,447
National Health and Medical Research Council	
Projects	8,496,269
Fellowships	2,522,033
	11,018,302

3/ FUNDS CARRIED FORWARD TO 2007

University of Queensland Operating Grant	5,896,159
University of Queensland Research Grants	99,749
Post Graduate Scholarships	46,913
State Government	3,060,830
SRC Grant	(44,721)
Fellowships (as approved by funding bodies)	94,671
Overseas Grants funded mid year	25,962
Contract Research	2,201,249
Project Grants (as approved by funding bodies)	60,458
	11,441,270

4/ EDUCATION PROGRAMS

Postgraduate scholarships	279,180
Postgraduate recruitment & training	53,739
Total Education Services	**332,919**

5/ ADMINISTRATION

Annual Report	23,138
Marketing	48,438
Personnel Recruitment and Training	61,671
Visiting Scientists/Seminars	22,963
Fees	58,262
Quinquennial Review	0
Entertaining	41,006
Photocopying	121,274
Postage and Freight	627
Printing & stationery	44,804
Telephone	63,388
Travel Expenses	19,265
Board Fees	16,907
Total Administration	**521,743**

6/ INFRASTRUCTURE

Building Maintenance	120,116
Rental -Storage	11,400
Safety Equipment	42,932
Laundry	5,584
Minor Equipment & Furniture	19,164
Equipment Maintenance	234,652
Animals	318,674
Computer Services	680,584
Glass washing and replacement	56,670
Reticulated gases, RO water & dry ice	137,123
Cost Recovery	-9,326
Stores	244,638
Total Infrastructure	**1,862,212**

7/ CAPITAL EQUIPMENT

Scientific Equipment	4,786,617
Minor Equipment	370,209
Total Capital Equipment	**5,156,825**

8/ FUNDS CARRIED FORWARD TO 2008

University of Queensland Operating Grant	7,468,461#
University of Queensland Research Grants	53,647
Post Graduate Scholarships	84,768
State Government	3,036,824#
SRC Grant	(292,297)
Fellowships (as approved by funding bodies)	541,148
Overseas Grants funded mid year	294,675
Contract Research	2,639,402
Project Grants (as approved by funding bodies)	1,814,376
	15,641,004

Of this, $1.4m is the carry forward on IMB Group Leader core accounts, $1m relates to oustanding 2007 equipment commitments

GLOSSARY OF TERMS

Actin A protein, along with myosin, responsible for muscle contraction.

Adipose Fat or fatty tissue.

Agonist A molecule that interacts with a receptor, triggering a cellular response.

Allele One of a number of possible versions of a gene. Each person inherits two alleles per gene, one from each parent.

Amyloid An abnormal protein deposit associated with tissue degeneration, such as Alzheimer's.

Analogue A characteristic or structure that evolved separately in different organisms but shares a similar form or function.

Angiogenesis Formation of new blood vessels.

Antagonist A molecule that blocks a chemical from binding to its receptor.

Antibody A protein produced in response to an antigen to fight foreign substances.

Antigen A molecule that triggers an immune response in the body.

Antinociceptive Counters the effect of anything caused by, or in response to, pain.

Assay Qualitative or quantitative analyses of a substance performed in order to determine its components.

Atherosclerosis The process whereby arteries harden and narrow over time.

Autoimmune Any condition where the immune system does not distinguish between foreign substances and the body's own cells, causing it to attack normal tissue.

Axons The neurons that conduct electrical impulses in the nervous system.

Bioinformatics The collection, organisation and analysis of large amounts of biological data using networks of computers and databases.

Biopolymer Any polymer found in nature, eg. DNA, proteins.

Bioscience Any of the branches of science dealing with the structure and behaviour of living organisms.

Biosynthesis The production of chemical compounds in living organisms.

Biotechnology Any technology that uses biological systems or living organisms to make or modify products or processes.

BRET Bioluminescence Resonance Energy Transfer. A cell-based assay allowing the direct study of complex protein-protein interactions in living cells.

BSE Bovine spongiform encephalopathy. Commonly known as mad cow disease.

Cadherin A class of transmembrane protein, which ensures cells adhere to one another within a tissue.

Carbohydrate An organic molecule of carbon, hydrogen and oxygen. They are a major source of energy for the body.

Caveolae A small pocket extending from the outside to the inside of a cell. Sites of uptake and expulsion of materials into and out of the cell.

Chelate An organic molecule that has bonded to a metal to form a ring-shaped structure.

Chemotaxis Movement of a cell or organism stimulated by a chemical.

Chromatin The complex of DNA and proteins that form a chromosome.

Chromatography A method of separating chemical compounds into their base constituents by transporting the compound in liquid form through a porous substance. The different rates of absorbency of the constituents mean that as they pass through the substance they will separate.

Chronic Obstructive Pulmonary Disease A general term for degenerative lung diseases including emphysema and cystic fibrosis.

Clathrin The protein that largely forms the vesicle responsible for transportation of proteins into and out of the cell.

Combinatorial Chemistry Methods used to synthesise numerous, related chemical compounds.

Conotoxin A group of toxic peptides isolated from the venom of the marine cone snail.

CREB Factors that bind to specific DNA sequences and alter the transcription of certain genes.

Cryo-electron microscope A microscope that uses frozen samples in order to decrease distortion and increase resolution.

Crystallography The use of X-rays to determine the structure of crystallised molecules.

Cytokines Small proteins released by cells that affect the behaviour of other cells.

Cytokinesis The point in somatic cell division where the cytoplasm splits, as opposed to the splitting of the nucleus, which occurs first.

Cytoplasm All of the contents of a cell, excepting the nucleus.

Cytoskeleton The protein framework of a cell.

Cytotoxin A toxin harmful to cells.

De novo Not previously present.

Dedifferentiation The process whereby specialised cells revert back to being multipotent, where they can produce cells of any type.

Deterministic Something that is predictable, not random, given known initial conditions. The opposite of stochastic.

Diabetes A disease that occurs when the body cannot produce or cannot use insulin, which regulates blood sugar levels.

Dimer An organic molecule formed by combining two smaller molecules.

DNA Deoxyribonucleic acid. The chemical chain that carries the genetic instructions for making a living organism.

Drosophila A genus of flies commonly known as fruit flies. *Drosophila melanogaster* is often used in genetic and developmental research as a model organism.

EGFR Epidermal growth factor receptor.

Electrolyte The dissolved form of a mineral, capable of conducting an electrical current. Helps regulate the proper balance of body fluids.

Endocrine Relating to hormones, and the glands that produce them, that are secreted directly into the blood or lymph system.

GLOSSARY OF TERMS

Endocytosis Uptake of material into a cell.

Endosome An organelle involved in protein trafficking.

Enzyme A protein produced by living organisms that catalyses chemical reactions of other substances without being altered itself by the reactions.

Epifluorescence A type of microscopy using a very bright light source. This light is used to energise the sample into re-emitting light (or "fluorescing") at various wavelengths, which allows researchers to produce an image of the sample.

Epigenomic Pertaining to the biochemical reactions that regulate gene expression.

Epithelium Membranous cellular tissue that covers the internal and external surfaces of the body.

Epitope The site on the surface of a foreign substance that triggers the production of antibodies, and to which these antibodies bind.

ERK A messenger kinase belonging to the MAPK family.

Erythropoiesis The development of mature red blood cells.

Etiology The cause, or the study of the cause, of disease.

FACS Fluorescent-Activated Cell Sorting. A method of sorting a heterogeneous group of cells using the light scattering and fluorescent characteristics of each cell.

Factor A sequence of DNA involved in producing a polypeptide chain.

FRET Fluorescence Resonance Energy Transfer. A method of quantifying molecular dynamics such as protein-protein interactions.

Gene Considered the basic unit of heredity, a gene is a region of DNA that encodes all of the information to make a protein.

Genome All DNA contained in an organism or cell.

Genomics The study of genes and their function.

Globin The compound in red blood cells that binds to oxygen.

Glucose A six-carbon sugar that is a major energy source for the body.

Gram-positive Bacteria that have a single cell wall; many species are pathogenic.

GTPase A large family of enzymes that can bind and break down GTP, a type of nucleotide. GTPase is involved in a number of processes, including translation, transport, signal transduction and cell division.

Haemoglobin A protein in red blood cells that carries oxygen around the body.

Haplotype A group of closely linked alleles that are generally inherited as a unit.

Helminths Parasitic worms that often carry disease.

Hematopoietic Pertaining to anything that affects or triggers the formation of blood cells.

Histidine A type of amino acid, which binds to form proteins. Histidine is found in proteins involved in the repair and growth of tissue.

Histology The study of the microscopic structure of tissues.

Homeodomain A protein motif in a homeobox (a highly-conserved DNA sequence) found in genes that regulate embryo development.

Homeostasis A condition where the body uses negative feedback processes to maintain its systems at a constant equilibrium.

Homodimerize The joining of two identical subunits to form a dimer, as opposed to heterodimerize, which would involve the joining of two non-identical subunits.

Hormone A chemical secreted by one part of the body that has a specific regulatory effect on other cells or tissues.

Immunoprecipitation The process whereby an antigen is formed in a solution using a specific antibody.

In silico A process that has been simulated on a computer.

In situ In its natural place.

In vitro A process occurring in an artificial environment that would normally occur in an organism.

In vivo A process occurring within an organism.

Innate immunity A generalised response to foreign substances with which one is born; it is not associated with a specific antigen.

Insulin A hormone that regulates sugar concentration in the blood.

Introns The non-coding regions of a gene.

Islet of Langerhans Clusters of cells in the pancreas that secrete insulin.

Kinase An enzyme that catalyses the transfer of a phosphate group from a donor to a target molecule.

Kruppel-like factor A family of transcription factors homologous to the *Drosophila* Kruppel protein.

Lentivirus A virus with a long period between infection and symptoms appearing. This period of latency enables the virus to be used for delivering genetic information into a cell.

Lipid Any of a group of heterogeneous fat or fat-like compounds that are insoluble in water.

Locus The location of a gene on a chromosome.

Lymphatic Pertaining to the circulatory network of vessels that produce and store the cells that fight infection.

Lysosome An organelle capable of digesting microorganisms and cellular debris.

Macrophage A large cell that engulfs and absorbs waste material, harmful microbes or other foreign bodies in the bloodstream and tissues.

Macropinocytosis The formation of fluid-filled macropinosomes – large heterogeneous, dynamic vesicles.

MAPK Mitogen-Activated Protein Kinase. A kinase that responds to extracellular stimuli and regulates activities such as mitosis and gene expression.

Meiosis The process by which cells divide to produce eggs and sperm.

Melanin A pigment that gives the skin, eyes and hair their colour and protects them from UV rays.

Melanocytes Cells that produce melanin.

Mesenchyme Cells that have developed into connective tissue, blood vessels and lymphatic tissue.

Mesoderm The middle layer of cells in the early embryo.

Metabolites A chemical involved in or produced during metabolism.

Metabolomic Relating to all of the metabolites in a sample at any given time.

Metastasis Migration of cancer cells from their original site to other parts of the body.

Microarray A technique for studying how large numbers of genes interact and how a cell's regulatory network controls vast amount of genes simultaneously.

MiRNA MicroRNAs, RNA molecules around 20 nucleotides long that regulate gene expression.

Mitosis The process where a non-reproductive cell divides to become two identical cells.

Morphogenesis The process where cells differentiate into different structures.

Mutagenesis The process of intentionally creating mutations in an organism's DNA.

Mutant A gene or an organism that has experienced a mutation (a change in its genetic sequence).

Myosin A protein, along with actin, responsible for muscle contraction.

Myostatin A growth factor that limits muscle tissue growth.

Nanovesicles Small, dense vesicles.

Nematode Colloquially known as roundworms.

Neuron A nerve cell.

Neuropathic Pain from nerves themselves, as opposed to injured or diseased body parts.

NMR Nuclear Magnetic Resonance. A spectroscopic technique that analyses the disruptions to a high magnetic field to elucidate the chemical structure and molecular dynamics of a sample.

Nucleic Acid A molecule consisting of a chain of organic molecules that are sequenced with one another to create genetic information.

Nucleus A large, membrane-bound, usually spherical structure within a living cell, containing the cell's hereditary meaterial and controlling its metabolism, growth and reproduction.

Organelle A discrete subcellular structure with a specialised function.

Orthologous Any gene found in more than one species that can be traced back to the same common ancestor.

Osteoclast A large, multinuclear cell involved with the absorption and removal of bone.

Osteolytic Causing the breakdown of bone.

Paralogous Two genetic sequences that have the same evolutionary ancestor and arose through gene duplication.

Pathogen A disease-causing organism.

Pathophysiology A change in function caused by a disease or condition.

Peptide A compound of two or more amino acids.

Phagocytosis The process by which cells engulf material in order to destroy or digest it.

Pharming Farming genetically modified animals and plants to produce drugs.

Phenotype The characteristics of an organism resulting from the interaction between its genotype and its environment.

Phosphatase An enzyme that removes a molecule containing phosphorous acid from a nucleic acid or protein.

Phosphoregulators All mouse protein kinase and phosphatase genes.

Phosphorylation The process whereby a phosphate group (phosphate and oxygen) is added to a chemical compound.

PKA Protein Kinase A.

Polymorphism The existence of multiple forms of a gene or DNA sequence.

Primordia The earliest stage of an organ's development.

Pronuclear injection The injection of DNA into the nucleus of an unfertilised egg.

Prostaglandin Any of a group of compounds derived from fatty acids with a variety of actions and effects on cells.

Protease Any enzyme that causes the interior peptide bonds of a protein to split.

Protein A large molecule composed of one or more chains of amino acids in a specific order. Proteins are required for the structure, function and regulation of the body's cells, tissues and organs, and each protein has a unique function. Examples are hormones and antibodies.

Proteome The complete set of proteins being expressed at any one time by a cell, tissue or organism.

Radioligand A radioactive substance injected into tissue that binds to receptors and allows researchers to study its behaviour.

Redox A reduction/oxidation reaction, where the oxidation number of an atom changes.

Retromer complex A protein complex that is involved in the transport of proteins to the Golgi.

RNA A chemical similar to a single strand of DNA, except that RNA contains ribose instead of deoxyribose and uracil instead of thymine. RNA delivers DNA's message to the site of protein synthesis.

RNAi RNA interference. Occurs when a double-stranded RNA molecule is introduced into a cell, triggering the degradation of specific messenger RNA, and silencing the expression of target genes.

Rnomics The study of functional RNAs at the genomic level.

Soleus A muscle in the back of the calf of the leg.

Somatic Refers to any of the non-reproductive parts of the body, also used to mean a condition that is non-inherited.

Spectroscopy The study of the interaction between matter and radiation (eg. light).

Splicing The process where introns are removed from an RNA molecule.

Stochastic A process that is governed by random chance.

Synthase A class of enzyme that triggers a synthesis process.

Teleosts A class of bony vertebrate fish.

Tetraploid A cell that has four sets of chromosomes, two from each parent. Usually, an organism only has two sets of chromosomes, with one coming from each parent.

Thalassaemia An inherited disease where adult red blood cells are not able to produce haemoglobin.

Tomography The process of creating a series of detailed pictures of areas inside the body, created by a computer linked to an X-ray machine.

Transcription The formation of RNA from a DNA template.

Transcriptome All of the messenger RNA transcribed from genes within a given genome.

Transgenic An organism that has a transferred gene (transgene) incorporated into the chromosome of all its cells.

Transposon A DNA sequence capable of moving from one location in the genome to another.

Triglycerides A compound that is the major component in animal fats.

Urogenital Pertaining to the reproductive and urinary organs.

Vascular Pertaining to anything related to or containing conductive vessels, eg. blood vessels.

Vesicle A closed membrane shell.

Zinc finger A DNA-binding protein domain in which the zinc ion is crucial.

2007 PUBLICATIONS

DIVISION OF GENOMICS AND COMPUTATIONAL BIOLOGY

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9 ENCODE Project Consortium, Birney, E., *et al.* (including Mattick, J.S.) (2007). Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature* **447**: 799-816.

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11 Guipponi, M., Toh, M.Y., Tan, J., Park, D., Hanson, K., Ballana, E., Kwong, D., Cannon, P.Z., Wu, Q., Gout, A., Delorenzi, M., Speed, T.P., Smith, R.J., Dahl, H.H., Petersen, M., Teasdale, R.D., Estivill, X., Park, W.J., and Scott, H.S. (2007). An integrated genetic and functional analysis of the role of type II transmembrane serine proteases (TMPRSSs) in hearing loss. *Human Mutation* **29**: 130-141.

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