The IMB acknowledges and thanks our supporters and partners

Recommended further reading in conjunction with this Annual Report

• IMBcom Annual Report 2003
• SRC for Functional and Applied Genomics Annual Report 2003
• ARC for Bioinformatics Annual Report 2003
Creativity, motivation and intellectual freedom are the vital components of scientific discovery and technological progress, 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 our 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.

“Far better it is to dare mighty things, to win glorious triumphs even though checkered by failure, than to rank with those poor spirits who neither enjoy nor suffer much because they live in the grey twilight that knows neither victory nor defeat.”

Theodore Roosevelt
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CHAIR'S REPORT

The Institute for Molecular Biosciences (IMB) is one of The University of Queensland's premier research institutes and I am delighted with the many achievements detailed in this publication.

In May 2003 the IMB, along with CSIRO, took possession of the Queensland Bioscience Precinct, situated at the St Lucia Campus. This $105 million state-of-the-art facility has placed the IMB – and Queensland scientific research – firmly on the map.

Biological technology in its many forms is one of the major growth areas for the future. Since its establishment in 2000, the IMB has earned a reputation as one of our region's leading research institutes. The IMB is playing an increasingly important role in providing the foundation for Queensland's economic development and defining the future high technology industrial base of south-east Queensland.

The superb Queensland Bioscience Precinct brings together 700 scientists from the IMB and CSIRO – this collaborative research environment is ensuring major research advancements in biological, medical and agricultural sciences.

I would like to thank The Atlantic Philanthropies, the Federal and Queensland governments, CSIRO, research industry and private partners for their vision and support in helping to bring the Queensland Bioscience Precinct to fruition. Their funding has helped to create a climate in which investment in biotechnology is encouraged. We can see this approach already paying dividends with the establishment of a series of spin-off companies that will create many new jobs.

The IMB is part of a strategic cluster of research excellence at UQ - the Australian Institute for Bioengineering and Nanotechnology (AIBN) and the Queensland Brain Institute (QBI) currently under development are modelled on the successful IMB.

As Chair of the IMB Board, I would like to express my sincere thanks to the members of the IMB Board and Scientific Advisory Board for the contribution of their time, skills and energy to manage and develop the Institute.

Professor John Hay AC
Vice-Chancellor
The University of Queensland
2. Organisational Chart
3.

Professor John Mattick AO

DIRECTOR’S REPORT

2003 was a milestone year for the IMB. It was the year that our 480 staff and students, who had previously been housed in six different buildings across the University of Queensland were brought together under one roof, at the Queensland Bioscience Precinct (QBP).

This outstanding facility, located at the University of Queensland’s St Lucia site, was officially opened by Queensland Premier Mr Peter Beattie and Federal Minister for Education Dr Brendan Nelson in May 2003. The opening was accompanied by a major scientific symposium featuring the research of IMB and that of a number of our scientific advisors from Australia, Japan, Singapore, the United States and Europe.

The state-of-the-art laboratories and facilities represent a significant investment by both the State and Federal Governments in the future of bioscience and biotechnology research in Australia. The onus is now on IMB researchers to capitalise on this opportunity to propel Australian research to the forefront by conducting innovative and paradigm-shifting science. To this end we are developing a suite of integrated core programs with the ability to change the international landscape in molecular bioscience. These programs are (1) Mammalian Genomics and Genetic Programming, (2) Organogenesis, Tissue Damage and Regeneration, (3) Cell Architecture and Membrane Dynamics, (4) Chemical and Structural Genomics, and (5) Issues in Genetic and Cellular Medicine and Technologies.

The relocation to our new facilities has allowed further growth and development of IMBs intellectual and physical resources with several new research groups commencing operations. Professor Rob Capon joined IMB to head the new Centre for Molecular Biodiversity, which seeks to develop discover and develop natural compounds that have bioactivity. Professor Jeff Gorman, an IMB-CSIRO joint appointment, is establishing a joint IMB-CSIRO Proteomics Laboratory. This key facility will promote synergies with CSIRO’s Divisions of Livestock Industries and Plant Industry, with whom we share the QBP.

We have also substantially increased our strength in cell biology by the appointments of Professor John Hancock, Professor Rob Parton, Professor Mike Waters, and Associate Professor Alpha Yap, all of whom had previously had joint appointments with IMB but were located in other departments of the University.

I am also delighted to report that the University of Queensland has appointed Professor David Weisbrot, Head of the Australian Law Reform Commission in Sydney, Professor Nic Nicola, Assistant Director of the Walter and Eliza Hall Institute of Medical Research in Melbourne, Professor Yoshhide Hayashazaki, RIKEN Genomic Sciences Center in Tokyo, and Professor Gene Myers, University of California at Berkeley, as Honorary Professors at the Institute for Molecular Bioscience. We thank them for honouring us by accepting this appointment.

In other developments, IMB is the lead partner in the Australian Research Council’s Centre for Bioinformatics, headed by Professor Mark Ragan. IMB has also further developed its very important strategic research alliance with RIKEN Genome Sciences Center in Tokyo, an alliance that was symbolically recognised by RIKEN last August when the IMB was presented with RIKEN’s first distributed copy of the Mouse Genome Encyclopedia.

IMB also attracted significant funding from the US National Institutes of Health (NIH) through major grants to Professors John Hancock and Rob Parton, and to Associate Professor Jenny Stow and Professor David Hume, for their work to understand the dynamics of the cell surface and the regulation of important biological functions in cancer and inflammation. In addition a consortium of scientists from around Australia, led by Associate Professor Melissa Little, was awarded a major NIH grant for their project in kidney regeneration.
DIRECTOR’S REPORT CONTINUED

Our success in the national competitive ARC and NHMRC schemes for funding in 2004 was also pleasing. We were awarded seven Discovery, two Linkage and one LIEF grant in the ARC round, with a total value of approximately five million dollars, and we were successful in 15 NHMRC project grant applications, with a total value of nearly six million dollars. In addition, Professor John Hancock was awarded an NHMRC Principal Research Fellowship and Dr Rohan Teasdale was awarded an NHMRC R D Wright Career Development Fellowship, as well as a University Research Excellence Award. NHMRC Industry Fellowships were awarded to Norelle Daly and Brownyn Battersby.

In my last Director’s Report I bade farewell to Professor Peter Andrews, who resigned from the IMB as a Co-Director at the end of 2002. The new CEO of IMBcom, Dr Peter Isdale, joined us early in 2003 and he and Dr Peter Riddles have worked tirelessly to identify and develop the many commercial opportunities arising from the Institute’s research, assisting with grant applications, providing advice and guidance to students and facilitating smooth relations between stakeholders and the IMB. It has been a pleasure working alongside the IMBcom team over the past year and I look forward to many productive years to come.

I am delighted to report that Peter Andrews was honoured for his contributions to the development of a research-based pharmaceutical industry by appointment as an Officer in the Order of Australia (AO) in the Australia Day Honours list. Peter has also been appointed to the new post of Chief Scientist of Queensland. In addition, the Vice Chancellor and Chair of the IMB Board, Professor John Hay, was appointed as a Companion in the Order of Australia, this nation’s highest honour, for his enormous contributions to the development of this and other universities, including the development of IMB, for which we are truly grateful.

I would like to thank the IMB’s senior executive team, in particular Professor Brandon Wainwright (Deputy Director Research) who is responsible for overseeing the research management of the Institute, and Dr Ian Taylor (Deputy Director Systems and Infrastructure) who is responsible for the management of the Institute’s administration and support facilities, and whose experience was critical in the design of the building and its exceptional features. Additionally I thank IMB’s Division Heads Professors Mark Ragan, George Muscat, John Hancock, Paul Alewood, as well as Professor David Hume, Director of the ARC Special Research Centre for Functional and Applied Genomics, and Professor Wayne Hall, Director of the Institute’s Office of Public Policy and Ethics for their invaluable contributions to the development and running of the Institute. We also welcome Dr Lindsay Hood, who will manage the Institute’s high performance computing and information technology systems.

Finally, I would like to thank the Vice Chancellor Professor John Hay, the Senior Deputy Vice Chancellor Professor Paul Greenfield, the Deputy Vice Chancellor (Research) Professor David Siddle and our other senior colleagues at the University of Queensland for their ongoing support of the Institute. We are also fortunate to have very experienced and committed IMB Board and Scientific Advisory Board members, many from interstate and overseas, who give of their extremely valuable time to provide governance, advice on strategic development, and critical review of the performance of the Institute. My final thanks go to the State and Federal governments, without whom the wonderful new facilities we now occupy would have remained a dream.

We look forward to demonstrating to the community that their investment is well placed and will yield large dividends in terms of our contributions to world knowledge in biomedical science, and to the development of knowledge-based industries in Queensland and Australia.

Professor John Mattick AO
Director
Institute for Molecular Bioscience
We look forward to demonstrating to the community that their investment in us is well placed and will yield large dividends in terms of our contributions to world knowledge in biomedical science, and to the development of knowledge-based industries in Queensland and Australia.
4.

**IMB Advisory Board**

**Professor John Hay AC (Chair)**  
(Pictured 1)  
Professor John Hay has been Vice-Chancellor and President of The University of Queensland since 1996. He is a graduate of the University of Western Australia and Pembroke College, Cambridge where he held a Hackett Research Fellowship. He held the Chair of English and was Head of the Department in the University of Western Australia where he was also Deputy Chair of the Academic Board. At Monash University, he was Dean of Arts and Chair of the National Key Centre for Australian Studies and was then appointed Senior Deputy Vice-Chancellor of Monash University. In 1992 Professor Hay was appointed Vice-Chancellor and President of Deakin University in Victoria. In 2002 Professor Hay was appointed to the Higher Education Review Reference Group. Professor Hay was Chair of the Group of Eight, Australia’s leading research-intensive universities from January 2002 to May 2003. He is currently Chair of the Australian Universities Teaching Committee, and Universitas 21, a consortium of international research-intensive universities.

**Professor John Mattick AO (Director)**  
(Pictured 2)  
Professor Mattick was responsible for the development of the IMB with Professor Peter Andrews. In 1988 he was appointed the Foundation Professor of Molecular Biology and Director of the Centre for Molecular Biology and Biotechnology at the University of Queensland. The Centre was subsequently designated a Special Research Centre of the Australian Research Council (1991-1999) and was re-named the CMCB. He was responsible for the development of one of the first recombinant DNA-based vaccines, and was the recipient of the 1989 Pharmacia-LKB Biotechnology Medal from the Australian Biochemical Society, and the inaugural (2000) Eppendorf Achievement Award from the Lorne Genome Conference. Professor Mattick is a member of the Australian Health Ethics Committee and the Research Committee of the NHMRC. He is a foundation member of the recently established International Molecular Biology Network (Asia-Pacific), was a foundation member of the Board of ANGIS (the Australian National Genome Information Service) from 1991-2000 and is currently a member of the Board of the Australian Proteome Analysis Facility.

**Mr Paul Fennelly**  
(Pictured 3)  
Appointed as Director-General, Department of State Development and Co-ordinator General of Queensland in February 2002. Mr Fennelly has recently been appointed as Director-General of the newly established Department of State Development and Innovation. The Department is responsible for driving the economic development of Queensland and the delivery of the Government’s Smart State Strategy.

The Department’s activities involve:
- Major Projects & Infrastructure
- Investment Attraction
- Public Private Partnerships
- Industry Development
- Innovation
- Small Business

From January 2000 to January 2002, Mr Fennelly was the State Director of Australian Industry Group, Victoria’s largest business organisation, representing approximately 6,000 companies. Mr Fennelly was also the Queensland Director of MTIA / Australian Industry Group from 1993 - 1999. Mr Fennelly holds degrees in Law and Arts, as well as a Graduate Diploma in Industrial Law.
The IMB is part of a strategic cluster of research excellence at UQ - the Australian Institute for Bioengineering and Nanotechnology (AIBN) and the Queensland Brain Institute (QBI) currently under development are modelled on the successful IMB.
Mr Scott Flavell
(Pictured 4)
Scott Flavell has been the Director-General of the Department of Innovation and Information Economy, Sport and Recreation Queensland since 3 June 2002. Prior to his current position, Scott was the Executive Director of the Office of Energy. He has worked as an economist and policy advisor in senior positions in the Commonwealth and Queensland Governments for the past 18 years, including Queensland Treasury, the Department of the Premier and Cabinet, the Department of the Prime Minister and Cabinet and the Department of Finance.

Professor Frank Gannon
(Pictured 5)
Since 1994, Frank Gannon has been the Executive Director of the European Molecular Biology Organisation (EMBO), Secretary-General of the European Molecular Biology Council (EMBC), and Senior Scientist at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany. He is also Senior Editor of EMBO Reports and Associate Editor of the EMBO Journal. He serves on a number of scientific advisory boards at institutes throughout the world.

Professor Paul Greenfield
(Pictured 6)
Professor Greenfield is Senior Deputy Vice-Chancellor of the University of Queensland. After graduating Bachelor of Engineering, first-class honours in chemical engineering, from the University of New South Wales (UNSW), Professor Greenfield worked in the private sector before completing a PhD at UNSW. He 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 the Scientific Advisory Committee overseeing the $5.2 million Moreton Bay and Brisbane River Wastewater Management Study (since 1994); the Waste Technical Working Group, Basel Convention (since 1995); and the Advisory Board of I.P. Australia (since 1999). He is also a Director of several University companies including UniQuest Pty Ltd. 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
(Pictured 7)
Dr. Howard is Maxygen’s Chief Executive Officer and one of the company’s co-founders (founded in 1997). Originally trained in biochemistry and chemistry, Dr. Howard has spent over 20 years studying infectious diseases, primarily malaria. Before joining Maxygen, Dr. Howard served as the President and Scientific Director of Affymax Research Institute, an institute employing combinatorial chemistry and high throughput target screening to discover drug leads. Prior to joining Affymax, Dr. Howard held various research positions at DNA Research Institute and the National Institutes of Health. Dr. Howard received his Ph.D. in biochemistry from Melbourne University, Australia. In addition to numerous patents, Dr. Howard has over 140 publications in peer-reviewed journals. Today, Maxygen is focused primarily on development of protein pharmaceutical drugs, with other therapeutics programs in vaccines. Maxygen spun-out its chemicals manufacturing division, Codexis, in 2002 and retains its wholly-owned Agbiotech subsidiary, Verdia.

Dr Peter Isdale
(Pictured 8)
Peter Isdale was appointed Chief Executive Officer of IMBcom Pty Ltd in March 2003. He spent 15 years as a marine scientist before trading his wetsuit for a business suit at the Australian Institute of Marine Science (AIMS), the country’s marine national science agency, where he had been a Principal Research Scientist who is the author or co-author of more than 30 papers in his special field of research. As the Business Director and Executive at AIMS, Dr Isdale directed the strategic development of AIMS’ business and commercial interests, including licensing and company spinouts, and managed the Institute’s legal and intellectual property affairs. Dr Isdale has had 17 years of directorship on company boards, and a record of achievement in the operation
and governance of both private, public and ASX-listed companies in Australia, Asia and the Pacific Rim. He is a Member of the Australian Institute of Company Directors, and currently holds the positions of non-executive director, Great Barrier Reef Research Foundation, non-executive chairman of The Wetlands and Grasslands Foundation, Senior Fellow, Chaiyong Limthongkul Foundation, Bangkok, Thailand and Adjunct Professor, Department of Land Development and Environmental Planning, School of Architecture, Texas A&M University.

Ms Helen Lynch AM  
(Pictured 9)
Helen Lynch AM is Deputy Chairman of Pacific Brands Limited, Chairman of the Sydney Symphony Orchestra, and a Non-Executive Director of Southcorp Limited, Westpac Banking Corporation. Helen Lynch’s previous directorships include Chairman of OPSM Group Limited until 2003, Director of Coles Myer Ltd 1995-2003, Chairman of the Superannuation Funds Management Corporation of South Australia 1995-2000. Current involvements include member of Advisory Board Caliburn Partnership and External Advisor Mallesons Stephen Jaques. External Board Member Institute of Molecular Bio-Science University of Queensland. Helen Lynch had a distinguished career, spanning 35 years, in the Banking and Finance Industry at Westpac Banking Corporation including being a member of the Bank’s executive committee. She left Westpac in 1994 and was appointed a Non-Executive Director of the Bank in 1997. In 1990 Helen Lynch was the Bulletin/Qantas Business Woman of the Year. Helen was made a member of the Order of Australia in 1994 for services to the Banking and Finance Industry. In 2003, Helen received the Centenary Medal in recognition of her service to Australia: Society in Business Leadership.

Professor Mick McManus  
(Pictured 10)
In 1998, Mick McManus was appointed Executive Dean of the Faculty of Biological & Chemical Sciences and prior to this he was Head of the Department of Physiology & Pharmacology from 1993 to 1997. Mick’s initial appointment to the university was as Foundation Professor of Pharmacology and he was President of the Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists from 2000 - 2001. He came to the University from a National Health & Medical Research Council Principal Research Fellowship position in the Department of Clinical Pharmacology at Flinders University in Adelaide. He was initially trained as a pharmacist at Curtin University of Technology and completed his PhD at the University of Western Australia in 1978. Mick has held research positions at the Royal Postgraduate Medical School, University of London and the National Cancer Institute, National Institutes of Health in Bethesda, Maryland, USA. He continues to have a strong research interest in the area of xenobiotic metabolism, especially on the role human sulfotransferases play in this process.

Mr Ross Rolfe  
(Pictured 11)
Ross Rolfe was appointed the Director-General of the Department of State Development and Co-ordinator General in 1998. In 1996, he was the Director-General of the Department of Environment and Heritage, under the previous Labor Government. Mr Rolfe has a background in issues relating to land management, the energy industry and the environment. Mr Rolfe’s expertise and knowledge has been utilised by such companies as Chevron Asiatic, Powerlink Queensland, BHP - Coal Division, industry associations and a range of development companies.

Sir Sydney Schubert  
(Pictured 12)
Sydney Schubert has had a career spanning 40 years with the Queensland Government, including Co-ordinator General and Director-General between 1976 and 1988. He was Executive Chair of Daikyo Group of Companies, Australia and New Zealand, from 1988 to 2000. Currently he is Chair of the CRC for Great Barrier Reef World Heritage Area, CRC for Tropical Rainforest Ecology and Management and CRC for Torres Strait. He is also Director of the Australian Tropical Forest Institute and Australian Canopy Crane.
The highlights for 2003 were varied from outstanding research achievements, relocation to our new home in the Queensland Bioscience Precinct and visits from internationally acclaimed researchers.

**FACILITIES**

**Opening of the Queensland Bioscience Precinct**

The opening of the Queensland Bioscience Precinct (QBP) and subsequent relocation of the IMB into its new home was a watershed for the emergence of Queensland as a regional and international centre for advanced bioscience research. Opened by the Federal Minister for Education, Science and Training Dr Brendan Nelson and Queensland Premier Peter Beattie on 21 May 2003, the QBP brings together for the first time under one roof all aspects of the IMB. The Precinct offers IMB research and support staff a work environment the equal, if not better, than any other research facility in the nation.

**UQ’s equipment sharpening the cutting edge**

The ability of IMB and UQ researchers to solve extremely difficult molecular problems has taken a giant leap forward with the installation of Australia’s most powerful X-ray crystallography instrument. This new weapon in the research arsenal of IMB and UQ will help in the fight against many human diseases such as cancer, diabetes and Alzheimer’s to name a few.

The high resolution and exquisite sensitivity of this new piece of equipment can only be bettered by a synchrotron facility, which at a cost of over $150 million and the size of a large football field, is currently unavailable to Australian researchers.

**New building allows new appointments**

Two internationally recognised scientists migrated north to join the IMB and further their research exploring Australia’s biodiversity and setting up a world class proteomics facility.

Professor Jeff Gorman (Molecular and Cellular Proteomics) and Professor Rob Capon (Centre for Biodiversity) were attracted by the leading edge facilities and collaborative opportunities available at IMB and the QBP. Prior to joining IMB, Jeff Gorman was a senior principal research scientist with CSIRO/The Biomolecular Research Institute in Victoria. He is on the editorial boards of several leading journals in the field of protein and proteomic research.

Rob Capon was formerly a Professor of Chemistry at the University of Melbourne where he led the Marine and Natural Products Research Group.
RESEARCH

Anti-obesity gene flexes its muscle
A critical target in the war against obesity, which may lead to improved treatments, was identified in a world first by a research team from the IMB.

Obesity has reached epidemic proportions as poor diet and sedentary living have equalled tobacco as the leading cause of death in the US with Australia expected to follow this trend.

George Muscat and his research team showed that activation of the gene PPAR-delta in muscle cells increases lipid metabolism and the production of HDL or 'good' cholesterol.

The nature of venom reviewed in Nature

Cancer signal localised
IMB scientists John Hancock and Rob Parton broke new ground this year with their studies on the ras signalling pathway and provided novel insights as to how a cell receives information from its environment and transmits it to the nucleus.

Ras signalling is perturbed in many forms of cancer and essential for the normal functioning of mammalian cells. The Hancock and Parton team, recent recipients of an NH&MRC Program Grant, demonstrated that ras signalling occurred in localised microdomains throughout the plasma membrane. Differential spatial localisation within this framework can likely account for the distinct signal outputs from Ras proteins.

This work has far reaching consequences for our understanding of cell signalling and identified an organisational structure which had not been suspected previously. The work required an integration of powerful cell biology techniques including advanced microscopy and the development of a novel statistical treatment of cell signalling.

Medication has helped reduce Australian suicide rate
Access to antidepressant medication had a significant impact on suicide deaths in Australia a major national study found.

Wayne Hall along with researchers from the University of New South Wales and the Commonwealth Department of Health and Ageing, analysed national trends in suicide rates and antidepressant prescribing from 1991 to 2000.

The study found that while overall suicide rates remained constant over the ten year period studied, there was a decline in the suicide rate for older men and women.

Assigning function to the transcriptome
IMB scientists led by David Hume, played a vital role in the international consortium that provided the functional annotation to the mouse transcriptome project (FANTOME2).

This resulted in a special issue of the journal Genome Research providing an overview of the FANTOM2 project.

Inflammatory argument
The treatment of inflammatory disease is a major unmet clinical need world wide. David Fairlie and colleagues from the Physiology and Pharmacology Department of the University of Queensland have identified a potent class of molecules with anti-inflammatory activity.

Using a rational drug design approach the IMB group synthesised a molecule targeted at a human complement receptor, C5a. This receptor is not normally associated with pathology such as inflammatory bowel disease (IBD) but Fairlie and colleagues argued that it may have a role. This was borne out when potent novel agonist of the C5a receptor significantly reduced inflammation in a rat model of IBD.

These findings are an additional demonstration that chemistry allied to detailed biological knowledge can generate novel therapeutic insights applicable in many areas.

Venom switches function
A collaborative research team headed by Paul Alewood along with scientists from UQ’s Biological and Chemical Sciences Faculty demonstrated that specific conotoxins from the venom of marine cone snails could switch function.

Until recently it was thought that α-conotoxins could act solely in an antagonistic manner, blocking the nicotinic receptors that play a vital role in human neuronal transmissions. This discovery demonstrated that a minor chemical change to an α-conotoxin could open up an as yet unexplored realm of therapeutic lead development.
AWARDS

Centenary Honour
IMB Director John Mattick was awarded a Centenary Medal in 2003. These medals were created to recognise Australians who have made a significant contribution to our society or government.

National honour for Queensland researcher
Australia’s peak scientific body the Australian Academy of Science awarded IMB’s Melissa Little the prestigious Gottschalk Medal for medical sciences.

The award recognises Melissa’s groundbreaking work to understand the complex genetic messages controlling kidney development and how this may be applied to prevent or cure chronic renal failure.

New mining technology to help identify genes
IMB researcher Rohan Teasdale won a $75,000 UQ Foundation Research Excellence Award to continue his important work using ‘database mining’ to extract valuable information about how cells work.

Rohan is essentially digging through the incredible wealth of information contained in the genomes of mice and humans to understand the role of cell membranes.

IMB researcher tops world list
Queensland’s reputation as the Smart State was further enforced when an IMB researcher was rated as one of the world’s most cited authors.

The US based Institute for Science Information identified Director of IMB’s Office of Public Policy and Ethics, Wayne Hall, as one of the foremost experts in his research field and ranked him in the top 0.5 percent of publishing authors worldwide over the last 20 years.

Researcher rewarded with Federation Fellowship
The Federation Fellowship is awarded to leading Australian researchers working in fields of national benefit. Valued at over $1.15 million over five years, the Fellowship supports internationally competitive research resulting in economic, environmental and social benefits for Australia.

Kevin Burrage, from UQ’s Department of Mathematics, School of Information Technology and Electrical Engineering and a Joint Appointment with IMB uses computational biology to provide a foundation for developing improved pharmaceuticals and genetic treatments for human diseases like obesity, different types of cancer and Alzheimer’s disease to name a few.

(From left) Melissa Little; Rohan Teasdale; Wayne Hall; Kevin Burrage (2nd from right) and other Federation Fellows with The Hon. Dr Brendan Nelson Minister for Education (4th from right).
**Grants**

**US supports IMB research**

Two IMB research teams were awarded approximately US$1 million (about A$1.6 million) each by America’s premier science funding body the National Institutes of Health.

These grants enable the research teams to investigate and design new therapies for debilitating human diseases like chronic inflammatory bowel disease, cancer and arthritis and to develop anti-cancer therapeutics.

Jennifer Stow and David Hume are investigating the cellular processes that regulate the secretion of tissue necrosis factor alpha (TNFα) by macrophages, a process vital to fighting bacterial infections. However excess TNFα is a major cause of tissue damage in chronic inflammatory diseases and cancer.

Meanwhile John Hancock and Rob Parton are investigating the molecular switches that control many human biochemical and signalling pathways and are frequently mutated in human tumours.

**Boost for Australia’s health research – NHMRC and ARC grant success**

IMB research performed exceptionally well in the Australian Research Council (ARC) and National Health and Medical Research Council’s (NHMRC) 2003 funding rounds.

IMB researchers were successful in three ARC categories attracting over $5.2 million through Discovery, Linkage and Linkage - Infrastructure Equipment and Facilities Project categories.

In addition IMB researchers were awarded over $5.6 million for project investigating the molecular basis of human diseases and developing drugs to assist in treating these conditions.

A highlight of the IMB’s grant applications was the high level of collaboration with other research organisations boosting the Institute’s capacity to undertake globally important research in the biosciences.

**New research centre in bioinformatics**

Understanding how all the information encoded in the human genome actually ‘comes to life’ was boosted when the Federal Government announced almost $4 million funding for the Australian Research Council Centre for Genome-Phenome Bioinformatics, based at IMB.

Spread over five years the ARC funding will enable researchers to model and visualise complex molecular processes in mammalian cells based on the transformation of genetic information into cellular form and function.

**Conferences**

**ISMB Conference**

IMB was integral in the successful running of the prestigious Intelligent Systems in Molecular Biology (ISMB) conference held in Brisbane in July.

This was the first time the conference had been held outside North America and Europe and attracted world leaders in the fields of computational biology and bioinformatics.

Hosting this internationally important event cemented the IMB as a key driver of Australian research at the nexus of traditional biology and information technology.

**IMB Symposium**

The first major event held in the IMB’s new home, the QBP, was the IMB Symposium.

IMB hosted an exciting convergence of research specialists discussing the topic ‘Towards Systems Biology’.

The Symposium featured international leaders in the field and showcased groundbreaking research conducted at the IMB and abroad.
COMMERCIALISATION

CEO boosts Queensland’s commercialisation

IMBcom, the company set-up by the University of Queensland to commercialise research of the IMB, appointed in January 2003 its new Chief Executive Officer.

Chair of IMBcom’s Board of Directors Emeritus Professor Ted Brown AC announced that Dr Peter Isdale was the new person responsible for the strategic oversight of the practical application of IMB’s leading research.

Commercialisation boost for Queensland research

Research into repairing damaged kidneys and a company developing a remarkable Queensland technology that bar-codes chemicals were boosted by the Innovation Start Up Scheme grants announced by the Minister for Innovation and Information Economy Mr Paul Lucas in December.

IMBcom, the commercialisation company for the IMB, was instrumental in the success of the application for Nephrogenix Pty Ltd and helped Nanomics Biosystems Pty Ltd with the application in the state-wide competitive selection process.

CEO of IMBcom Dr Peter Isdale said he was delighted with the success of these grants and that IMBcom’s translation of research into high value applied and commercial outcomes was reaping rewards for Queensland’s burgeoning biotechnology industries.
6.

IMB Research

Every individual inherits around 3 billion bits of information from each parent. This information is stored in our genome and programs the entirety of human development and all of the components of our body.

The research focus of the Institute for Molecular Bioscience is to investigate the basis of human and mammalian growth and development, at the genetic, molecular, cellular and organ levels.

We wish firstly to understand the wonderful process of normal development from a single fertilized cell to an adult, and the various stages and transitions that occur from conception to aging.

We also wish to understand what aspects of the process go awry in various disease processes, including cancer and other complex diseases that are the major health burden of our population.

Finally, arising from these insights, we also wish to develop pharmaceutical and cellular therapies, technologies and diagnostics to prevent or repair such diseases, and to pursue other opportunities for the practical applications of our understanding of mammalian genetic programming and molecular architectures, which have the capacity to transform and to create new industries both in biology and in information technology.

The following pages outline the IMB’s research projects and achievements in 2003.

The IMB is a highly collaborative environment where researchers from different fields combine to contribute to strategic research programs. This is underpinned by our highly developed infrastructure in informatics, genomics, chemistry, structural biology, cell and developmental biology and genetics. Consequently, IMB researchers may pursue a powerful combination of technical approaches and biological systems in order to gain insights mammalian biology.

“If you’re going to be a biologist and alive at any point in time in human history, you’d choose to be alive right now.”
Professor Brandon Wainwright, Deputy Director Research.
MAMMALIAN GENOMICS AND GENETIC PROGRAMMING

Focussing on

• Comparative mammalian and vertebrate functional genomics
• Rnomics
• Computational modelling of genetic and cellular regulatory networks

This program includes the ARC Centre in Bioinformatics and intersects with the University of Queensland Department of Mathematics and School of Information Technology and Electrical Engineering.

Research Group Leaders

Tim Bailey
Kevin Burrage
Steve Barker
Sean Grimmond
Jennifer Hallinan
Geoff McLachlan
John Mattick
Mark Ragan
Tim Bailey

**COMPUTATIONAL BIOLOGY, BIOINFORMATICS, STATISTICAL MODELING**

**Research overview**

In 2003 we concentrated on development of algorithms for modelling DNA sequences responsible for transcriptional regulation. We developed and algorithm for searching genomic DNA for regions containing statistically significant clusters of sites matching known transcription binding factor signals. We also continued work on improving motif-discovery algorithms.

**Collaborators**

Kevin Burrage, Department of Mathematics, UQ and IMB

Mark Ragan, IMB

Rohan Teasdale, IMB

Sean Grimmond, IMB

Bill Noble, Department of Genome Sciences and Department of Computer Science and Engineering, University of Washington, Seattle, USA

**Staff and Students**

**Undergraduate research scholars**

Deanne Hummelstad

Bryce Shepherd

**Grants**

ARC Centre in Genome/Phenome Bioinformatics

ARC discovery grant Membrane Proteins within the Mouse Transcriptome – Annotation of their Organisation and Subcellular Localisation

**Publications**

Kevin Burrage

BIOINFORMATICS

This group works on developing simulation and visualisation methodologies for understanding the behaviour of genetic regulation. The simulation models take into account stochastic effects, while the visualisation focuses on three-dimensional display.

Project

Stochastic models and simulations for chemically reacting systems

In microscopic systems formed by living cells, the small numbers of reactant molecules can result in dynamical behaviour that is discrete and stochastic rather than continuous and deterministic. This research introduces a new class of discrete stochastic methods based on Poisson processes that more accurately reflect the underlying cellular models.

The stochastic simulation algorithm (SSA) due to Gillespie has become a fundamental tool for simulating individual molecular reactions in the modelling of cellular behaviour and regulation. However, this method can be computationally quite demanding. We introduce a new class of numerical methods, called Poisson Runge-Kutta methods, that generalise this approach.

A general formulation and order theory for this class of Poisson Runge-Kutta methods is given, and high order methods constructed. Attention is given to such issues as stiffness and efficient implementation. Numerical simulations illustrate the performance of these new simulations on some important cellular models.

We have investigated bistability and switching issues in the Genetic Regulatory networks of lambda phage using these approaches.

We have also started to develop a three dimensional visualisation framework for simulating cellular models, both within a cell and for colony of cells.

Collaborators

Professor Perry Bartlett, Queensland Brain Institute, UQ.

Dr Santiago Schnell, Centre for Mathematical Biology, University of Oxford, UK.

Grants 2004

ARC Centre for Genome/Phenome Bioinformatics
ARC Discovery 2004 - 2006

Publications

5 papers have been written in the above areas.

Staff and Students

Tianhai Tian
Francis Clark
Nick Hamilton
David Woolford
Steve Barker

ARTHROPOD EVOLUTIONARY GENETICS

Research Overview
While most animals are arthropods, their genomes and evolutionary genetics are poorly understood. Our research focuses on the mitochondrial genomics of ticks and lice, the evolution of resistance to insecticides in lice and mosquitoes, and the phylogenetic relationships of lice and other insects.

Projects
Mitochondrial genomics
Mitochondria have their own genomes, and in most groups of animals the order of genes is remarkably similar.
However, we discovered two extraordinary exceptions: a group of hard ticks, and lice and their kin. The arrangement of the 37 genes in the mitochondrial genomes of these animals has changed so many times it is difficult to reconstruct the evolutionary path of these mitochondrial genomes.

By studying the mitochondrial genomes that have changed a lot, we hope to learn why the arrangements of genes in mitochondria evolve so slowly.

Resistance to insecticides
The insecticides that people rely on to control pests like lice and mosquitoes do not always work effectively because the insect develops resistance to the chemicals in the insecticide.

Our group studies the epidemiology of resistance and also seeks to understand the genetic and biochemical basis behind it.

Evolutionary relationships of lice
Human head lice are a severe social problem in developed countries yet body lice, which are associated with diseases like Typhus, are not.
The two are closely related and may even be the same species. We are studying whether the head and body lice of humans are interbreeding and therefore conspecific.

We also study the evolution of all lice (order Phthiraptera) and their relationships to the free-living Psocoptera.

Collaborators
Dr Michael Whiting, Brigham Young University, Utah, USA
Professor Masahito Fukunaga, Fukuyama University, Hiroshima, Japan
Associate Professor Rick Speare, James Cook University, Townsville Australia

2003 Grants
Uniseed Pty Ltd Seed funding for Hatchtech Pty Ltd
Biotechnology Innovation Fund to Hatchtech Pty Ltd
A novel strategy for controlling lice of humans
ARC Linkage Grant Resistance to pediculicides in head lice, Pediculus humanus capitis
ARC Grant Origins of parasitism in the Psocodea insecta
Fisheries Research & Development Corporation (FRDC) Control of Perkinsus disease in abalone
(Left) This is Pediculus humanus, the head louse of humans; (Right) A cattle tick from Zimbabwe, Amblyomma hebraeum
(Opposite page above) A wildlife tick from Australia, Haemaphysalis bremneri; (Opposite page below) The cristae of the mitochondria of
a louse

Staff and Students

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<thead>
<tr>
<th>Postdocs</th>
<th>PhD students</th>
<th>Honour students</th>
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<tbody>
<tr>
<td>Renfu Shao</td>
<td>Natalie Leo</td>
<td>Cassie Jansen</td>
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<tr>
<td>Anna Murrell</td>
<td>Cath Covacin</td>
<td>Conor McMeniman</td>
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<tr>
<td>Steven Cameron</td>
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<td>Carl Davis (with CSIRO Livestock</td>
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<td>Industries, QBP)</td>
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Publications


Sean Grimmond

**EXPRESSION GENOMICS**

**Research Overview**

The central focus of my research is to capture information associated with global gene expression and use it to define the key gene products that control important biological processes and pathological conditions.

Undertaking this sort of research requires an integrated pipeline that uses

1) Microarray technology to capture all transcriptional consequences of a challenge to a biological system (e.g., chemical, environmental, genetic mutation, growth factor) gene expression,

2) Bioinformatics for annotating putative functions to all active genes,

3) Computational tools to identify genes whose expression pattern correlates with the challenge and

4) High throughput functional genomic assays for validating the role of lead genes generated by this and other pipelines. Once established this pipeline is a powerful tool for lead gene discovery in almost any biological system.

Since the completion of mammalian genome and transcriptome sequencing projects, the full complement of genes in the mouse and the human have been elucidated. The key challenges for my laboratory are to catalogue putative roles for all gene products, exploit genomic tools to fast track the discovery of lead genes and develop better understanding of the networks that control key processes. Integrating global assays of promoter activity, globally defined gene expression and phenotypic events attain these insights.

**Projects:**

Annotating the mammalian transcriptome:

2003 saw the systematic compilation of functional annotations to every gene present on the human and mouse microarrays generated in house. Genomic, transcriptomics, proteomic and ontological data have been collated from public sources (e.g., ENSEMBL, Swiss Prot, GenBank), collaborative efforts (e.g., FANTOM2) as well as results of our own initiatives (the secretome, Phosphoregulators, cell cycle related genes etc).

Temporal expression profiling of kidney development:

As part of the “Towards Renal Regeneration” Stem Cell Genome Anatomy Project (NIDDK-NIH) we have undertaken expression profiling of murine kidney development. This data has been combined with the annotation described in the previous project to rapidly identify putative functional leads that are now being studied further to determine their role in metanephric development. Efforts into the expansion of in situ expression profiling as a tool for providing high resolution spatial expression data have also commenced.

Advances in microarray based technology:

In addition to gene expression profiling microarray technologies can be used to perform other massively serial assays. This year has seen the development of methodologies and resources for perform reverse transfection or cell based microarrays as well as genomic based array technologies for studying promoter activity and DNA dosage. Reverse transfection has been used to perform a high throughput analysis of novel protein-protein interacting partner defined by RIKEN genome sciences. This project has demonstrated that reverse transfection can be used to rapidly assay transient transfection events and has provided important insights into PPI data quality.

**Collaborations**

NIDDK NIH Stem Cell Genome Anatomy Project:

- Melissa Little, IMB

IMB-RIKEN Sub-Cellular Localisation Project:

- Rohan Teasdale, IMB
- Harukazu Suzuki, Genome Sciences RIKEN, Japan
- David Hume, IMB

**Grants awarded**

ARC Centre for Genome/Phenome Bioinformatics
Publications and papers


Jennifer Hallinan

COMPLEX SYSTEMS NETWORKS

Research overview
The cell is a complex system of a myriad of different interacting molecules. DNA, RNA, proteins and biochemicals interact to maintain the cell in a robust, dynamic non-equilibrium state.

We are interested in the structure, dynamics and evolution of intracellular interaction networks ranging from metabolic networks through protein-protein interaction networks to the intricate networks of genetic regulation, which determine the type and activity of the cell.

Our research aims to understand how critical biological phenomena, such as homeostasis, mutational robustness and flexible gene regulation arise from interactions between the components of a complex biological system. We use the techniques of network analysis, already applied in fields as diverse as sociology, economics, physics, computer science and mathematics, to pursue this goal.

Projects
Development and analysis of computational models of networks
Using the IMB’s High Performance Computing facilities, we use a variety of algorithms, developed by our own researchers and those from other groups, to investigate the way interesting emergent behaviour unfolds in intracellular interaction networks. Highlights include the development of an Artificial Genome (AG) model for the study of genetic regulatory networks. The AG model was used to investigate the question of how interesting dynamic behaviour, in the form of fuzzy limit cycles, can arise in asynchronous networks, in which the nodes are not all updated simultaneously. Asynchronous networks are more biologically plausible than synchronous ones, but generally lack interesting behaviour. We have evolutionary algorithms to “evolve” more biologically plausible models of network behaviour.

Network models based on biological data
Jennifer Hallinan recently received an Early Career Researcher grant to support the development of a database of the genetic regulatory interactions surround the important oncogene, p53, mutations in which are associated with many cancers. This very large database will eventually bring together data currently widely scattered throughout the research and medical literature, as well that generated by the molecular biologists of the IMB. It will provide the basis for the development of detailed genetic regulatory network models targeted towards an understanding of the systems biology of cancer.

Grants awarded
UQ Early Career Researcher Grant The structure and dynamics of the p53 genetic regulatory network.
ARC Australian Centre for Genome-Phenome Bioinformatics.
Collaborators

Associate Professor Janet Wiles, The Complex and Intelligent Systems Group, School of Information Technology and Electrical Engineering, The University of Queensland.

Dr Ricarda Thier, Department of Physiology and Pharmacology, The University of Queensland.

Staff and Students

PhD student

Ben Skellett

Publications and papers


Speaking engagements

IEEE Congress on Evolutionary Computation,
The First Australian Conference on Artificial Life
7th International Conference on Knowledge-Based Intelligent Information and Engineering Systems.
Department of Pathology, University of New South Wales.
Geoff McLachlan

DATA MINING AND COMPUTATIONAL STATISTICS

Research overview
My research in statistics is in the related fields of classification, cluster and discriminant analyses, image analysis, 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 EM algorithm.

A common theme of my research in these fields has been statistical computation, with particular attention being given to the computational aspects of the statistical methodology. This computational theme extends to my interests in the field of data mining.

More recently, I have become actively involved in the field of bioinformatics with the focus on the statistical analysis of microarray gene expression data.

Grants (2003)
Australian Research Council Unsupervised Learning of Mixture Models in Data Mining Applications
Australian Research Council Classification of Microarray Gene-Expression Data
National Health & Medical Research Council Hierarchical finite mixture modelling of health outcomes: a risk-adjusted random effects approach
Innovation Access Program Development of market driven computational biology infrastructure for advanced education and training

Collaborators
Dr Christophe Ambroise, University of Compiagne, France
Dr Kim Anh-Do, MD Anderson Cancer Center, University of Texas, USA
Professor Christine McLaren, University of California, Irvine, USA
Dr Kelvin Yau, University of Hong Kong
Professor Kaye Basford, School of Land and Food, UQ.
Dr Andy Lee, School of Public Health, Curtin University of Technology, Perth, Western Australia

Staff and Students

Research officers
Richard Bean
Liat Jones
Abdollah Khodkar

PhD students
Soong Chang
Justin Zhu
Katrina Monico
Prizes/keynote addresses


**John Mattick**

**RNA-BASED GENE REGULATION IN EUKARYOTIC DEVELOPMENT**

**Research Overview**

Our group takes a genomic and molecular genetic approach to the role of noncoding RNA in the programming of differentiation and development in humans and other complex organisms.

For a number of years our group has been developing an interest in one of the great mysteries of biology – what, if anything, is the function of the vast amount of introns and intergenic sequences in the genomes of the higher organisms that do not appear to have any function?

These sequences are usually assumed to be evolutionary debris ("junk DNA"). However many of these sequences are expressed as non-protein-coding RNAs, and account for around 98% of all genomic output in humans. Therefore either the human genome is replete with useless transcription, or these RNAs are fulfilling some unexpected function(s).

Perhaps the most fundamental belief in molecular biology is that genes are generally protein-coding, as an extension of the central dogma and the fundamental ethos of biochemistry. This is essentially correct for prokaryotes, wherein the early experiments that defined our understanding of genes and gene expression were carried out. It has been assumed that the same is true in multicellular organisms, despite the fact the proportion of protein-coding sequences declines as a function of complexity and is only a small minority of the genomic programming of complex organisms like mammals.

We have advanced the hypothesis that the higher organisms have in fact evolved an advanced and highly parallel genetic operating system based on digital RNA signals derived from the introns of protein-coding genes, as well as other genes that do not encode protein at all, which integrate complex suites of gene activity and control the trajectories of differentiation and development. This hypothesis is consistent with all of the known data, and if correct has the capacity to transform our understanding of the genetic programming of higher organisms, their evolution and diversity, with considerable practical consequences for medicine, agriculture and information science, in terms of genetic diagnostics, therapies, advanced genetic selection and engineering, and the design of artificial systems capable of self-referential assembly.

We are using bioinformatic techniques to identify and map RNA regulatory networks in a variety of key organisms from yeast to mammals, developing new databases and microarray chips to examine the expression of noncoding RNAs in humans and mice during development and in different disease states, and undertaking genetic and molecular genetic experiments to test crucial parts of the hypothesis. We are also using computational modelling to examine the ability of such networks to evolve and to program the ontogeny of complex organisms and to test the power of the system and its potential for rational design of complex systems.

**Collaborators**

Professor Yoshihide Hayashazaki, RIKEN Genome Sciences Centre, Yokohama, Japan

Professor Claes Wahlstedt, Karolinska Institute, Stockholm, Sweden

Professor Peter Arctander, University of Copenhagen, Denmark

Dr John Logsdon, University of Iowa, USA

Dr David Haussler, Dr Gil Bejerano, Dr Jim Kent, University of California Santa Cruz, USA

Dr John Doyle, California Institute of Technology, Pasadena, USA

Dr Weisan Chen, Ludwig Institute for Cancer Research, Melbourne

Professor Robert Giegrich (Bielefeld University, Germany)
Staff and Students

**Research officers**
Dr Michael Gagen  
Dr Evgenj Glazov  
Dr Igor Makunin

**PhD students**
Khairina Tajul Arifin  
Michael Pheasant  
Cas Simons

**Masters student**
Stuart Stephen

**Honours student**
Michael Lai

**Research assistants**
Kelin Ru

**Visiting scholars**
Marcus Hinchcliffe  
Ken Pang  
Hidayat Trimarsanto

**Visiting researcher**
Professor Peter Arctander

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**Publications**


Keynote and invited lectures at national and international conferences


Invited talks at other institutions


Awards

Honorary Fellowship of the Royal College of Pathologists of Australasia (FRCPA)

Australian Government Centenary Medal, for services to biotechnology
For a number of years our group has been developing an interest in one of the great mysteries of biology – what, if anything, is the function of the vast amount of introns and intergenic sequences in the genomes of the higher organisms that do not appear to have any function?
Mark Ragan

COMPARATIVE AND COMPUTATIONAL GENOMICS

Research overview
We use advanced bioinformatic, computational and database methods to investigate similarities and differences among genomes and the proteins they encode. Our goal is to make quantitative inferences about how genomes have come to have their observed contents of genes, how protein families have diversified, and how cellular function has evolved.

Projects
Automated inference of vertical and lateral gene transmission in prokaryotic genomes
For nearly 150 years, biologists believed that all genetic information was transmitted “vertically” from parents to offspring. The very few exceptions – as in the spread of antibiotic resistance among bacterial populations – were seen as extraordinary, highly specialised phenomena. Within the past few years, this orthodoxy has been turned on its head. Lateral gene transfer – the transmission of genetic information across, not within, genealogical lineages – is now suspected to be much more common than previously imagined. The evidence remains somewhat controversial, but in the case of many bacterial genomes is increasingly convincing. If diverse types of bacteria participate in a common gene pool, the consequences could be immense throughout environmental science, biotechnology, agriculture and medicine.

We are constructing an automated computer-based system to collect and manage bacterial genome sequences, identify protein families, generate and optimise multiple sequence alignments, rigorously infer phylogenetic trees, and find all statistically supported instances of incongruence among them. Our “phylogenetic pipeline” has already spun-out challenging projects in algorithmics, computational modelling, distributed and parallel computation, data handling and information integration. Although designed to search for laterally transferred genes, the system will also yield comprehensive libraries of protein motifs and other information useful in applied areas of bioscience, including drug design and metabolic engineering.

Component and related projects
- Hybrid Markov-plus-linkage-based approach for high-throughput recognition of protein-sequence clusters
- Automated recognition of maximally representative clusters of protein sequences
- Word-oriented objective function for scoring and ranking multiple sequence alignments
- Application of pattern discovery to alignment-free inference of molecular phylogenetic trees
- Bayesian and maximum likelihood phylogenetic analyses of protein sequence data under branch-length bias and model violation
- New algorithms to describe and compare protein folds
- Information integration in bioinformatics
- Workflow-enabled pipeline for bioinformatics
- Java interfaces for bioinformatic tools on IBM p690

ARC Centre in Bioinformatics
The Australian Research Council (ARC) Centre in Bioinformatics, with headquarters at IMB, started-up unofficially in late 2003 ahead of a formal start in early 2004. This Centre coordinates research (for 13 investigators across five institutions) in bioinformatics, cellular network modelling, advanced bioinformatic databases, 3D visualisation, and high-throughput experimental validation focused on understanding the mammalian cell as a complex system of regulatory and molecular interaction networks.

Mark Ragan is Centre Director (Director of Research, and Chief Operations Officer) for the ARC Centre in Bioinformatics.
Grants Awarded

**ARC Centre in Bioinformatics**

ARC Computational infrastructure for high-throughput genome bioinformatics.

**Australian Partnership for Advanced Computing**

Comparison of protein families among completely sequenced genomes.

Collaborators

Robert Charlebois, University of Ottawa, Canada and Neurogadgets Inc.

Jonathan Keith, Peter Adams and Darren Bryant, Department of Mathematics, University of Queensland

Isidore Rigoutsos, IBM Thomas J. Watson Research Center, USA

Nicholas Hamilton, Thomas Huber and Kevin Burrage, Advanced Computational Modelling Centre and Department of Mathematics, University of Queensland

Robin Gutell, Jamie Cannone, Usman Roshan, and Tandy Warnow, Institute for Cellular and Molecular Biology, University of Texas at Austin, USA

Samuel Thoraval, Université Montpellier, France

Catherine Letondal, Institut Pasteur, Paris, France

Jess Mar, Harvard School of Public Health, Boston, USA

Phoebe Chen, Deakin University, Melbourne

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<th>Staff and Students</th>
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<tr>
<td><strong>Research officers</strong></td>
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<tr>
<td>Robert Beiko</td>
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<td>Nicholas Hamilton</td>
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<td>Josef Pánek</td>
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<td><strong>PhD students</strong></td>
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<td>Cheong Xin Chan</td>
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<td>Alex Garcia</td>
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<td>Michael Höhl</td>
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<td><strong>Research assistant</strong></td>
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<tr>
<td>Timothy Harlow</td>
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<td><strong>Database administrator/developer</strong></td>
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<td>John Opitz</td>
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<td><strong>Postgraduate trainee</strong></td>
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<tr>
<td>Adrian Miranda</td>
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<tr>
<td><strong>Volunteer</strong></td>
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<tr>
<td>Chikako Ragan</td>
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<tr>
<td><strong>International intern</strong></td>
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<tr>
<td>Samuel Thoraval</td>
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<tr>
<td><strong>Administrative assistants</strong></td>
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<tr>
<td>Edith Hii</td>
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<tr>
<td>Lanna Wong</td>
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Publications and Papers


Published Abstracts


Conference Papers/Lectures

24th Lorne Genome Conference, Lorne, Victoria, February 2003

Second IMB Symposium (on the occasion of the opening of IMB), University of Queensland, May 2003

Australian Partnership in Advanced Computing APAC03, Gold Coast, October 2003 (Keynote address)

Canadian Institute for Advanced Research, Program in Evolutionary Biology, White Point Beach, Nova Scotia, September 2003

Australian Mathematics Society Institute, Summer Symposium in Bioinformatics, ANU, Canberra, December 2003 (Invited plenary)

First Australian Conference on Artificial Life, ANU, Canberra, December 2003 (Invited plenary)

Association of Asian Societies of Bioinformatics, Yokohama, December 2003
ORGANOGENESIS, TISSUE DAMAGE AND REGENERATION

Focussing on
- Urogenital development
- Inflammation
- Cell signalling and cancer
- Molecular genetics and molecular biology of aging

This program includes IMB’s participation in the Cooperative research Centre for Chronic Inflammatory Diseases; the ARC Centre of Excellence in Stem Cell Biology; the Centre for Biotechnology and Development; and the NIH funded project Nephrogenix, an initiative designed to develop new therapies for renal regeneration.

Research Group Leaders
David Hume
Stuart Kellie
Peter Koopman
Melissa Little
George Muscat
Joe Rothnagel
Rick Sturm
Brandon Wainwright
Michael Waters
Carol Wicking
MACROPHAGES AND OSTEOCLASTS

Research overview

The central issue being addressed in the Macrophage and Osteoclast Biology Research Group is the mechanism controlling the differentiation of macrophages and osteoclasts from their progenitor cells and the regulation of the function of these cells in health and diseases.

The group is a major node of the Cooperative Research Centre for Chronic Inflammatory Diseases, which focuses on identifying targets for the development of drugs to treat diseases such as osteoarthritis, rheumatoid arthritis and chronic obstructive lung disease (emphysema). We also have collaborations addressing the roles of macrophages in renal disease, tissue regeneration, malignancy, cystic fibrosis and inflammatory bowel disease.

We are interested in the signalling pathways that permit macrophages and osteoclasts to respond to agents such as growth factors (macrophage colony-stimulating factor, CSF-1; RANK ligand) and microbial products such as lipopolysaccharide and microbial DNA.

To assess the function of individual gene products we utilise a combination of transfection analysis and transgenics using new technologies developed in the group, including macrophage and osteoclast-specific transgenes.

We are developing systems biology approaches based upon cDNA microarray expression profiling, proteomics, high throughput structural genomics and computational network modelling, to try to gain an overview of how macrophages and osteoclasts function and to predict the way that they will respond to external agents including candidate drugs.

Projects

Functional Regulation (Matthew Sweet and Kate Stacey)

Macrophages express a number of receptors that regulate cellular function. The CSF-1 receptor allows for proliferation and differentiation of macrophages in response to the growth factor, CSF-1. It is also inappropriately expressed in a number of cancers and is likely to contribute to metastasis. We have used cDNA micro-arrays to identify CSF-1-regulated genes in macrophages. Such genes are likely to be involved in a diverse range of functions including differentiation, phagocytosis and tumour biology.

During pathogenic challenge, macrophages detect foreign products such as bacterial CpG DNA, lipopolysaccharide and bacterial lipoproteins. This activates the innate immune response and triggers the development of the acquired immune response. Bacterial CpG DNA in particular is a potent activator of a Th1-type immune response and has been used therapeutically as an adjuvant in anti-cancer vaccines and for the treatment of allergies. We are characterising CpG DNA responses in macrophages and the role of CpG DNA during pathogenic challenge in vivo.

Genetic Networks underlying Macrophage Activation (Christine Wells and Tim Ravasi)

By surveying the transcripts expressed in macrophages under different activation or differentiation contexts, we are able to measure the genetic network underlying macrophage responses. We use DNA microarray technology, coupled with bioinformatics-based genomic analysis and traditional genetic mapping strategies to look for these genetic networks. This approach has allowed us to identify genetic and epigenetic elements that modify the activation potential of inflammatory macrophages. The data generated from these studies form the “target-identification” side of the CRC pipeline designed to identify and test potential therapeutics for chronic inflammatory diseases.

Gene expression in macrophages and osteoclasts (Dmitry Ovchinnikov)

The ultimate goal of my research is to establish a versatile and reliable set of modern mouse molecular genetics tools for the alteration of gene expression in macrophages and osteoclasts. These tools will allow us to overexpress genes and/or inactivate them, in...
spatially and temporally controllable fashion. This will provide a novel approach to gene “replacement”, allowing the simultaneous control of both gene inactivation and overexpression.

**Osteoclast and bone biology (Ian Cassady)**

My research interests centre on gene regulation in bone-resorbing osteoclasts and their general role in bone biology and homeostasis. Bone is a dynamic organ that not only provides structural support for the body but also acts a sink and source of Ca\(^{2+}\) and P to maintain serum mineral homeostasis. A precise balance is required between the synthetic activity of osteoblasts and the resorptive activity of osteoclasts. Dysregulation of either arm of these activities can result in bone diseases such as osteoporosis. Osteoclasts have a central role as the effector cells of bone homeostasis and as such have been the target of therapeutic intervention. In spite of their importance the biology of osteoclasts remains poorly understood. To address this issue I have established a number of projects either directly in this laboratory or by collaboration with other groups to focus on the following areas:

- Gene regulation during osteoclastogenesis,
- Modulation of gene expression in osteoclasts *in vitro* or *in vivo* by transgenesis,
- Comparative promoter analysis of osteoclast marker genes and the role of PPARs,
- Specific gene expression in osteoclasts with therapeutic objectives,
- Analysis of the gene expression in bone in response to mechanical stress,
- Characterization of the functional role of TRAP in osteoclasts and in bone biology,
- Osteoclast and macrophage activity towards novel bone biomaterials.

**Studies on macrophage inflammatory proteins (Ian Ross)**

We are analysing the pathogen sensor molecule Nod2 (a susceptibility gene for the chronic inflammatory diseases Crohn’s disease, Blau syndrome and psoriasis) to help reveal the way the inflammatory cascades are controlled and how this fails in chronic inflammation. We are also using proteomic discovery approaches to reveal proteins with altered expression or location within the macrophage as a result of stimulation with microbial molecules such as lipopolysaccharide, peptidoglycan and muramyl dipeptide. This approach is identifying potential drug targets, which we are in the process of validating for biological effects.

**Grants**

- **NHMRC Project grant** Th2-Promoting Stimulus, ES-62
- **NHMRC Project grant** TLR 9 and response to foreign DNA
- **NHMRC Project grant** Osteoclast-specific gene regulation
- **NHMRC Project grant** COX-2 regulation of bone turnover and mechanically induced bone formation
- **UQ Research Development grant** Design and prototyping of a novel dynamic mechanical bioreactor for bone tissue engineering
- **ARC Discovery grant** Discovery of novel macrophage proteins
- **ARC Linkage grant** Development of tyrosine kinase inhibitors
- **CRC for Chronic Inflammatory Diseases** (supplementary funding)
- **US National Institutes of Health** Cytokine trafficking and secretion in macrophages
- **Amgen Development grant**
### Staff and Students

**Senior research fellow**
- Ian Cassady

**Senior research officers**
- Roy Himes
- Ian Ross
- Kate Stacey
- Matthew Sweet

**Research officers**
- Barbara Fletcher
- Dmitry Ovchinnikov
- Allison Pettit (NHMRC, CJ Martin Fellow)
- Liza-Jane Raggatt (NHMRC, Doherty Fellow)
- Tim Ravasi
- Tedjo Sasmono
- Kathy Speed

**Administrative officer**
- Julie Osborne

**Lab manager**
- Greg Young

**Research assistants**
- Jane Clarkson
- Stephen Cronau
- Geoffrey Faulkner
- Greg Kelly
- Jane Mooney
- Visala Rao
- Elke Seppanen
- Angela Trieu

**Database manager (CRC)**
- Xiang Liu

**PhD students**
- Guy Barry
- Myrna Constantin
- Tamarind Hamwood
- Katherine Irvine
- Nicholas Meadows
- Vera Ripoll
- Tara Roberts
- Kate Schroder
- Brendan Tse
- Nicole Walsh
- Christine Wells
- Andy Wu
- Richa Dave

**Honours students**
- Ming Chang

**Vacation scholar**
- Chien-chi Lo

### Publications


### Cassady, A.I., Luchin, A., Ostrowski MC, Hume DA.


**Patents**

CSF-1 Immunomodulation patent has entered PCT Phase Publication Date 10th April (2003)

**Key Conference Presentations**

**Hume D.A.** Invited speaker: International Society for Interferon and Cytokine Research Annual Meeting, Cairns, Australia, October 2003

**Hume, D.A., Sasmono, T., Ravasi, T., Wells, C.A.**

**Himes, S.R.** Transcriptional Regulation of Macrophage Differentiation. Lorne Genome Conference, Lorne, Australia

**Hume, D.A.** Transcriptional control in macrophages. European Macrophage and Dendritic Cell Society, Leicester, UK
Stuart Kellie

MACROPHAGE SIGNALLING

Research overview
As part of the CRC for Chronic Inflammatory Diseases, my laboratory collaborates closely with David Hume and groups in Monash and Melbourne to identify and investigate the function of a number of genes regulated in macrophages after cytokine activation. The aim of this work is to identify those genes or proteins which are aberrantly expressed during chronic inflammation, and to show an involvement in chronic inflammatory diseases such as rheumatoid arthritis and chronic obstructive pulmonary disease (COPD). The long-term aim is to generate inhibitors of these genes for therapeutic use in chronic inflammation, in collaboration with industrial CRC partners.

Projects
Generation of target validation platforms for functional analysis of macrophage genes
We have identified numerous genes whose expression is regulated by inflammatory cytokines, however in many cases the function of these genes in macrophages has not been investigated. To identify such genes as valid targets for therapy it is important to establish their role in macrophage biology. A number of cellular and molecular approaches are being established to investigated gene product function in macrophages: these include the establishment of inducible macrophage cell lines, siRNA, protein transduction methodology and the use of dominant-negative mutants.

Tyrosine phosphatases in macrophage function
Tyrosine phosphorylation is central to many aspects of cellular responses to extracellular stimuli. Whilst much is known about tyrosine kinases and their role in cell activation, less is known about how protein tyrosine phosphatases (PTPs) act as a biochemical counterbalance to the kinases to regulate tyrosine phosphorylation. PTPs are a large gene family and individual members exhibit substrate selectivity and control specific aspects of intracellular signalling. In recent years they have been recognised as both initiators and regulators of signalling in the immune system. A number of PTPs have been shown to be enriched in macrophages, however for the most part their function is unknown. We are investigating the expression and function of several PTPs in macrophages using a combination gene array technology, PCR, heterologous expression using a number of systems.

Kinases in macrophage function
Cytokines or stress leads to the activation in the MAPK/jun pathway in many cells types which in turn leads to new gene expression. This pathway appears to be particularly important for macrophage function and survival. There are still gaps in our knowledge about the molecular mechanisms controlling this signalling pathway. We have been investigating a class of intracellular signalling molecules termed STE20-related kinases. These are the most membrane-proximal kinases of this pathway, and in model systems regulate jun kinase and thus new gene expression. Using mutagenesis and expression we are investigating the regulation of activity of these molecules. Such studies will give insight into important activation pathways in inflammatory cells such as macrophages.

The long-term aim is to generate inhibitors of these genes for therapeutic use in chronic inflammation, in collaboration with industrial CRC partners.
MOLECULAR GENETICS OF MAMMALIAN DEVELOPMENT

Research Overview

We are studying the genes that control the formation of various organs during the development of a mammalian embryo. In particular we are striving to understand the events that regulate the development of the embryo as a male or a female, and the laying down of an intact and functional network of blood vessels.

Projects

Sex Determination and Gonadal Development

Development of two distinct sexes is critical to the survival of animal species, and defects in sexual development in humans are both common and distressing. My group is studying the molecular and cellular biology of Sry and several other genes in order to understand their role in male sex determination and the defects that can result in sex reversal. We are also searching for other genes downstream in the sex-determining pathway, using expression screening approaches such as microarrays. We have recently begun to characterise the molecular events leading to ovarian development in the embryo, an important process about which little is currently known.

Sox Gene Function and Evolution

As well as providing a point of entry to the sex-determining pathway, the discovery of Sry has led to the identification of a family of structurally related genes called Sox genes. The Sox gene family comprises 20 genes in humans and mice, known to be active during embryo development in specific subsets of tissues. We have identified several new members of this gene family and are examining their roles in mouse development. We are also interested in the phylogeny, evolution, and functional relationships between the various Sox genes and the factors they encode.

Molecular Genetics of Vascular Development

We discovered a gene, Sox18, that is expressed transiently in endothelial cells during vascular formation in the embryo and in the adult. Mutations in Sox18 disrupt vascular development and/or function. We are currently studying the genetics and biology of the role of Sox18 and related genes in vascular development, and exploring the possibility that angiogenesis can be modulated by enhancing or suppressing Sox18 activity.

Development of Male Germ Cells

As members of the ARC Centre for Excellence in Biotechnology and Development, we have begun to examine the specification and differentiation of the male germ line. This collaborative group aims to dissect the complex developmental networks underlying germ cell differentiation, with the aims of identifying genes involved in testicular and childhood cancers, elucidating mechanisms underlying idiopathic male infertility, developing new approaches to transgenic animal production, identification new targets for pest control, reprogramming germ cells for applications in biotechnology, and formulating innovative strategies for enhancing or suppressing fertility.
**Publications**


**Plenary or keynote speaker**


**Invited seminars**


Melissa Little

RENAL DISEASE

Research Overview

The central theme of this laboratory is the molecular basis of the development of the kidney.

Each of us has a pair of kidneys that function to excrete waste products in the form of urine. The kidneys do this by filtering our entire blood volume around 30 times per day through tiny filters called nephrons. Yet only around 2 litres of fluid is lost from the body in the form of urine due to the enormous capacity of the kidney to reabsorb water, ions and nutrients. The kidneys therefore also 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.

Loss of renal function is not compatible with life. Hence, chronic renal failure (CRF) is a devastating disease and an expensive one to treat. It is estimated that 60,000 Australians between 12 and 74 yrs have CRF. Each year, approx. 4000 Australian adults will be diagnosed with CRF, costing the health system >$30 million.

The most common cause of end stage renal failure (ESRF) is glomerulonephritis. However the current steady rise in ESRF rates is primarily due to an increase in the number of people with Type II diabetes. There is a critical need for the development of new therapeutic strategies for the treatment of CRF. A greater understanding of the processes involved in normal kidney development will underpin such developments and hence unravelling the molecules directing kidney development is the focus of our laboratory.

Projects

A master gene involved in generating a kidney

The WT1 gene encodes a nuclear regulatory protein essential to giving us kidneys. Without it no kidneys develop. Mutations in this gene later in life lead to a variety of kidney diseases, including the childhood kidney cancer, Wilms’ tumour. Hence, normal function of WT1 is critical for both kidney development and the ongoing function of the kidney after birth. Our research has focussed on how this regulatory protein works to create a kidney and keep it functioning by examining the genes it regulates, what proteins and nucleic acids it interacts with and to what end. This research is likely to identify other genes involved in kidney development and function and a mutation in which leads to kidney cancer or disease.

Using comparative biochemistry to understand function

One of the genes that we have discovered plays a role in the development of the kidney is Crim1. This gene makes a protein that determines the ability of a number of other growth factors to move around as well as regulating the cells they can act on. We have shown that a loss of this gene results in a number of kidney defects in mice. We have also used comparative biology to study the biochemical function of this protein in fish, in which more is known about the role of the growth factors regulated by Crim1. And so the fish, an organism with a very simple excretory system, can tell us more about the kidneys of more complex animals like humans.

Towards new therapies for renal disease

It has long been assumed that development of the kidney ceased at birth with no prospect of regeneration of new functional units after that time. Developments in stem cell biology over the past 5 years has brought in to question similar assumptions in other organs and we now know that the brain contains neural stem cells and that these can indeed change into many cell types. What about the kidney? Is there a renal stem cell and might it be used to treat renal disease?

The other milestone in stem cell biology has been the isolation of human embryonal stem cells bringing with it the prospect of regenerating tissue even if there is no persistent stem cell population. Could we regenerate a kidney or repair kidney damage using embryonal stem cells?

These two long-term questions are being tackled in this laboratory by systematically cataloguing all the secreted and cell surface proteins produced during kidney development using the genomic technique of expression profiling using glass microarray chips. Novel growth factors isolated from these screens are then assessed for their role in kidney development.
using organ culture assays. They can then be assayed for their ability to direct embryonal stem cells towards renal fate. In addition, we have established an embryonal kidney transplantation assay in which we can test the effect of novel growth factors on the development of the kidney in vivo. Novel cell surface markers are being used to isolate putative renal stem cells or purify renal progenitors from differentiating embryonal stem cells.

Our work on developing new therapies for CRF forms part of a national consortium linking our laboratory with others within the IMB, University of Queensland, Monash University and the Monash Institute for Reproduction and Development. The group is referred to as the Renal Regeneration Consortium and our research is supported by the National Institutes of Health, USA, along with the Australian Kidney Foundation (recently renamed Kidney Health Australia, http://www.kidney.org.au). Our renal stem cell work forms part of an international consortium of NIH funded groups referred to as the Stem Cell Genome Anatomy Project (http://www.scgap.org). The kidney component of this work is described at http://kidney.scgap.org.

Grants awarded in 2003

NHMRC Project grant: The role of Crim1, a novel TGFB superfamily modulator, in early vertebrate patterning, vascular and renal development

Publications


George Muscat

NUCLEAR HORMONE RECEPTORS AND GENE REGULATION

Research overview

My research interests focus on the molecular regulation of fat metabolism, cholesterol and energy homeostasis in skeletal muscle by nuclear hormone receptors (NHRs). Specifically, we aim to understand the role of skeletal muscle in cardiovascular disease and to elucidate the functional role of orphan receptors in metabolism.

Projects

Obesity is recognized by the World Health Organisation as one of the top ten global health problems. It is the leading cause of heart disease, cancer and stroke - the top three causes of death in the USA, and also causes hypertension, high cholesterol and diabetes. Obesity has now reached epidemic proportions, as poor diet and sedentary living have equalled tobacco as the leading cause of death in the westernised world. Moreover, obesity leads to syndrome X, a disorder that includes elevated levels of triglycerides and LDL (bad) cholesterol, low levels of HDL (good) cholesterol and hypertension. These are cardiovascular risk factors for diseases such as atherosclerosis and type II diabetes.

In this context, skeletal muscle is a major mass peripheral tissue that accounts for 40% of the total body mass and is a primary site of glucose and fat metabolism. Consequently, it has a significant role in the blood lipid profile, insulin sensitivity, and cardiovascular health. Skeletal muscle has a major protective role by burning fats and sugars, and the production of HDL-cholesterol.

Metabolism is regulated by Nuclear Hormone receptors (NRs) which function as hormone activated transcription factors that bind DNA and control gene expression NRs function as the conduit between physiology and gene expression. Furthermore, these hormone regulated DNA binding proteins mediate the link between genome and phenotype, by operating at the nexus of pathways that control cell specific transcription, signalling, differentiation and metabolism.

Specific projects in our laboratory include:

• Genetic programs induced by the oxy-cholesterol dependent nuclear receptor, LXR, in skeletal muscle: regulation of cholesterol metabolism
• Understanding the role of Peroxisome Proliferator-Activated Receptors in skeletal muscle energy and lipid homeostasis.
• Structure/Function and mechanistic analysis of orphan nuclear receptor mediated transcription (e.g Nur 77, NOR-1, ROR, and Rev-erb)
• Elucidating the metabolic role of the orphan nuclear receptors in skeletal muscle and cardiovascular disease.
• Regulation of gene expression and mammalian differentiation by tissue specific transcription factors (e.g Sox 18) and chromatin remodeling factors (e.g protein arginine methyl transferases).
• Understanding the role of Sox18 in fat metabolism

In 2003 we identified a ‘drugable’ gene, PPAR delta, that plays a key role in increasing metabolic rate and reducing cellular energy stores in a major mass peripheral tissue. With diet and fat metabolism the most significant factors in controlling weight gain, the identification of PPARdelta opens up new strategies and targets for the development of fat burning drugs that increase the metabolic rate.

The functional role of the NR4A subgroup of nuclear receptors remains obscure however the group has been implicated in cell proliferation, differentiation, T-cell apoptosis, chondrosarcomas, neurological disorders, inflammation, and atherogenesis.

Using structure-function analysis we recently identified the first small molecule regulator of this class of orphan NRs. The NR4A subgroup is selectively activated by the purine anti-metabolite and anti-neoplastic/anti-inflammatory compound 6-Mercaptapurine. Analogues of which are used in the treatment of leukemias, autoimmune disorders and prevention of organ transplant rejection, gout and herpes virus infections.
This suggests that the signalling pathways inhibiting proliferation via inhibition of de novo purine and/or nucleic acid biosynthesis are involved in the regulation of NRA4A activity. Furthermore, we hypothesize that the NRA4A subgroup mediates the genotoxic stress response, and believe this subgroup may function as sensors, which respond to genotoxicity.

The NRA4A subgroup clearly represents an exciting scientific challenge, and unlocking the molecular mechanisms that mediate NRA4A-dependent transcription provides the platform for the identification of novel drug targets.

**Grants awarded**

**NHMRC** Understanding the mechanism of action and pathophysiological function of the NOR-1 and Nur77 orphan nuclear receptors.

**NHMRC** Genetic programs induced by the nuclear hormone receptor, PPARd, in muscle: control of lipid and energy homeostasis.

**UQ Research & Development Grant** PPAR delta in breast cancer: gene transcription and molecular mechanisms. (With Dr Sarah Roberts-Thompson)

**UQ Research & Development Grant** Understanding the pathophysiological role of the orphan nuclear receptor, Nur1 in Neurological disease: pharmacogenomic identification of Nur1 genes. (With Dr Helen Cooper)

**Collaborators**

Peter Koopman, IMB

Professor Peter Leedman, Deputy Director, Western Australian Institute for Medical Research, Perth

Dr Jonathan Harris, School of Life Sciences, Queensland University of Technology, Brisbane

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Catherine Jones
Publications


Speaking engagements

Oct 2003 Induction of Fatty Acid Oxidation and Energy Uncoupling in Skeletal Muscle Cells by PPAR Delta: PPAR Alpha, Delta and Gamma Have Distinct Roles US Endocrine Society Hot Topics in Endocrinology meeting: The Role of Nuclear Receptors in Cardiovascular Disease

Feb 4-Feb 9, 2003 'Hot to Press' speaker PPARs: Transcriptional Regulators of Metabolism and Metabolic Disease Keystone meeting Keystone, Colorado


Anything Else

• Member of the editorial board for Nuclear Receptor. A journal to be published by Biomed central limited.
• Editorial board member of Journal of Biological Chemistry. 2003-2008
Specifically, we aim to understand the role of skeletal muscle in cardiovascular disease and to elucidate the functional role of orphan receptors in metabolism.
Joe Rothnagel

MOLECULAR ANALYSIS OF CUTANEOUS SYSTEMS

Research overview
Molecular genetics and molecular cell biology using the mammalian epidermis as the model system.

Keratinocytes are the major cell type of the epidermis and have evolved to make terrestrial life possible. In laying down their lives, they provide a barrier that protects the organism from harmful UV radiation and from viral, fungal and bacterial invasions as well as preventing desiccation. Keratinocytes express a unique subset of proteins depending on their state of development, differentiation or proliferation. These characteristics make the skin a valuable resource for obtaining expression sequences. In addition, the accessibility of skin makes it the model system of choice for testing gene expression constructs that could be used in gene therapy applications.

Projects
A major focus of this laboratory is currently directed towards the use of tissue specific promoters for use in expression vector constructs. We use keratin promoters as the model system because they show cell type and differentiation state specific expression.

In addition, they are some of the most efficient mammalian promoters thereby ensuring high levels of expression. In parallel to the promoter studies we are also investigating the role of post-transcriptional mechanisms in regulating the final levels of gene products. This has led to the development of short cis-sequences (GeneDimmer & GeneBooster) that can be used to turn up or down gene expression.

In addition we have examined alternative splicing of key transcripts expressed by keratinocytes using both data mining and candidate gene approaches. This has resulted in the amazing finding that the kinesin light chain gene has the potential to produce over 280,000 alternative forms from the differential splicing of exons 13 to 23. We have also analysed the alternatively-spliced exons of the GlI oncogene that result in 5' leader sequences with differing translational capacities. Only the transcript with the highest translational capacity was associated with basal cell carcinoma. We have also characterised the mouse and human Frizzled-3 genes and identified several alternatively spliced variants that are predicted to interact with each other to modulate Wnt signalling.

Grants
NHMRC Alternative splicing of GLI1 and its role in tumorigenesis
Uniquest Pty Ltd GeneDimmer Development grant
Publications


Collaborators

Brandon Wainwright, IMB
Ross Smith, Department of Biochemistry and Molecular Biology, UQ
Timothy Rayner, Child Health Research Institute, Adelaide

Pritinder Kaur, Peter MacCallum Cancer Centre, Melbourne
Paul Bowden, University of Wales College of Medicine, Cardiff, UK
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MELANOCYTE BIOLOGY AND PIGMENTATION GENETICS

Research overview

The pigmentary system is dependent on the production of the light absorbing biopolymer, melanin and is responsible for skin, hair and eye colour. Melanocytes within human skin are situated on the basal layer between the dermis and epidermis and have a number of dendritic processes that interdigitate with the surrounding keratinocytes. The characterisation of proteins responsible for the pigmentation pathway has provided the basis to the biochemical understanding of some of the mouse coat colour and human albinism conditions. Darker forms of melanin protect the skin from solar radiation exposure, however melanocytes are also the cell-type from which malignant melanoma can originate. We are studying the human pigmentation system to understand the genetic basis of cellular differentiation, tissue-specific gene expression and cellular transformation induced by solar UV light.

Primary melanocyte and melanoblast precursor cells have been cultured from human skin and the pigmentation, growth and differentiation characteristics of each cell-type are being investigated.

The major goal of our research efforts is to understand the genetic basis of human pigmentation and to assess the phenotypic association of these physical traits with skin UV-sensitivity and skin cancer promotion. The group has isolated and characterised several human genes that encode enzymes, structural proteins, signaling molecules and receptors that are involved in this process. Functional analysis of this gene set will ultimately provide a full appreciation of this biological system.

Projects

MC1R polymorphism in skin cancer risk phenotypes

Population studies have revealed the coding region of the human melanocortin-1 receptor (MC1R) gene to be remarkably polymorphic, with over 30 allelic variants so far identified.

Several of the MC1R variant alleles have been associated with the red hair and fair skin (denoted RHC; red hair colour) phenotype, a condition that is caused by the synthesis of a high level of pheomelanin which can place individuals at a higher risk of skin cancer.

MC1R encodes a seven-transmembrane G-protein coupled receptor belonging to the melanocortin receptor family and binds the α-melanocyte stimulating hormone (α-MSH). Hormonal stimulation of MC1R expressed on the cell membrane surface is central to the tanning response of human melanocytes following UV irradiation.

Stimulation of the MC1R receptor results in a rise in intracellular cAMP levels to elicit changes in melanocyte gene expression largely through the microphthalmia transcription factor (MITF), which appears to be critical for activation of the eumelanogenic pathway producing the black/brown eumelanin pigment. Combined treatment of melanocytes with UV and α-MSH also potentiates cell dendricity and transfer of pigment to keratinocytes.

Given that pigmentedary traits such as fair skin, lack of tanning ability and propensity to freckle have been identified as risk factors for both melanoma and non-melanocytic skin cancer (NMSC), it follows that MC1R variants that are associated with these pigmentedary traits should also be found in association with an increased risk for these forms of skin cancer.
Several of the studies of the MC1R variants in relation to the RHC phenotype have suggested their association with the number of freckling sites or sun-induced lentigines. In most cases two MC1R variants are required to express the red hair-fair skin phenotype. In particular the R151C, R160W and D294H variants are the most commonly associated variants seen in the South East Queensland population with at least one of these alleles found in 93% of those with red hair.

We have examined MC1R variant allele frequencies in the general population and a collection of adolescent dizygotic and monozygotic twins to determine statistical associations of pigmentation phenotypes with increased skin cancer risk. This included hair and skin color, freckling, mole count and sun exposed skin reflectance. Nine variants were studied and designated as either strong R (OR = 63; 95% CI 32-140) or weak r (OR = 5; 95% CI 3-11) red hair alleles. Penetrance of each MC1R variant allele was consistent with an allelic model where effects were multiplicative for red hair but additive for skin reflectance.

**Functional testing of MC1R variant alleles**

To address the cellular effects of MC1R variant alleles in signal transduction these receptors were expressed in permanently transfected HEK293 cells. Measurement of receptor activity via induction of a cAMP-responsive Luciferase reporter gene, found the R151C and R160W receptors were active in the presence of α-MSH ligand but at much reduced levels compared to that seen with the wildtype receptor. The ability to stimulate phosphorylation of the CREB transcription factor was also apparent in all stimulated MC1R variant allele expressing HEK293 cell extracts as assessed by immunoblotting. In contrast human melanocyte cell lines showed wide variation in their ability to undergo cAMP-mediated CREB-phosphorylation. Culture of human melanocytes of known MC1R genotype may provide the best experimental approach to examine the functional consequences for each MC1R variant allele. With this objective we have established over 300 melanocyte cell strains of defined MC1R genotype. These include strains which are MC1R wildtype consensus, variant heterozygotes, and homozygotes for strong R alleles R151C and R160W. Ultrastructural analysis demonstrated that only consensus strains contained Stage III-IV melanosomes in their terminal dendrites whereas R151C and R160W homozygote strains contained only immature Stage I-II melanosomes. Such genetic association studies combined with the functional analysis of MC1R variant alleles in melanocytic cells should provide a link in understanding the association between pigmented phototypes and skin cancer risk.

**Culture of human melanoblast stem cells from skin**

Many diseases of pigmented cells, from vitiligo and piebaldism to melanoma, are caused by aberration in melanocyte growth or differentiation. Investigations into the pathways of melanocyte formation and differentiation from precursor melanoblast cultures are essential for the analysis of basic mechanisms in cell commitment and differentiation, for comparison with poorly-differentiated cells from melanoma, and for the molecular analysis of the many known genetic disorders of melanocyte development. Recently methods for establishing mouse melanoblasts have been published and while there are differences in mouse and human skin we sought to adapt these techniques to investigate the human melanocyte stem cell from neonatal foreskin. The ability to grow melanoblasts will provide an invaluable source of cells to allow the study of the pathway of melanocyte differentiation and cancer formation.
Oculocutaneous albinism in a Polynesian community

We have initiated a study of an original human oculocutaneous albinism (OCA) phenotype in a South Pacific island community of Polynesian descent to establish the nature of its inheritance through extensive pedigree analysis and to experimentally determine the genetic cause. Oculocutaneous albinism type 2 (OCA2) is a human autosomal recessive hypopigmentation disorder associated with pathologic mutations of the P-protein. The functional interaction of the OCA2 gene encoding the melanosomal P-protein product within the biosynthesis of melanin pigment has not yet been defined however, its disruption results in a generalised reduction of pigment in the skin, hair and eyes plus associated visual impairment. In the last few decades there has been little published about OCA in the South Pacific Region and no causative molecular mutation has so far been previously reported. In this study, we investigated a form of OCA in a Polynesian population with an observed phenotype characterised by fair skin with green or blue eyes. Hair presented with a unique red colouration since birth, with tones ranging across individuals from Yellow-Red to Brown-Red/Auburn. We have genetically screened for mutations in the P-protein and MC1R as their products have previously been shown to be associated with red hair/ fair skin and OCA2.

Grants awarded

Queensland Cancer Fund Role of Beta3 integrin induced osteonectin expression in melanoma metastasis.

NHMRC The role of MC1R polymorphism in skin cancer risk phenotypes.

ARC Parallel genetic and cellular analysis of melanogenesis: A new paradigm to study variation in pigmentation.

Collaborations

Nicholas Hayward, Queensland Institute of Medical Research.

Helen Leonard, Queensland Institute of Medical Research.

Nicholas Martin, Queensland Institute of Medical Research.

Peter Parsons, Queensland Institute of Medical Research.

Jenny Stow, IMB

Dorothy Bennett, Department of Basic Medical Sciences, St. George’s Hospital Medical School, London, UK.

Meenhard Herlyn, Wistar Institute, Philadelphia, USA.
Publications and papers


Conferences


Other

Associate Editor of Pigment Cell Research

Associate Editor of Melanoma Research

The major goal of our research efforts is to understand the genetic basis of human pigmentation and to assess the phenotypic association of these physical traits with skin UV-sensitivity and skin cancer promotion.
Brandon Wainwright

Molecular Genetics of Human Diseases

Research Overview
Our research group is focused on elucidating molecular pathology of human genetic disease, primarily through the analysis of the single gene disorder, cystic fibrosis and through the discovery of patched, the gene responsible for both the inherited and sporadic forms of basal cell carcinoma of the skin.

Projects
Our group examines the molecular pathology of two distinct genetic diseases. Cystic fibrosis (CF) is the most common inherited lethal disorder in caucasian populations affecting the lung and digestive system. CF patients have a chronic infection with the bacterial pathogen Pseudomonas aeruginosa. Accordingly we examine the role of the cystic fibrosis gene (and modifier genes) in responding to inflammation and bacterial infection in the lung.

By cloning the gene mutated in inherited skin cancer we identified the tumour suppressor gene patched. Analysis of patient material has indicated a role for this gene and its signalling pathway in many tumour types. Our laboratory applies genetic information from patient analysis to further our understanding of the patched pathway. A powerful approach to the analysis of human genetic disease is the use of model systems, such as the mouse. Consequently, many of our studies are directed at understanding gene function in murine systems. As a result of these studies we have a particular interest in the interface between developmental biology and human genetics, and in therapeutic strategies such as gene therapy.

Key Projects include:
• Structure/function of the patched tumour suppressor gene
• The cellular origin of basal cell carcinoma and common brain tumours
• Regulation of the inflammatory response by CFTR
• Origin of the cystic fibrosis inflammatory response
• Novel mouse modifier genes affecting lung development and inflammation

Staff and Students

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Jack King-Scott
Publications


Our research group is focused on elucidating molecular pathology of human genetic disease, primarily through the analysis of the single gene disorder, cystic fibrosis and through the discovery of patched, the gene responsible for both the inherited and sporadic forms of basal cell carcinoma of the skin.
Michael Waters

GROWTH HORMONE AND CYTOKINE SIGNALLING

Research overview

The final height of an individual is determined by the actions of growth hormone during childhood and adolescence. In the adult, growth hormone is an important metabolic agent regulating body composition and strength, 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, from high resolution protein structures to genetically engineered animals.

The centrepiece of these studies is the action of the growth hormone receptor, which determines the degree of the cell response to growth hormone, and which we cloned collaboratively with Genentech.

Projects

Being able to modify the functioning of this receptor allows us to control body growth, body composition and ageing, liver regeneration and certain cancers. Currently, our research has:

1) Elucidated the signalling mechanism used by the hormone to activate the receptor at a molecular level through X-ray crystallography, fluorescence and bioluminescence resonance energy transfer, site directed mutagenesis and the creation of receptors which are active in the absence of hormone. We propose that the hormone activates a preformed receptor dimer by rotating its transmembrane domains, switching on the JAK tyrosine kinases bound to the receptor below the cell membrane, allowing them to initiate the growth signal.

2) Determined the cellular domain of the receptor responsible for postnatal growth by creating genetically engineered mice with deletions and mutations in the internal signalling sequences of the receptor.

3) Determined which genes are regulated by the different signalling domains within the internal signalling sequence of the receptor, using gene microarrays.

4) Defined novel actions of growth hormone, particularly related to exacerbation of inflammation, through the use of these engineered mice and the gene microarrays. This may be important in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.

5) Defined a role for the growth hormone receptor which is found in the cell nucleus, and the mechanism used to transport it there. Our data supports a role in cell proliferation, especially during liver regeneration. This is potentially important in breast and colon cancer.

6) Created several 'superactive' porcine growth hormones for use in increasing food conversion efficiency and lean meat accretion in the pig industry.
Grants awarded

NHMRC Proliferative role of nuclear GH and cancer.

NHMRC The genetic programs induced by growth hormone.

NHMRC A transgenic analysis of the physiological roles of signalling domains in the growth hormone receptor.

NHMRC Structure – function studies on the growth hormone receptor.

Collaborators

International

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Kate Palethorpe

Publications


Conferences, invited lectures

Plenary lecture for Asia-Oceania Medal of the Society for Endocrinology, Royal College of Physicians, London

Symposium on role of GH in embryo and fetal development, Australian Society for Medical Research.
Carol Wicking

DEVELOPMENTAL GENES AND HUMAN DISEASE

Research overview
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, supporting the conservation of molecular processes governing the development of these structures. We are involved in isolation of novel genes involved in embryonic development of the limb and face, as well as more fully characterising the role of these and other known genes in embryogenesis and disease.

Projects
Regulation of the hedgehog pathway by intracellular trafficking and sterol levels
The hedgehog signalling pathway is central to the correct development of an embryo, as well as being involved in a range of tumour types. The elucidation of the steps involved in the correct functioning of this pathway is likely to shed light on a range of disease processes. The regulation of this pathway at the cellular level is extremely complex and has been shown to involve intracellular trafficking events and sterol levels. We are investigating the subcellular localisation of members of the hedgehog pathway at both the light and electron microscopy levels. To date this analysis has focussed on the receptor molecule Patched and Rab23, a vesicular transport protein known to negatively regulate vertebrate hedgehog signalling.

Microarray analysis in a mouse model of limb development
We have used microarray technology to investigate expression differences in the embryonic limb of the mouse mutant extra-toes (XtJ) versus the wild-type limb bud. This mutant involves a deletion of the gene encoding the Gli3 transcription factor which, together with Gli1 and Gli2, is involved in mediating the output of the hedgehog signalling pathway. As a result of our microarray analysis we have identified a number of known developmental genes as well as completely novel genes which are regulated by Gli3 in the developing limb. Given that Gli3 is a key molecule in patterning of the embryonic limb bud we believe that many of the genes we have identified will encode molecules which are also important to this process.

Identification of genes involved in craniofacial development
Defects in facial development are a common feature of human dysmorphology syndromes. Using the mouse as a model system, we have adopted a genomics approach based on subtractive hybridisation to enrich for genes expressed in pharyngeal arches, the precursors to the mammalian face. As a result we have isolated a large number of both novel and previously identified genes whose expression pattern during embryogenesis suggests a specific role in the development of a range of organ systems. Functional and cell biological characterisation of a number of these genes is currently underway.
Collaborators
Rob Parton, IMB
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Marcelo Bento Soares, University of Iowa, USA
Pete Scambler, Institute of Child Health, London, UK
Joy Richman, University of British Columbia, Vancouver, Canada
Andrew Lidral, University of Iowa, USA
S. Peter Klinken, University of Western Australia

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Natalie Butterfield
Kelly Lammerts van Bueren
PhD students
Tim Evans
Edwina McGlinn
Jenny Bennetts
Summar scholar
Vicki Metzis

Publications


Conferences & Seminars
Identification and analysis of genes involved in mammalian craniofacial development COMBIO, October 2003, Melbourne, Australia

We are involved in isolation of novel genes involved in embryonic development of the limb and face, as well as more fully characterising the role of these and other known genes in embryogenesis and disease.
CELL ARCHITECTURE AND DYNAMICS

Focussing on
- Visual cell project
- Cell architecture and trafficking
- Virtual membrane project

This program has received considerable support from the NANO major national research facility, the Australian Cancer Research Foundation and NIH, and is a major initiative of the IMB with the application of cyro-electron microscopy, cell tomography, advanced visualisation and high performance computing. It also includes the ARC Centre in Bioinformatics.

Research Group Leaders
John Hancock
Ben Hankamer
Alisdair McDowall
Rob Parton
Jennifer Stow
Rohan Teasdale
Alpha Yap
John Hancock

SIGNAL TRANSDUCTION

Research overview
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 anti-cancer therapeutics.

Projects
Ras proteins operate as molecular switches in signal transduction pathways downstream of tyrosine kinase and G-protein coupled receptors. This is a fascinating model system because there are three highly homologous Ras isoforms that generate different signal outputs despite sharing a common set of effector and activator proteins. Our studies strongly suggest the existence of parallel Ras signalling pathways that are based on different plasma membrane microdomains. A major thrust of our current program is to dissect the composition and function of these microdomains. Specific themes include:

• Molecular mapping of the proteins and lipids of plasma membrane microdomains.

• Electron microscopic visualization and quantitative characterization of surface microdomains to build up a high-resolution 2D map of the microdomains of the inner plasma membrane.

• Investigation of the dynamic regulation of microdomain localization of Ras and Ras-interacting proteins in response to physiological stimuli.

• Mechanism of Raf-1 activation, to characterize the multistep Raf-1 activation process spatially within the plane of the plasma membrane.

• Characterization of the mechanism(s) whereby K-ras is transported to the plasma membrane and how Ras proteins engage different endocytic pathways.

Collaborators
Yoav Henis and Yoel Kloog, University of Tel Aviv, Israel
Mark Philips, New York University, USA
Brian Gabrielli, Queensland Institute of Medical Research

Grants
National Institutes of Health Plasma membrane microdomains and Ras function
Queensland Cancer Fund Switch-like signaling in the Raf/MEK cascade
ARC Investigation of the mitotic function of MEK
NHMRC Plasma membrane structure and function

Staff and Students

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Angus Harding
Michelle Hill

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Chi-Yan Lau

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Annette Lane
Cornelia Muncke
Elizabeth Westbury

Research fellow
Kim Yap-Weber
Publications


Understanding the basic biology of Ras has major implications for the development of novel anti-cancer therapeutics.
Ben Hankamer

MEMBRANE PROTEIN STRUCTURES

Research Overview
Our group is focused on developing a broad based platform for the structure determination of membrane proteins and macromolecular assemblies, based upon single particle analysis, electron and X-ray crystallography.

A strong research focus of the group involves automation to increase the rate of protein structure determination. A selection of proteins involved in a range of important biological processes and biotechnology applications (e.g. Biohydrogen) are also currently being investigated as part of the IMB’s Visual Cell program.

Projects
Structural Biology

Single Particle analysis
Single particle analysis (SPA), when coupled with electron cryo-microscopy, is ideal for the structure determination of large membrane proteins and macromolecular assemblies. In essence, SPA is the process of determining 3D reconstructions of macromolecules from their constituent 2D projection images captured by electron cryo-microscopy.

Images of randomly oriented particles supported in a thin layer of vitreous ice are aligned and classified according to their orientation. The class averages are then merged to produce 3D reconstructions.

Electron Crystallography
Electron crystallography requires the use of 2D crystals. These are particularly well suited for membrane protein structure determination as the crystallised proteins are arrayed within a near native lipid bilayer.

The 2D crystals are imaged over a range of tilt angles and the processed images merged to facilitate 3D image reconstruction. New processes of monolayer and bilayer crystallogenesis methods are being developed to facilitate template mediated crystal production.

Cubic Phase crystallization
The use of cubic phase lipids for the purpose of membrane protein crystallisation is also being explored. Cubic phase lipid structures are highly ordered, contorted bilayers, which are continuous and organized in 3D space.

Membrane proteins can be inserted into these cubic phase lipid matrices and induced to form highly ordered three-dimensional crystals well suited for high resolution X-ray crystallographic analysis. The method can be thought of as a hybrid between 2D bilayer and 3D crystal production.

Biology and Biotechnology

Bio-Hydrogen
The development of a clean, sustainable and economically viable energy supply for the future is one of the most urgent challenges of our generation, given that oil production is estimated to peak in 5-33 years time.

There is now a concerted international effort to switch from a fossil fuel to a hydrogen economy. We are exploring the use of a green algal system that uses solar energy to split water ($H_2O$) into hydrogen ($H_2$) and oxygen ($O_2$), for large scale $H_2$ production. Subsequent combustion of $H_2$ yields only $H_2O$ eliminating both net $H_2O$ use and the production of harmful greenhouse gases, associated with the burning of fossil fuels.

The identification of marine algae capable of producing $H_2$ has the added benefit that $H_2$ production could be coupled with $H_2O$ purification, as the product of $H_2$ combustion is pure $H_2O$. 
Grants

ARC Discovery grant *High resolution single particle analysis of biological macromolecules*

UQ Research Development grant *Structural biology of macromolecular assemblies as part of the visual cell program*

Collaborations

Dr Olaf Kruse, Department of Biology, University of Bielefeld, Germany

Professor Bernard Pailthorpe, VisLab and School of Physics, The University of Sydney

Dr Paul Young, Department of Microbiology and Parasitology, The University of Queensland

Dr Jasmine Banks, Advanced Computational Modelling Centre, The University of Queensland

Associate Professor Alasdair McDowall, IMB

Dr Geoff Ericksson, Advanced Computational Modelling Centre, The University of Queensland

Staff and Students

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<th>Research officer</th>
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<th>Honours student</th>
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<td>Jens Rupprecht</td>
<td>Rosalba Rothnagel</td>
<td>Cameron Votan</td>
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<td>Michael Landsberg</td>
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Publications and papers


Conferences

Boden Artificial Photosynthesis Conference 2003

Broome Crystallography Conference 2003

Seefeld Electronmicroscopy Conference 2003

Combio 2003

(Opposite page) A Chlamydomonas reinhardtii cells (biohydrogen), B Photosystem II structure determined by electron crystallography

(Above) A Single particle images, B 3D Reconstruction of PSPA, C 2D Crystal of photosystem II, D Cubic phase matrix
Alasdair McDowall

CRYO-ELECTRON MICROSCOPY OF VITREOUS SECTIONS

Research overview
Our group is studying biological structures by cryo-sectioning vitreous bulk material for cryo-electron microscopy (cryo-em). Considered the dream method of structural cell biologists, it involves vitrifying a native sample of cells or tissue by rapid cooling, cutting into ultra-thin <100nm sections and cryo-em observation of the perfectly preserved details.

In collaboration with the Centre for Microscopy and Microanalysis at UQ, Brad Marsh at the IMB and Professor Jacques Dubochet from the University of Lausanne we are using high pressure freezing and cryosectioning to investigate bulk structure systems of mammalian cells, bacteria and chloroplast organelles. We are also using cryo-electron microscopy together with thin cryo-preparations to investigate plasma membrane protein packing arrangements in collaboration with the Parton group at the IMB.

Cryo-electron microscopy of vitreous sections (CEMOVIS) demonstrates its full potential when combined with computerized electron tomography for 3-D reconstruction.

Projects
3D electron (cryo ET) tomography of cellular organelles
As seen in figure 1, the detail of this cryo-section of native cellular chloroplast ultrastructure is well defined. Studies are underway to incorporate 3D tomography of similar structures providing valuable new insights into the 3D ultrastructure of the light capturing machinery of Chlamydomonas reinhardtii and may yield new information on the functional interaction between mitochondria and chloroplasts.

The ultimate vision of the Visual Cell Project Technologies as described here are at the front end of a series of projects to provide a web-based graphical user interface (GUI) which in time will link researchers to individual "Visible Cell" projects i.e. 3D reconstructions of entire cells at ≤5nm resolution. Examples include the pancreatic beta cell (Marsh group at IMB), C. reinhardtii (Hankamer group at IMB), and cyanobacteria Lyngbya majuscula (Dubochet group, University of Lausanne).

In the "Visible Cell" environment researchers will be able to manoeuvre within the raw 3D cellular volumes together with their accompanying 3D model data to selectively inspect and visualize organelles, macromolecular assemblies (modelled into the tomograms) and the structures of individual subunits of these assemblies.

With the installation in 2004 of the MNRF- NANO 300keV cryo electron microscope, 3D electron tomogram reconstructions will be built from stacks of thick (300-400nm) serial sections cut from cells and imaged by dual-axis EM tomography with a target resolution of ≤5nm. This resolution is sufficiently high to allow us to determine the feasibility and limitations of trying to resolve macromolecular complexes within the 3D cellular data by virtue of their structural signatures alone.

Collaborators
Professor Jacques Dubochet, University of Lausanne, Switzerland
Dr Mark Blackford, Australian Nuclear Science and Technology Organisation, ANSTO, , Menai, N.S.W
Dr Minoo Moghaddam and Dr Gerald Both, CSIRO Molecular Science, North Ryde, NSW 1670, Australia

2003 Grants
ARC Discovery Project High resolution single particle analysis of biological macromolecules
Publications

Our group is studying biological structures by cryo-sectioning vitreous bulk material for cryo-electron microscopy (cryo-em).
Rob Parton

CELL SURFACE IN HEALTH AND DISEASE

Research overview

Our research interests focus on the organisation, dynamics, and functions of the plasma membrane. In particular, we are interested in the formation and function of caveolae, small pits, which cover the surface of many mammalian cells, and in a related domain termed a ‘lipid raft’. 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 (see opposite page), have been implicated in a number of disease states including tumour formation, atherosclerosis, and muscular dystrophy. We are using a number of systems in order to understand how caveolae form and their role in cellular function. In addition, our studies are providing new insights into the organisation and function of lipid raft domains.

Projects

Caveolin functional studies

To address the role of caveolae and caveolins in cellular function we investigated whether caveolin mutants would act as dominant negative inhibitory mutants making use of our earlier finding that entry of the virus, SV40, occurs via caveolae. Two mutants had a specific inhibitory effect on SV40 infection. With John Hancock we showed that one of the mutants was a highly potent inhibitor of Ras signalling and this inhibition was specific to the palmitoylated form of Ras, H-ras, with no effect on the related but non-palmitoylated isoform, K-ras. Inhibition was overcome by adding cholesterol to the cells.

These studies suggested that H-ras signalling requires cholesterol-enriched lipid raft domains and provided a system and tools to characterise these domains. Secondly, our findings suggested a hitherto unexpected link between caveolin, cholesterol regulation, and lipid bodies. These two areas are actively being pursued in the laboratory as outlined below.

Characterisation of Ras microdomains; novel methods and new paradigms

In order to characterise the domains with which H-ras and K-ras associate, we employed subcellular fractionation and developed new electron microscopic (EM) techniques. The studies generated a new concept in cell biology; dynamic lipid raft association regulated by the GTPase state of the Ras protein. The novel technique we have developed with the Hancock laboratory involves a statistical analysis of the spatial distribution of proteins on the surface of the plasma membrane and provides a completely unbiased quantitative analysis of the distribution of proteins. This has allowed us to identify and characterise several distinct domains. Our future studies are aimed at mapping other proteins with respect to these domains and understanding the molecular basis of microdomain formation and function.

Caveolin, cholesterol, and lipid bodies; in vitro and in vivo studies

The other avenue of research developed in response to our studies of the inhibitory caveolin mutants was aimed at understanding the molecular basis of the inhibition of H-ras function. We showed that the mutant caveolin which associated with lipid bodies disrupted lipid regulation, a completely unexpected finding which has generated great interest in the field. These studies have implications for understanding the role of lipid bodies in cellular function and provide a model system for studying lipid body biogenesis and function.

We have now extended these studies to examine the effect of the caveolin mutant at the molecular level and to examine the role of caveolins in lipid body function. We have shown that the caveolin mutant inhibits microtubule-dependent lipid body motility and inhibits loss of lipids from lipid bodies. In addition, we have shown that endogenous caveolins can associate with lipid bodies and this is regulated by fatty acids (see following page).

This may have physiological importance as we have found that in regenerating liver, in which lipid bodies accumulate to high levels, endogenous caveolin redistributes from plasma membrane caveolae to lipid bodies. Experiments are in progress to examine whether liver regeneration is affected in caveolin-1 null mice.
A major focus of future experiments is to understand the role of caveolin in lipid regulation and to test the hypothesis that regulated association of caveolin with lipid bodies and surface caveolae plays a role in cholesterol homeostasis. These studies have implications for many disease states including atherosclerosis and Niemann-Pick disease.

**Caveolae and caveolin-3 in muscle**

Some years ago, we discovered a second member of the caveolin family (now termed caveolin-3). We showed that caveolin-3 localises to the surface caveolae of mature muscle but during development associates with the developing Transverse (T)-tubule system suggesting a novel role in T-tubule formation.

A major aim of our future studies is to determine the role of caveolin-3 in muscle, particularly in view of a series of papers from other groups showing that caveolin-3 is mutated in some forms of muscular dystrophy and other muscle diseases. We generated a series of caveolin-3 mutants corresponding to those occurring in patients with the muscle diseases; the analysis of these mutant proteins is ongoing. We showed that one caveolin-3 point mutant associated with muscular dystrophy specifically inhibits H-ras signalling suggesting that like the inhibitory mutant described above it perturbs lipid raft domains.

These results provide new insights into the effect of caveolins on raft signalling and the molecular defects which may contribute to the disease phenotype. We have also established collaborations with Kathryn North (Sydney) to identify dystrophy patients with abnormal levels of caveolin-3 and caveolin-3 interacting proteins.

**Caveolins in zebrafish**

Studies of caveolin knockout mice have provided new insights into the role of caveolins. However, the exact role of caveolae is still far from clear. We are using zebrafish as an in vivo system to examine caveolae function.

The well-characterised developmental pathways in the zebrafish, the ease of knockout of protein expression, and the amenability to microscopic characterisation provide tremendous advantages for these experiments.

We have characterised caveolae distribution by electron microscopy and we have cloned and characterised caveolins from zebrafish. The proteins are well conserved; for example those amino acids in human caveolin-3 which are mutated in muscle disease patients are conserved in the zebrafish.

We have localised caveolin-1 and caveolin-3 and have ablated the expression of both successfully. This is providing new insights into caveolin function. For example, we have shown a role for caveolin-3 in myoblast fusion and myotube differentiation and have mimicked this by expression of a dystrophy-associated mutant protein. Future experiments will aim to elucidate the precise role of caveolae in muscle and non-muscle cells in the zebrafish.

**Caveolae Biogenesis**

Finally we are interested in how a caveola is generated. How can such a uniformly shaped structure be formed (see following page) and what is the role of caveolin in this process?

We have shown that lymphocytes lack caveolae but that expression of a single protein, caveolin, in these cells caused caveola biogenesis. This represents a unique system in cell biology allowing us to dissect the information in the caveolin molecule which causes the formation of both the characteristic morphology of the caveolae as well as their unique molecular composition.

We are currently using caveolin-null fibroblasts, which totally lack caveolae, to address the molecular determinants involved in caveolae formation. We are also using cryoEM and electron tomography to examine caveolae structure at high resolution.
Grants awarded

**NHMRC Program Grant** *The role of membrane microdomains in cellular function*

**National Institutes of Health** *Plasma membrane microdomains and Ras function*

Collaborators

Prof. Jean Gruenberg, University of Geneva, Switzerland

Dr. Gisou van der Goot, University of Geneva, Switzerland

Dr. Elina Ikonen, National Public Health Institute, Helsinki, Finland

Dr. Marino Zerial, Max Planck Institute, Dresden, Germany

Dr. Jitu Mayor, National Centre for Biological Sciences, Bangalore, India

Dr. Carlos Enrich and Dr. Albert Pol, University of Barcelona, Spain

Prof. Monte Westerfield, University of Oregon, USA

Prof. Richard Pagano, Mayo Clinic, USA

Prof. Michel Desjardins, University of Montreal, Canada

Dr. Teymur Kurzchalia, Max Planck Institute, Dresden, Germany

Prof. Kathryn North, Institute for Neuromuscular Research, Sydney

Dr. Wendy Jessup, Department of Medical Sciences, The University of New South Wales, Sydney

Prof. John Hancock, IMB

Prof. David James; Garvan Institute for Medical Research, Sydney

Associate Professor Alpha Yap; UQ, IMB;

Dr. Carol Wicking, IMB;

Dr. Rohan Teasdale, IMB

Prof. Brian Key; School of Biomedical Sciences, UQ

*Caveolae and caveolins, the major proteins of caveolae, have been implicated in a number of disease states including tumour formation, atherosclerosis, and muscular dystrophy. We are using a number of systems in order to understand how caveolae form and their role in cellular function.*
## Staff and Students

### Research officers
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- Sally Martin

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- Susan Nixon

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- Robert Luetterforst
- Ayanthi Richards
- Annika Stark

### Visiting scientists
- Aki Fujitsu
- Manuel Fernandez Rojo

## Publications


## Conferences


Jennifer Stow

PROTEIN TRAFFICKING IN HUMAN DISEASE

Research Overview
Protein trafficking is the process by which each of the many proteins made by cells are transported to different intracellular destinations or to the cell surface for secretion (release). The protein trafficking machinery of each cell is highly complex involving many gene products. Deciphering how individual proteins are trafficked is important for understanding their cellular function, regulation and role in disease. Our lab is studying the trafficking of key proteins in epithelial cells and in macrophages with a long term view to converting proteomic and genomic information into dynamic visual and functional maps of these pathways within cells. Generating this information for the epithelial cells and macrophages being studied in our lab is vital to developing new therapeutic approaches for use in cancer and immunological disease.

Projects

Cadherin trafficking in epithelial cells
E-cadherin is a key cell adhesion protein, in complex with catenins, other regulatory molecules and receptors on the lateral surface of epithelial cells, it performs essential roles in cell polarity and cell-cell contact. E-cadherin is also a powerful tumour suppressor and its loss or dysfunction is an early event in many metastatic tumours. Our studies involve characterizing the endocytic and exocytic pathways for E-cadherin trafficking in normal epithelial cells and in breast cancer cells. Our experimental approaches include mutagenesis and expression of proteins, in vitro vesicle assays, immuno-electron microscopy and fluorescence microscopy in fixed and live cells. Current projects include:

• define roles for specific trafficking machinery proteins in the transport of E-cadherin, including, sorting signals, adaptors and vesicle coats, actin-modifying proteins, GTPases and SNAREs.
• the assembly and role of the cadherin-catenin complex and cell surface receptors in trafficking and alternative functions of E-cadherin.
• the role of endocytosis in regulating cell adhesion during cell growth and differentiation and in cancer.

Together our findings provide a context for understanding how and when adhesion complexes become functional and how cell adhesion and polarity can be regulated during the development and maintenance of epithelia and in tumorigenesis.

Cytokine secretion in inflammatory macrophages
Macrophages perform essential functions in innate and acquired immunity. During inflammatory responses macrophages secrete proinflammatory cytokines, one of the most powerful of which is tumour necrosis factor alpha (TNF). Excess TNF is a key cause of tissue damage and a major clinical problem in chronic inflammation diseases such as inflammatory bowel disease and rheumatoid arthritis. Little is currently understood about how macrophages traffic or secrete proinflammatory cytokines. Our group has developed gene and protein screens and single cell assays to identify strategic components of the trafficking machinery in cytokine secretory pathways. Proteomic analysis of vesicles, morphological and molecular analysis of specific proteins are used in fixed and live cells to characterize the pathways and regulators of cytokine secretion. Our studies to date have defined some of the important features of these pathways, such as the identification of SNARE complexes for vesicle docking and fusion. Some of the proteins we have identified are being investigated as potential drug targets for the development of new anti-TNF therapies in inflammatory diseases. Macrophages and other cells at sites of inflammation in various inflammatory and autoimmune disease models are being studied to determine how trafficking contributes to immune responses. Ultimately our studies will more fully define how cytokines are trafficked and secreted by macrophages and how specific trafficking proteins contribute to other immune functions such as antigen presentation, cell recruitment and cell and pathogen killing.
Vesicle budding on Golgi membranes

Proteins destined for secretion from, or delivery to, the cell surface are packaged into vesicular carriers at the trans-Golgi network. Many molecules are required to assemble and generate or bud vesicles for the transport of specific cargo - an essential and abundant process for cell viability. We have a long-standing interest in determining how membrane budding occurs. The nature of vesicle carriers, their budding, transport and fusion and the roles of G proteins, and their regulatory molecules are being studied by high resolution fluorescence imaging in live cells. Joint work with collaborators is aimed at also defining the roles of actin and actin binding proteins (with Gunning laboratory) and molecular tethers (with Gleeson laboratory) in vesicle budding. Outcomes from these studies will contribute to our understanding of normal cellular function and of cell dysfunction in cancer and other diseases.

Grants awarded

NHMRC Trafficking of E-cadherin in epithelial cells.
National Institutes of Health, USA Cytokine Trafficking and Secretion in Macrophages.

Collaborators

Rohan Teasdale (IMB)
Rick Sturm (IMB)
Alpha Yap (IMB)
David Hume (IMB)
Peter Gunning, The Children's Hospital at Westmead, Sydney
Paul Gleeson, The University of Melbourne
David James, Garvan Institute of Medical Research, Sydney
Sharad Kumar, Hanson Centre for Cancer Research, Adelaide
Michael Caplan, Yale University School of Medicine, New Haven, Connecticut, USA

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David Bryant
Shannon Joseph

Jason Kay,
Chris Le,
John Lock,
Daniele Sangermani,

Honours student
Stephanie Wood

Publications


Rohan Teasdale

COMPUTATIONAL CELL BIOLOGY

Research overview
The application of computational biology techniques to cell biology is opening up new areas of scientific exploration. Our group is developing new techniques to predict the function of novel proteins based on their sequence.
Possessing the combination of cellular and bioinformatic skills allows our group more intuitive insights into the application of computational biology within cellular biology.

Our major research focus is to utilise bioinformatics or “database mining” to identify novel proteins or genes, which are then characterised by our group or through active collaborations.

Our work includes identification of novel proteins implicated in membrane trafficking and the identification of the signals that proteins utilise for localisation to different regions of the cell.

This research has had a major impact on understanding the signals responsible for targeting membrane proteins to various subcellular regions within the cell. This is based on our experimental characterisation and exploitation of localisation signals to develop computational approaches capable of accurately predicting the membrane organisation and localisation of novel proteins.

We have also applied a range of cellular and developmental techniques to characterise novel proteins localised to distinct regions of the cell including the Golgi, polarised cell surface membranes, nucleus, endosomes and proteins secreted into the extracellular environment.

As a result, we recently defined the protein composition of the human retromer complex and showed it was associated with mammalian endosomes.

Our projects combine bioinformatics techniques with traditional experimental approaches such as molecular cloning, expression in mammalian cells, immunolocalisation and microscopy.

Projects
Bioinformatic discovery of new genes, proteins and pathways
A major advance in the biological sciences over the last decade is the sequencing of genomes from different organisms. The challenge today for medical scientists is to utilise this mass of information to expand their knowledge of the biological processes they are currently researching. Traditional cell biology combined with a strong understanding of biological sciences allows for a more intuitive “mining” of this wealth of information for novel sequences using various bioinformatic approaches. These “on silica” observations have catalysed numerous new avenues of scientific exploration for researchers in our group and with collaborators.
The Golgi Apparatus: Computational discovery and functional genomics of novel Golgi proteins

The Golgi is an organelle central to the biosynthetic pathway of eukaryotic cells. It plays a principal role in the post-translational modification of newly synthesised proteins and in the sorting, packaging and distribution of these proteins to various destinations. It is estimated that at least 1000 proteins make up the protein complement of the Golgi, of which less than 200 are currently characterised. Efficient screens that identify novel Golgi proteins would clearly enhance our present understanding of the biological role of the Golgi. Based on an exhaustive computational interrogation of the genomes of various organisms for predictable novel Golgi resident proteins combined with the experimentally validation of their localisation we intend to define the full protein complement of the Golgi. We have successfully applied this strategy to predict greater than 300 putative Golgi residents, of which, we have already experimentally validated eight novel Golgi proteins. In addition, we will commence the development of a functional genomics approach focused on defining the function of novel Golgi resident proteins. This will include grouping the novel Golgi proteins based on computational defined features; localisation to sub regions of the Golgi, co-expression during cellular and developmental stages and mapping protein-protein interaction networks.

Annotation of the membrane organisation and subcellular localisation of proteins associated with the mammalian secretory pathway.

A major issue in cell biology today is how distinct intracellular regions of the cell maintain their unique composition of proteins. The signals that direct a given protein’s movement through the intracellular organelles, and thereby determine its eventual location in the cell, are contained in its amino acid sequence. Many of these sorting signals have been experimentally defined and are able to be predicted utilising computational approaches. I am currently annotating the predicted localisation of membrane and peripheral membrane proteins which accumulate in the various intracellular organelles (namely the endoplasmic reticulum, Golgi apparatus, endosomes and plasma membrane). This has been performed on the protein open-reading frames from the 60,000 full-length mouse cDNA generated by RIKEN. We are currently expanding this project to additional protein databases.

Characterisation of novel proteins involved in endosomal membrane trafficking: - The Retromer Complex

The endosomal/lysosomal system of mammalian cells is a highly dynamic trafficking pathway that includes membrane transport from both the late Golgi and the plasma membrane. The primary function of endosomes is the sorting and segregation of receptors and ligands, a process that is necessary for many cellular operations. The molecular details of protein trafficking and biogenesis of the numerous subcompartments of the mammalian endosomal/lysosomal system are poorly defined. One strategy to identify proteins that function in the trafficking of proteins from endosomes to the TGN is to characterise human homologues of proteins that have been experimentally implicated in endosomal function in other organisms predominantly yeast. The aim of this project is to gain insight into the biochemistry and membrane sorting functions of mammalian VPS protein homologues, primarily the peripheral membrane proteins Vps26p, Vps29p, Vps30p and Vps35p. The principal objective of this proposal is to determine if these mammalian VPS proteins function in an analogous manner to that in yeast. In particular, we aim to determine the intracellular compartments that these peripheral membrane proteins associate with, to determine if these proteins function in membrane transport from the mammalian endosomal system to the TGN.

Intracellular Localisation signals.

How do distinct intracellular regions of the cell maintain their unique composition of proteins and lipids? For these organelles to maintain their function integrity, specific resident proteins must be retained while non-residents proteins allowed passage through them. Individual proteins must have "signals" that are responsible for their intracellular localisation. We are currently in the process of identifying such signals on several different proteins. In addition, we are identifying novel proteins that contain these localisation signals within the human genome. These novel proteins are then tested for localisation to particular organelles and then functionally characterised.
Towards renal regeneration
Stem cell-based therapy, utilising either adult or embryonic stem cells, is an unproven approach to the treatment of kidney disease. Our group is a member of a consortium formed to perform the basic research required to define the potential of renal regeneration. Our role in the consortium is to provide the expertise in cell biology and computational analysis to novel genes of interest identified throughout this research effort.

Reverse Transfection Microarrays
One of the greatest challenges in the post-genome sequencing era is to develop strategies to rapidly assign biological roles to each member of the gene complement. Recently, a microarray based, massively parallel, transfection strategy has been described. Unlike expression profiling, this technology provides the opportunity to directly assay biological endpoints rather than transcriptional consequences. We have established this technology within the IMB and are currently developing a range of novel applications of this technology.

Grants awarded in 2003
University of Queensland Foundation Research Excellence Awards.
NHMRC Career Development Award RD Wright Biomedical Development Award
NHMRC Project Grant Sorting nexins and their role in endosomal trafficking.
ARC Discovery Project Grant Membrane proteins within the mouse transcriptome-annotation of their organisation and subcellular localisation.

Collaborations
Sean Grimmond IMB
Melissa Little IMB
Jenny Stow IMB
Mike Waters IMB
Tim Bailey IMB
Malcolm McConvile, Department of Biochemistry and Molecular Biology, University of Melbourne
Paul Gleeson, Department of Biochemistry and Molecular Biology, University of Melbourne

Staff and Students

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<td>Research officer</td>
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China Scholarship Board Scholarship Program
Publications and papers - 2003


The application of computational biology techniques to cell biology is opening up new areas of scientific exploration. Our group is developing new techniques to predict the function of novel proteins based on their sequence.
**CADHERIN SIGNALING AND MORPHOGENESIS**

**Research overview**

My group studies the role of cadherin cell adhesion molecules in morphogenesis and tumor development. E-cadherin is a key mediator of cell-cell recognition: it participates in tissue patterning and its dysfunction contributes to tumor progression and invasion. We seek to understand the cellular basis of cadherin recognition, and how this controls cell movement and organization. Our current work builds on two recent discoveries made by my lab:

1. We found that E-cadherin, the principal cadherin molecule found in epithelial tissues, functions as an adhesion-activated cell signalling receptor. In particular, upon adhesion E-cadherin activates signalling via the small GTPase, Rac, and the lipid kinase PI3-kinase.

2. An important potential target of this signalling receptor is the Arp2/3 complex, a protein machine that nucleates assembly of actin filaments. We were the first to discover that E-cadherin interacts with the Arp2/3 complex to mark sites for actin assembly within cells. We are now exploring the general hypothesis that cadherin-activated signalling controls the subcellular localization and activity of Arp2/3 to modulate cell shape changes and motility in response to productive cell-cell recognition.

**Projects**

Members of my group are studying

1. The molecular mechanism responsible for recruiting Arp2/3 to E-cadherin

2. The molecular regulators of Arp2/3 activity at cadherin contacts (including WASP/WAVE proteins, cortactin and ena/VASP family proteins)

3. The molecular basis of cadherin-activated Rac and PI3-kinase signalling.

4. The morphogenetic consequences of cadherin-activated cell signalling and cooperativity with the actin cytoskeleton.

**Grants**

**Collaborators**

Sean Grimmond IMB

Brian Key Department of Anatomy and Developmental Biology, UQ

Robert Parton IMB

Jennifer Stow IMB

Alan Fanning University of North Carolina, Chapel Hill, USA

Frank Gertler Massachusetts Institute of Technology, Boston USA

Aki Kusumi Nagoya University, Japan

Denise Montell Johns Hopkins University, Baltimore USA

Al Reynolds Vanderbilt University, Nashville, USA

David Sacks Harvard Medical School, Boston, USA

Lila Solnica-Krezel Vanderbilt University, Nashville, USA

Taodami Takenawa Tokyo University, Japan

Scott Weed University of Colorado Health Science Center, USA
Any prizes, keynote addresses or other honours in 2003

Publications


CHEMICAL AND STRUCTURAL GENOMICS

Focussing on
• Membrane protein structures
• Soluble protein and nucleic acid structures
• New drugs and therapies

This program has the most advanced equipment for structural biology in Australia, with projects exploring Queensland’s biodiversity for potential therapeutic agents. It has been responsible for a number of IMB spinout companies based on new platform technologies for drug discovery as well as developing novel drugs for human disease.

Research Group Leaders
Paul Alewood
Rob Capon
David Craik
David Fairlie
Jeffrey Gorman
Bostjan Kobe
Richard Lewis
Jenny Martin
Mark Smythe
Paul Alewood

**BIOACTIVE MOLECULES, CHEMICAL PROTEIN SYNTHESIS AND PROTEOMICS**

**Research overview**
The research interests of our group include the discovery and total synthesis of toxins from Australia’s venomous creatures, the chemical synthesis of proteins and bioactive peptides, development of new synthetic and analytical methods, and proteomics. Special emphasis is placed on determining the structure-function relationships of natural and designed molecules.

**Projects**

**Toxins**
Venom peptides make interesting pharmacological tools due to their action on ion channels and receptors. Conotoxins are small cysteine-rich peptides isolated from the venom of predatory marine snails. We have developed new synthetic approaches that employ selenium chemistry to access fully cyclic analogues with improved physical and biological properties. These analogues nicely mimic the original native structure and maintain high potency.

Significant progress has been made on the Australian paralysis tick with new bioactive molecules isolated and currently being sequenced.

Studies of the venoms from various species of Australian scorpions have now commenced as well as the glands of the freshwater stone fish (bull rout).

**Milk proteomics**
Glycosylation is a post-translational modification, which introduces great diversity into the proteome allowing numerous distinct molecular species to be generated from a single gene product. We have identified numerous different glycoforms of the major milk protein, k-casein. Using 2D electrophoresis and MALDI-ToF MS, differences in phosphorylation and glycosylation were identified. By analysing the glycopeptides generated from individual species we have been able to assign molecular identities to 30 of these in terms of genetic variant, number and location of phosphorylation sites, and the number of tri- and tetra-saccharides attached.

**New generation antibiotics**
The replication of DNA in eubacteria involves many proteins organised into a complex multifunctional machine termed the replisome. A central enzyme involved in replication is the multi subunit DNA polymerase (pol III). The processivity of the polymerase is conferred by the β subunit of pol III, which forms a clamp around the DNA. The subunit β is in turn loaded onto the DNA by a clamp loader complex comprised of single δ and δ’ subunits and three or four τ/γ subunits. The δ subunit of the clamp loader and the polymerase a, bind the β subunit at the same site or overlapping site.

In a collaborative program with Livestock Industries, CSIRO, an initial lead pentapeptide has now delivered a suite of novel peptidomimetic lead compounds with nanomolar potency that inhibit (in vitro) interaction of the α:δ and α:β proteins. Their capacity to enter cells is now under investigation.

**Protein chemical synthesis**
The current research project represents a novel approach using total chemical synthesis to study the enzyme action of the HIV-1 PR, an aspartyl protease essential for the replication of AIDS virus. The redesign of the catalytic apparatus will allow the investigation of molecular aspects of its action. The synthetic polypeptide chain will be folded and characterised for the correct folded structure by NMR, and assayed for enzymatic activity. It can be expected that significant new insights into the molecular basis of the properties of the HIV-1 PR will be obtained.

**Collaborators**
Professor Steve Kent, Institute for Biophysical Dynamics, University of Chicago, USA
Prof Ian Smith, Baker Heart Research Institute, Melbourne
Professor Ed Nice, Ludwig Institute for Cancer Research, Melbourne
Professor Carolyn Geczy, School of Medical Sciences, University of New South Wales, Sydney
Professor Phil Kuchel, The University of Sydney
Dr Jamie Vanderberg, Garvan Institute of Medical Research, Sydney

**Grants awarded in 2003**
ARC Grant *Tuning the catalytic apparatus of HIV-1 Protease*
NHMRC Development Grant *Development of a new class of antibiotics*
Publications


Rob Capon

CENTRE FOR MOLECULAR BIODIVERSITY

Research overview
Australia is uniquely positioned as the only scientifically advanced country endowed with mega biodiversity.

Australian tropical, sub-tropical and temperate marine and terrestrial ecosystems span an enormous geographic area and are home to an extraordinary array of unique and indigenous life forms, ranging through plants and animals, to invertebrates and microbes. These organisms produce molecules that enhance survival through such mechanisms as chemical defence, offence and communication.

Specialist toxins deter predators and paralyse prey, while trail, sex and alarm pheromones influence behaviour between individuals of the same and different species. Novel bioactive metabolites can protect against viral, microbial and parasitic infection, resist biofouling, and selectively modulate larval development.

Evolutionary pressures have refined natural chemical diversity to the point where exquisite biological potency and selectivity makes them attractive drug candidates, or leads that inspire the development of new drugs.

In 2003 my research team relocated from the University of Melbourne to the University of Queensland, to establish the Centre for Molecular Biodiversity (CMB) within the IMB. The CMB will accelerate the effective exploration of Australian biodiversity, as a means to discover new and improved drugs, with application in the areas of human and animal health, and crop protection.

Projects
Our research focus on the detection, isolation, identification and evaluation of novel naturally occurring bioactive metabolites, primarily from marine and microbial sources. This research requires the extensive use of chromatographic and spectroscopic technologies, and chemical synthesis, and draws on the collaborative expertise of many colleagues in biology, biochemistry and pharmacology. Our efforts have uncovered many rare and unique bioactive molecules, presenting exciting technical and intellectual challenges. These compounds span a wide range of molecular structure classes including the nematocidal agents thiocyanatin A (1) and marcfortine A (2), the antibiotics rugulotrosin A (3) and aspergillicin A (4), and the acetylcholine mimetic esmodil (5). Research into many other bioactive molecules remains work in progress and/or commercial-in-confidence.

Collaborations
Novartis Animal Health Australasia
Microbial Screening Technologies
PharmaMar
University of Melbourne, School of Botany

Grants Awarded
ARC Linkage Grant Anticancer Agents from Australian Marine Biodiversity
Conferences and Invited Lectures
19th Royal Australian Chemical Institute Organic Conference (Lorne)
CSIRO: Biopharmaceuticals, Concept to Clinic (Melbourne)
Queensland Government: Ideas@Powerhouse (Brisbane)
Queensland Government: Science Meets Parliament (Brisbane)
AusBiotech: Biodiscovery (Brisbane)
Queensland Department of Primary Industries: Microbes: Biodiversity, biodiscovery & biotechnology (Caloundra)
World Federation of Culture Collections (Melbourne)
Asia Pacific Biochemical Engineering Conference (Brisbane)

Other
Principle scientific consultant for ChemoType Pty Ltd, providing expert advice and guidance to industry (Nufarm), and the legal profession (patent defence, chemical regulations, forensic evidence).


Staff and Students

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<thead>
<tr>
<th>Research officers</th>
<th>Research assistant</th>
<th>PhD students</th>
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<tbody>
<tr>
<td>Mike Stewart</td>
<td>Ben Mooney</td>
<td>Ben Clark</td>
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<td>Nick Trotter</td>
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<td>Leith Fremlin</td>
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<td>Visiting student</td>
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<td>Ranjala Ratnayake</td>
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<td>Torsten Peterle</td>
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<td>Michelle McNally</td>
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Research assistant
Ben Mooney
PhD students
Ben Clark
Leith Fremlin
Ranjala Ratnayake
Michelle McNally
Ed Liu
Research overview

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. We have a particular interest in the discovery and structural characterisation of novel protein topologies.

Research Projects

In 2003 we solved the structures of novel proteins from bacteria, plants and animals. They have applications ranging from the development of new antibiotics, to anti-HIV therapy, to the development of new approaches to crop protection. A unifying theme is that we focus on proteins that have the novel feature of a cyclic backbone. Circular proteins were unknown until recently and represent an exciting new field of discovery.

Bioengineering of circular proteins:
The unique structures and functions of circular proteins makes them exciting prospects in drug design and agriculture. Circular proteins have no ends, making them exceptionally stable and resistant to enzyme digestion. Our group uses new approaches in chemistry, biochemistry and molecular biology to learn more about naturally occurring circular proteins. We also design and construct synthetic circular proteins with enhanced stability.

Discovery of new circular proteins:
The largest family of circular proteins is the cyclotides, discovered by our group over the last few years. Their exceptional stability is due to the unusual features of a cyclic backbone and a cystine knot structure. This year we continued our program of discovery and structure elucidation of cyclotides. With collaborators at the National Cancer Institute, USA, we recently published the structure of the largest known cyclotide, palicourein, a potent anti-HIV molecule derived from a South American tree. We also reported a series of papers defining the knotted topology and pharmaceutical applications of cyclotides.

Venom proteins:
Our group is actively involved in determining structures of disulfide rich proteins from animal venoms using NMR spectroscopy. Conotoxins continue to be of interest for their role as leads in drug design programs. Early this year we reported the structure of a new conotoxin, GID that has an unusual flexible “tail” at its amino-terminus. Mutagenesis studies are underway to elucidate the role of this tail. Our program on the development of improved conotoxin drug leads using cyclisation technology has led to several molecules with improved stability that are the subject of a patent application.
Grants

ARC Discovery Project grant Discovery of novel circular proteins. David Craik and Marilyn Anderson (La Trobe University)

ARC-CSIRO linkage grant Development of novel pesticides. Michelle Colgrave

ARC Linkage Grant Applying the CCK framework to angiogenic-based therapeutics

Biotechnology Innovation Fund grant Kalthera Pty Ltd. Proof of concept programs for applications of cyclotides in agriculture

Biotechnology Innovation Fund grant Cyclagen Pty Ltd. Proof of concept programs for applications of cyclotides in drug design

NHMRC Development of novel drugs for multiple sclerosis. David Craik and Claude Bernard (La Trobe University).

NHMRC Industry Fellowship Norelle Daly

2003 AMRAD Postdoctoral Award Justine Hill

Highlights

Filling the pod:
With the move to the new QBP building we installed two new high field NMR spectrometers in the NMR facility (affectionately known as the pod). These are to be used in a variety of drug discovery projects.

Structures in the news:
Our structure of the potent antimicrobial protein microcin J25 created much interest because of its unusual feature of a protein chain “threading the eye of a needle” whereby the C-terminal tail of the molecule penetrates though a novel ring structure at the N-terminus. The work was published in the Journal of the American Chemical Society (125, 12464, 2003) and was the subject of a commentary article by journalists in Chemical and Engineering News. It was also selected by the American Chemical Society as one of six highlighted achievements in structural biochemistry for the year 2003.

Major lectures:
Plenary lecture at the 18th American Peptide Symposium in Boston The study of cyclotides

Invited public lecture at Nanyang University in Singapore.

Reversing Nature:
In an exciting new application of chemical biology we showed that an enzyme such as trypsin, which normally cleaves peptide bonds, can be made to reverse its usual role and actually synthesise peptide bonds when presented with a suitable substrate. In this case a synthetic peptide corresponding to a linear derivative of a naturally occurring circular peptide from sunflower seeds was incubated with trypsin and was quantitatively cyclised. This novel finding paves the way for applications of enzymes in the cyclisation of proteins.

Saving cotton:
With our collaborator Associate Professor Marilyn Anderson we have shown that cyclotide molecules are potent “natural” insecticides that retard growth of Helicoverpa insect species, which are major pests in the cotton and corn industries around the world. Commercialisation of this discovery is underway.

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<td>Fiona Foley</td>
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<td>Norelle Daly</td>
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<td>Justine Hill</td>
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<td>Amanda Nourse</td>
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<td>Johan Rosengren</td>
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<td>Horst Schirra</td>
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<td>Manuela Trabi</td>
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<td>PhD students</td>
<td>Visiting researchers:</td>
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<td>Daniel Barry</td>
<td>Bin Chen</td>
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<td>Michael Korsinczky</td>
<td>Ulf Goransson</td>
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<td>Marco Retzlaff</td>
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<td>Seetharama Satyanarayanojis</td>
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<td>Visiting scholar</td>
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<td>Uta Kuepper</td>
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<td>Honours student:</td>
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<td>Louise Dempster</td>
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Erica Lovelace
Emma Millard
Jason Mulvenna
Manuel Plan
Maria Quimo
Angela Salim
Lillian Sando
Ivana Saska
Shane Simonsen

RRB
Published papers in 2003


(Opposite page - from left) Solution structure of palicourein, the largest cyclotide yet discovered, along with the South American plant, Palicourea condensata, from which it is derived. Cover from the Journal of Biological Chemistry from the issue in which we described the concepts of "twist, knots and rings" in proteins with reference to the cyclotide family of circular proteins; Structure of the novel conotoxin G14 determined by PhD student Emma Millard; Installation of our new high field NMR spectrometers in the NMR "pod" in the QBP complex; The unique structure of the antibacterial peptide microcin J25. It represents a rare example of a threaded protein structure;

(Above) Cover page from the Journal of Biological Chemistry from the issue in which we described the use of an enzyme to reverse its normal action and cyclise a small peptide, that itself is a potent inhibitor of the enzyme.
David Fairlie

CHEMISTRY AND HUMAN THERAPEUTICS

Research overview
Chemistry underpins all aspects of the molecular biosciences. Interactions between proteins and either small molecules, proteins, DNA or RNA determine the outcomes of all biological processes. Patterns are emerging in such molecular recognition and, by understanding the consequences of such interactions, we can expect to develop design strategies for creating generic classes of small molecules that mimic or interfere with biomolecular interactions. We aim to use rational chemical intervention to mimic proteins (Figure 1a,b), inhibit enzymes (Figure 1c), or antagonize receptors (Figure 1d) that are pivotal in normal human physiology, aberrant in disease, or crucial mediators of infection. We also use small molecules to better understand the roles of pivotal proteins in life, ageing, and death.

Research Overview
Our group is principally interested in chemical design and synthesis in order to study chemical reactivity, chemical structure, molecular interactions, and the molecular basis for biological processes, disease development, and drug action. Some group members also study enzymes and receptors on cell surfaces in order to design new, potent and selective, enzyme inhibitors or receptor antagonists for development into orally active drugs to treat inflammatory and neurodegenerative diseases, cancers, and viral/parasitic infections. Thus our research interests, while heavily centered on chemistry, extend to a molecular understanding of aspects of biochemistry, pharmacology, immunology, inflammation, virology, parasitology, cancer biology, and neurobiology.

Project Areas
Fundamental Chemical Studies
Members of the group are engaged in a wide range of fundamental chemical studies towards the discovery and development of new synthetic methodologies and reagents, investigation of molecular recognition, identification of the influences of constraints on molecular structure, understanding steric and electronic roles in chemistry and catalysis, and use of chemical templates in building nano-structures. The work is heavily based on organic synthesis, 2D-NMR spectroscopy, and uses a suite of other spectroscopic techniques for chemical analysis, purification and for assessing potential applications.

Drug Design, Discovery and Development
In addition to synthetic chemistry, researchers study macromolecule-ligand interactions using computer modelling, determine NMR and crystallographic structures, and conduct biochemical and pharmacological assays. As a result of our basic and strategic research, we have been able to develop generic approaches to the discovery of protease/lipase/transferase inhibitors, G protein-coupled receptor antagonists, and transcriptional regulators. We have created multiple classes of small orally active organic molecules and demonstrated their potent (IC50 < 1-100 nM) antitumour activity (Figure 2a), antiparasitic activity (malaria, giardia, schistosomal proteases), antinflammatory activity (blocking human TNF-a, IL-1b, IL-6, complement receptors, PAR, phospholipases (Figure 2b), antiviral activity (low resistance inhibitors of HIV, Dengue and West Nile viral proteins), and anti-Alzheimer’s activity (against beta secretase). Such non-peptidic compounds are in various stages of pharmacological, pre-clinical or clinical development.

Molecular Recognition
Our group uses computers to identify patterns in biomolecular recognition. We are attempting to understand the origin and reasons for such patterns, and are developing generic strategies for rationally creating small molecules that mimic or interfere with such interactions. We have recently completed computer modelling analyses of all known structures of protease-bound ligands, GPCR-binding proteins/peptides, and receptor-bound transcription factors. We have established the frequency with which such classes of receptors recognize their ligands in beta strand, turn, and helix shapes respectively. We have also created a database consisting of millions of sorted small organic molecules for use in silico in matching to pharmacophores or receptors during ligand- or receptor- based drug design.
Protein Surface Mimics
We are designing and synthesizing new classes of small organic molecules that mimic bioactive secondary (strand, sheet, helix, turns, combinations) and tertiary (multi-loop, multi-helix, multi-sheet bundles) structural surfaces of proteins. Multi-helix and multi-sheet molecules also led in some cases to supramolecular nanostructures resembling those formed by amyloidogenic proteins associated with neurodegenerative diseases. We use 2D NMR spectroscopy to determine structures for selected chemical mimics which are then compared with protein structures. Successful structural mimicry has translated into functional mimicry, and we are now attempting to discover how universal our generic approaches are for mimicking bioactive protein surfaces.

Other highlights were denaturation-resistant alpha helical mimics (Figure 2c), template-assembled nanofibres (Figure 2d), and macromolecules that mimic protein structures.

Collaborations
During the past 5 years our group has published in 5 branches of chemistry (organic, medicinal, biological, inorganic, theoretical) and 7 branches of biology (biochemistry, pharmacology, virology, immunology, parasitology, cancer biology, neurobiology) necessitating a wide range of Queensland, Australian, and International collaborators.

Grants
NHMRC Project Grant Convertase Inhibitors As A New Class Of Anti-Inflammatory Drugs
NHMRC Project Grant Design & Development Of Small Molecules To Regulate Protease Activated Receptor-2
NHMRC Project Grant Agonists and Antagonists of the Human Complement C3a Receptor
NHMRC Project Grant Design & Evaluation of Inhibitors of Phospholipases A2 as Anti-inflammatory Drugs
NHMRC Development Grant Developing Anti-Inflammatory Drugs Based on Inhibition of a Human Enzyme
ARC Discovery Grant Macro cyclic Peptidomimetics
ARC Discovery Grant Metal Clips For Folding Short Peptides Into Helices
ARC Seed Grant The Australian Protease Network
2nd Hans Werthen Scholarship Pia Kahnberg
NHMRC CJ Martin Fellowship Michael Kelso
ARC Australian Professorial Fellowship Fairlie

Figure 1: Cytokine structure (Fig1a) for which a loop (red) has been mimicked (Fig1b) by a small molecule (yellow); Structure of a beta strand inhibitor bound in the active site of caspase 3 (Fig1c); NMR structure for several cyclic and acrylic agonists and antagonist of a GPCR (Fig1d).
Publications 2003


**Conferences**

Among 11 international, 2 national, and 1 local conference presentations were:


“Mimicking Protein Structure in Short Peptides”, Fairlie DP Australian Peptide Symposium, Oct 2-6, 2003 (Daydream Is, Qld)

“Towards Small Molecule Mimics Of Bioactive Protein Surfaces” New Zealand Chemical Society, Nov 30-Dec4, 2003 (Nelson, NZ)

“Helix-Inducing Metal Clips In Short Peptides”, Fairlie, D. P. First International Symposium on Biomolecular Chemistry (ISBC 2003), Japan Chemical Society, Dec 2-5 2003 (Awaji Is, Japan).

“Towards Mimics Of Protein Surfaces” Fairlie, D. P. Symposium on Biomolecular Chemistry Kyushu University, Dec 6, 2003 (Fukuoka, Japan).

**Other Developments**

2003-, Co-Editor of Current Medicinal Chemistry

Started International and National protease research networks (www.protease.net, www.protease.net.au) to facilitate interdisciplinary research interactions in the field of proteases, their inhibitors and receptors. The networks involve over 100 international research groups and 90 Australian research groups.
Research overview
Research carried out by this new group will exploit the platform of contemporary protein chemistry and proteomics. This platform is broadly applicable to defining the chemical features of purified proteins, interactions between proteins at the molecular and cellular levels and the dynamics of the protein repertoires of cells in response to disease states and other stimuli.

Research topics of particular interest involve the interactions of viral proteins in assembled virus particles interactions between intracellular proteins and viral proteins during morphogenesis (virus particle formation) and interactions of viral proteins with cell membrane receptors during infection of cells.

Our research will be underpinned by our mass spectrometry expertise for the analysis of proteins and complemented by our excellent mass spectrometry infrastructure.

In addition to academic interest, our work has the potential to produce important leads for development of therapeutic agents to treat viral infections and other important medical conditions.

This group integrates the proteomics activities of CSIRO Livestock Industries through the establishment of a joint laboratory, as well as accommodating the proteomics needs of the SRCFAG.

Projects
Interactions and structures of proteins in assembled virus particles.

Viruses consist of nucleic acid genomes packaged within protein-containing coats. Coat proteins function to ensure efficient attachment to target host cells and transmission of the viral genomes into these cells in which the viruses replicate. Proteins also contribute to structural integrity of the viral particles and the viral genome as well as functioning in viral replication.

The process of assembly (morphogenesis) of the virus particles, stabilities of the assembled particles and functional activities of the viral proteins are governed by protein-protein interactions.

This project aims to develop and apply methods to better understand the interactions between viral proteins during morphogenesis and in the assembled particles.

Interactions of viral proteins with host cell proteins during infection and assembly.

There is a growing appreciation that viral proteins can interact in a variety of ways with cellular proteins during the viral replicative cycle. The interaction of viral attachment proteins with host cell receptors to initiate infection is well known, but there is growing evidence of interaction at other steps in the cycle, such as during RNA synthesis, viral assembly, and antagonism of host cell defenses.

Frequently, these interactions are essential for efficient viral replication and can have a major impact on pathogenesis. Relatively little is known about this area, in part because it has not been amenable to investigation by traditional biochemical approaches.

However, application of improved techniques of mass spectrometry and proteomic-related techniques have enabled the analysis of proteins present in low quantity or in complex mixtures, and provide new impetus for examining the effect of viral infection on the host proteome and possible physical interaction between viral and cellular proteins.

Regulation of signal-activated transcription factors by post-translational modifications and protein-protein interactions.

Transcription factors with a general basic helix-loop-helix/Per Arnt-Sim (bHLH/PAS) domain architecture act within the cell nucleus to coordinate transcription of specific genes. Heterodimerisation with the aryl hydrocarbon receptor nuclear translocator (Arnt) is essential to form DNA binding complexes. Other proteins are recruited to form the active transcription complexes. Ligand binding or other cellular signals can modulate nuclear translocation of the transcription factors and their ability to form active complexes.

In collaboration with Dr Murray Whitelaw’s group from the University of Adelaide, we have demonstrated that the transcriptional potency of hypoxia-inducible factor (HIF)-transcriptional complexes is inhibited by hydroxylation of a specific asparagine residue of HIF. Oxygen activates this post-translational modification and it also serves as the substrate for the hydroxylase (Factor that Inhibits HIF, or FIH) which hydroxylates the
regulatory asparagine of HIF. This normoxic hydroxylation inhibits the recruitment of the transcriptional co-activator p300/CBP to the DNA-bound complex, thereby repressing transcription. The purpose of this regulation is to prevent transcription of genes whose products are only required to respond to low cellular oxygen levels.

Other uncharacterised proteins are also recruited to the transcription complexes to influence the transcriptional activity of HIF. One of our current aims is to identify these unknown proteins and to determine their functional roles in the hypoxic regulation of transcription.

We have recently commenced work on a comparable transcription factor, the Dioxin (or Aryl Hydrocarbon) Receptor. This factor also appears to be regulated by post-translational modifications and our aim in this project is to define the modifications involved and the mechanisms by which they invoke control.

Collaborators
Prof John Bateman, Murdoch Childrens Research Institute, Melbourne
Professor John Hancock, IMB
Professor Rob Parton, IMB
Professor Paul Young, Department of Microbiology, University of Queensland
Dr Murray Whitelaw, School of Molecular and Biomedical Science, University of Adelaide
Dr Peter Collins, National Institutes of Health, Bethesda, Maryland, USA
Professor Mark Peeples, Columbus Children’s Research Institute and The Ohio State University, USA

Grants
ARC Linkage Infrastructure and Facilities Grant (LIEF) Time of Flight Mass Spectrometry and Robots
NHMRC Project Identification and functions of posttranslational modifications in the Dioxin/Arnt transcription factor. With Murray Whitelaw
AntiCancer Council of South Australia Role of the Hypoxia Inducible Factor in Tumourigenesis. With Murray Whitelaw and Daniel Peet.
Queensland Cancer Fund Proteomics approaches to the early detection of prostate cancer. With R. Gardiner, J. Clements, T. Walsh, J. Bartley, and T. Pettitt

Other
Member of the editorial boards of the journals Molecular and Cellular Proteomics and Protein and Peptide Letters

Staff and Students

Research officers
Gary Shooter
Professionals officer
Alun Jones

Research assistants
Ngari Teakle
Tristan Wallis

PhD students
Hong Soon Chin
Keyur Dave

Publications


**Bostjan Kobe**

**STRUCTURAL BIOLOGY OF PROTEIN – PROTEIN INTERACTIONS**

**Research overview**

Our research focus on protein structure and function, with the emphasis on understanding the structural basis of interactions formed by these macromolecules. The primary technique used in the laboratory is X-ray crystallography, combined with a plethora of other molecular biology, biophysical and computational techniques. Our research vision is to apply structural biology in functional annotation of proteins (functional genomics).

**Projects**

**Specificity of signal transduction pathways.**

The specificity of signal transduction pathways stems from specific recognition and regulatory properties of proteins involved in these pathways. We are studying a number of signaling molecules including protein kinases, the phosphopeptide-binding FHA domains, a novel class of G-proteins, and proteins involved in plant development and disease resistance. In parallel, we are developing bioinformatic tools for functional annotation of novel signalling molecules. To this end, we have developed the computational tool Predikin that can predict the substrates for Ser/Thr kinases based on their sequence alone, providing a powerful tool for genome-wide analysis of signaling pathways and identification of new therapeutic targets.

**Regulation of nuclear import.**

Nuclear proteins are synthesised in the cytoplasm and are imported into the nucleus through the nuclear pore complexes. Such transport is directed by special signals, the most common termed the nuclear localisation sequences (NLSs). Importin-alpha is the nuclear import receptor that recognises these NLSs. The ongoing crystallographic, biophysical and mutagenesis studies are aimed at shedding light on both regulation and NLS recognition by importin-alpha, as well as using this protein as a structural framework for engineering new binding specificities useful for diagnostic and biotechnology purposes.

**Structural genomics of macrophage proteins.**

Structural genomics is a large-scale effort to determine 3D structures of all representative proteins, as 3D structural information is one of the most effective ways to infer protein function. Our strategy is to use gene expression information from cDNA microarrays for target selection, and therefore selectively determine the structures of medically relevant proteins via a high-throughput approach. The structures are used to infer biochemical and cellular function and will serve as templates for structure-based drug design. Macrophage proteins are of central importance in a wide range of immunopathology, including infectious and inflammatory disease, cardiovascular disease and cancer.

**Grants awarded**

**ARC Discovery Structure and function of novel macrophage proteins using high throughput crystallography**

**Collaborators**

David Hume, Institute for Molecular Bioscience, University of Queensland

Jenny Martin, Institute for Molecular Bioscience, University of Queensland

Thomas Huber, Department of Mathematics, University of Queensland

Paul Young, Department of Microbiology and Parasitology, University of Queensland

Stuart Kellie, Department of Microbiology and Parasitology, University of Queensland

Jimmy Botella, Department of Botany, University of Queensland

Bernie Carrol, Department of Biochemistry and Molecular Biology, University of Queensland

David Fairlie, Institute for Molecular Bioscience, University of Queensland

Don McManus, Queensland Institute of Medical Research, Brisbane

Bruce Kemp, St. Vincent's Institute of Medical Research, Melbourne

David Jans, Department of Biochemistry and Molecular Biology, Monash University, Melbourne

David Jones, Research School of Biological Sciences, Australian National University, Canberra

Jeff Ellis, CSIRO Plant Industry, Canberra
Publications and papers in 2003


Conferences


Richard Lewis

Molecular Pharmacology

Research Overview
My group’s research focuses is on the discovery and characterisation of conotoxins acting at ion channels, receptors and transporters, especially those found in pain pathways (see figure Lewis3.jpg).

Currently we are investigating conotoxins that selectively target the nicotinic acetylcholine and NMDA receptors, the voltage sensitive calcium and sodium channels, the noradrenaline transporter and the α1-adrenoceptor. Complimentary interactions between conotoxins and their receptor are being established to better understand where and how they act. Research on characterising the toxins involved in ciguatera is also undertaken in the laboratory.

The aim of this research is to develop research tools and potential therapeutics for poorly treated diseases, such as chronic pain. This research involves assay-guided isolation of venom peptides, peptide synthesis, tissue pharmacology, radioligand binding and electrophysiological studies, as well as receptor mutagenesis, modelling and docking.

Projects
We are currently investigating conotoxins that selectively target:

1. The nicotinic acetylcholine receptor, a non-selective cation channel stimulated by acetylcholine and nicotine, is selectively inhibited by α-conotoxins. We have discovered several new α-conotoxins using receptors expressed in oocytes to guide crude venom fractionation. Several had unusual structure and subtype selectivity. Homology modelling and docking studies are allowing us to understand at the molecular level how these selectivity differences arise;

2. The NMDA receptor, an important non-selective cation channel in the brain, is inhibited by conantokin-G. Using specific analogues of conantokin-G, we have recently found that specific subtypes of the NMDA receptor are lost in Alzheimer’s disease. Currently we are trying to establish their identity to better understand how Alzheimer’s disease develops;

3. The voltage sensitive N-type calcium, a neuronal calcium channel found in pathways involved in the transmission of painful stimuli, is inhibited by μ-conotoxins. We have recently identified a novel variant of this channel using ω-CVID. The nature and role of this variant is now being investigated to understand its role in chronic pain;(figure Lewis1.jpg)

4. The voltage sensitive sodium channels, particularly those found in neurons that are inhibited by μ-conotoxins, are also under investigation. We have established that μ-conotoxins selectively target persistent forms of the TTX-sensitive sodium channel. The nature and role of these sodium channels is currently under investigation.

5. The noradrenaline transporter (NET) is the primary route of noradrenaline removal from synapses. We have identified χ-conotoxins as the first peptide inhibitor of NET, which is effective in the treatment of neuropathic pain and depression. We are presently establishing the complimentary interactions between χ-conotoxins and NET to understand where and how they act at the molecular level.

6. We are also developing an understanding of where and how the ρ-conopeptides act on the α1-adrenoceptor, and important target for treating cardiovascular disorders and benign prostatic hyperplasia.

7. Finally, we are characterising the novel substrate specific proteases found in cone snail venom that have homology to pathogenesis related proteins and are up regulated in stress and diseases such as cancer.

Grants
NHMRC grant Selectivity and Mode of Action of Rho-Conopeptide Tia: A Novel Inhibitor of Alpha1-Adrenoceptors
ARC Glyceroxin, a unique tool to investigate the dynamic interactions between N-type Ca2+ channels and the exo-endocytic machinery (with Frederic Meunier, Physiology and Pharmacology, UQ).
**Staff and Students**

**Research officers**
Denise Adams  
Marion Loughman  
Leonard Motin  
Annette Nicke  
Tina Schroeder  
Iain Sharpe

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Jenny Eckberg

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Lotten Ragnarsson  
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Vicky Tsai  
Taka Yasuda

**Honours student**
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**Visiting researcher**
Patricia Hung

**Visiting students**
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Pia Larsson  
Emma Larzenius  
Sofie Singbrant  
Angela Starke

**Collaborators**
Professor Jean-Paul Vernoux, University of Caen, France
Professor Heinz Bönisch, University of Bonn, Germany
Professor Robert Graham, Victor Chang Cardiac Research Institute, Sydney
Professor MacDonald Christie, Pain Management Research Institute, University of Sydney
Professor Gustaaf Hallegraeff, Department of Botany, University of Tasmania

Professor David Adams, School of Biomedical Sciences, UQ  
Dr Lesley Lluka, School of Biomedical Sciences, UQ  
Professor Paul Alewood, IMB  
Professor David Craik, IMB  
Professor Robert Capon, IMB
The aim of this research is to develop research tools and potential therapeutics for poorly treated diseases, such as chronic pain.
Jenny Martin

PROTEIN STRUCTURE AND PROTEIN INTERACTIONS

Research overview
We are interested in understanding the role of proteins in disease and developing novel inhibitors to modify the functions of disease-causing proteins. We use protein crystallography as the major biophysical approach to investigate protein structure and function, protein interactions, and as the foundation for inhibitor design.

Our goal is to develop, with other researchers at UQ, the best lab-based protein crystallography facility in Australia and to link these to high throughput approaches for protein structure determination. Together these facilities will be used to examine proteins of prime importance to human health and will thereby underpin the development of new medicines.

Projects
Structural Genomics of Mouse Macrophage Proteins
In 2003, as part of a collaboration with Bostjan Kobe and David Hume, we solved the first structure of a protein from this high throughput program. The structure determination required access to the ALS synchrotron in Berkeley, USA. We also established procedures for 96-well plate trials for most steps in the process from PCR to crystallisation.

Dsb Proteins are critical for protein folding in bacteria.
We solved the structure of DsbG, a disulfide bond isomerase, and showed that it had an unusually unstable disulfide bond at the active site. This appears to be unique amongst this class of proteins. Structure determination required access to the APS synchrotron at Argonne in the USA.

PNMT is the adrenaline synthesising enzyme.
In this collaboration with Joel Tyndall (IMB), Gary Grunewald (Kansas University) and Michael McLeish (University of Michigan) we aim to develop potent, selective and CNS-active inhibitors of PNMT with which to investigate the role of CNS adrenaline. The structure of PNMT, solved recently using in-house X-ray equipment, allows structure-based design of these inhibitors. We are currently investigating the structures of several PNMT:inhibitor complexes.

Sulfotransferases
The structure of the carcinogen-converting enzyme, SULT1A1, was solved in collaboration with Mick McManus (BACS, UQ) using in-house X-ray equipment and was published early in 2003 in Journal of Biological Chemistry. The structure showed that, unexpectedly, two substrate molecules could be accommodated at the active site simultaneously. We are currently investigating how other substrates bind to this protein.

SNARE proteins involved in insulin-regulated glucose transport.
In this collaboration with David James (Garvan) we have produced recombinant forms of all the SNARE proteins involved in the GLUT4 process as well as the regulatory SM protein Munc18c. We are currently investigating protein-protein interactions using the recombinant proteins.
Grants awarded for 2003
- **ARC Discovery Project** Investigating the structure, function and inhibition of the adrenaline-synthesizing enzyme PNMT
- **ARC Linkage Project** Structural studies on carbohydrate modifying enzymes
- **ARC Linkage Infrastructure and Equipment Funding** Queensland high throughput structural biology screening facility

Collaborations (not including those within IMB)
Gary Grunewald, Kansas University, USA
Michael McLeish, University of Michigan, USA
Linda Thöny-Meyer, ETH Zurich, Switzerland
Mick McManus, School of Molecular and Microbial Sciences, University of Queensland
Paul Young, School of Molecular and Microbial Sciences, University of Queensland
Judy Haliday, Alchemia Pty Ltd
David James, Garvan Institute for Medical Research, Sydney

Staff and Students

<table>
<thead>
<tr>
<th>Research officers</th>
<th>PhD students</th>
<th>Honours students</th>
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<tr>
<td>Anna Aagaard</td>
<td>Melissa Edeling</td>
<td>Elizabeth Westbury</td>
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<td>Nathan Cowieson</td>
<td>Cath Latham</td>
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<td>Niranjali Gamage</td>
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<tr>
<td>Christine Gee</td>
<td>Aditya Angadi</td>
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<td>Begona Heras</td>
<td>Frank Lin</td>
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<tr>
<td>Shu-Hong Hu</td>
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<td>Danny Loveday</td>
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<th>Research Assistants</th>
<th>Masters Students</th>
<th>Undergraduate Students</th>
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<tr>
<td>Kirra McConnell</td>
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<td>Vivian Chan</td>
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<td>Casey Pfluger</td>
<td>Aditya Angadi</td>
<td>Natalie Saez</td>
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<tr>
<td>Maria Somodevilla-Torres</td>
<td>Frank Lin</td>
<td>Rosemary Harrison</td>
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Publications and papers in 2003


**Conferences**


Christine Gee, M.J. McLeish, G.L. Grunewald, J.L. Martin. "Structural studies on PNMT, the adrenaline-synthesizing enzyme"

Melissa Edeling, Begona Heras, Linda Thony-Meyer, Jennifer L. Martin. "The Broad Substrate Specificity of the Thioredoxin Fold is adapted in CcmG to achieve a very specific function" (awarded prize for best student presentation)

*Combined AsCA and SCANZ meeting, Broome, August 2003* Anna Aagaard, P. Listwan, N. Cowieson, T. Huber, C. Wells, T. Ravasi, B. Kobe, D.A. Hume, J.L. Martin. "Structural studies of latexin, a novel carboxypeptidase inhibitor"


Christine Gee, M.J. McLeish, C.L. Grunewald, J.L. Martin. "Structural studies on PNMT, the adrenaline synthesising enzyme: improving crystallisation methods and diffraction resolution"

Begona Heras, M. Edeling, S. Raina, J.L. Martin: "Crystal structure of oxidized and reduced DsbG"

*ASCEPT, Sydney December 2003-12-03* J.L. Martin “Focus on Queensland - the IMB and DDD”

**Achievements in 2003**

- Together with Bostjan Kobe and David Hume we succeeded in solving what we believe to be the first “high throughput” crystal structure, that of latexin a novel mammalian carboxypeptidase inhibitor (see picture on previous page).
- Installation of the first (and only) high brightness FR-E X-ray facility in Australia (see picture on previous page).
- Currently establishing with Bostjan Kobe and David Hume a high throughput facility for protein expression screening (pictures in next year’s annual report).
Our goal is to develop, with other researchers at UQ, the best lab-based protein crystallography facility in Australia and to link these to high throughput approaches for protein structure determination.
**Mark Smythe**

**COMBINATORIAL CHEMISTRY AND MOLECULAR DESIGN**

**Research Overview**
Our research focuses on advancing drug design and synthetic organic chemistry to discover novel biologically active molecules against numerous targets and therapeutic indications.

**Projects**
Research undertaken can be summarised into the broad thematic areas outlined below:

**Development of new molecular design tools**
- Using advances in information science to facilitate rapid database searching to identify topological patterns in large databases of molecules
- Using experimentally derived structural data of molecules to determine the important physicochemical features of binding and function. To use these features as descriptors to design and synthesise biologically relevant arrays of molecules.

**Synthetic Chemistry**
- Develop new linkers and associated chemistries to rapidly prepare arrays of molecules
- To develop new synthetic strategies to rapidly access privileged substructures.

**Biology**
- To explore the advantages of combining structural based drug discovery with phage display for the development of topologically focussed arrays of rigid peptide molecules. Use these arrays of molecules to discover biologically active leads and drugs in a target-based discovery approach.
- Express proteins and develop assays to assist drug discovery.

**Drug Discovery**
- Use fragment based drug discovery approaches to identify small molecular fragments that bind to protein surfaces. Fragment based discovery involves the design and synthesis of libraries of molecules comprising a disulfide that are site specifically captured on a target protein containing a free cysteine and identified in a mass spectroscopy based assay. Fragments that bind to the protein surface are joined together in a combinatorial fashion and screened using more conventional assays.
- Use existing chemistry and design infrastructure to develop potent molecules to modulate the function of cytokines and GPCR’s, and to block virus and bacterial infection.

**Collaborators**
Professor Garland Marshall, Washington University, St Louis, USA
Professor Mike Waters, IMB
Dr Kritaya Kongsuwan Livestock Industries, CSIRO
Dr Gene Wijffels, Livestock Industries, CSIRO
Dr Peter Adams, Department of Mathematics UQ
Dr Darryn Bryant, Department of Mathematics UQ
### Staff and Students

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<tr>
<th>Research officers</th>
<th>PhD students</th>
<th>Research assistants</th>
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<tr>
<td>Greg Bourne</td>
<td>Andrew McDevitt</td>
<td>Justin Coughlan</td>
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<td>Andreas Ruhmann</td>
<td>Doug Horton</td>
<td>Jill Turner</td>
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<td>Steve Love</td>
<td>Stephen Long</td>
<td>Ngari Teakle</td>
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<td>Gerald Hartig</td>
<td>Jonathon Nielson</td>
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### Publications


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**Our research focuses on advancing drug design and synthetic organic chemistry to discover novel biologically active molecules against numerous targets and therapeutic indications.**
ISSUES IN GENETIC AND CELLULAR MEDICINE AND TECHNOLOGIES

This research program focuses on public understanding, issues and implications of the new genetics and cell technologies for the prevention and treatment of complex diseases. It explores ethical issues and problems raised by the genetic modification of plants, animals and humans.

It incorporates the IMB Office of Public Policy and Ethics.

Research Group Leader
Wayne Hall
Wayne Hall

OFFICE OF PUBLIC POLICY AND ETHICS

Research overview
The Office of Public Policy and Ethics undertakes research and analysis on ethical and public policy issues raised by advances in the molecular biosciences and their applications. By detailed analyses of important public policy and ethical issues, the Office aims to enhance public discussion and encourage participation in decisions about developments in biotechnology.

Projects
The Office's major current areas of research include the policy implications of the genetics of addiction and mental disorders. The Office has followed the Australian debate surrounding research on human embryonic stem cells and cloning and is investigating the social and policy implications of research on the genetics of melanoma and colorectal cancer. We are collaborating with the Queensland Cancer Fund and UQ’s School of Population Health to examine public perceptions of genetic science and molecular biotechnology in the context of cancer prevention and management.

Our work in the addictions field also encompasses the ethical issues raised by neuroscience research on addiction. We have investigated the ethical implications of developing a cocaine vaccine and we are studying the contribution of illicit drug use to the global burden of disease, as well as the policy implications of genetic research on tobacco use, nicotine dependence and the development of a nicotine vaccine.

Finally, we are also tackling the ethical and policy implications of research into the genetics of depression and we have collaborated in an evaluation of the impact of antidepressant prescribing on suicide mortality in Australia between 1991-2000.

OPPE has developed a seminar program for academics in the fields of biotechnology, ethics and public policy. Commencing in May 2003 the seminars have attracted leading thinkers in the fields of philosophy, education, psychology, genetics, sociology, genetic counselling, and social science. By bringing together these key researchers we are building an academic concentration in biotechnology ethics and public policy.

In addition we have developed a series of fact sheets on topical biotechnology issues ranging from embryonic stem cells to genetically modified food. These can be accessed on the OPPE website www.uq.edu.au/oppe/.

Grants/funding
Australian Institute of Criminology / Criminology Research Council
Queensland Cancer Fund
School of Population Health, University of Queensland
beyondblue: the national depression initiative
UQ New Staff Research Start-up Fund

Staff and Students

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<th>Visiting professors</th>
<th>PhD students</th>
<th>Specialist librarian</th>
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<tr>
<td>John Morgan</td>
<td>Lucy Carter</td>
<td>Sarah Yeates</td>
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<td>David Weisbrot</td>
<td>Jennifer Fleming</td>
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<tr>
<td>Adjunct senior research fellows</td>
<td>David Turnbull</td>
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<td>Susan Treloar</td>
<td>Katie Wilson</td>
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<tr>
<td>Kim Summers</td>
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<td>Angela Wallace</td>
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<td>Visiting research fellow</td>
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<td>Undergraduate research opportunities program student</td>
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<td>Martin Wilkinson</td>
<td>Marla Gwynne</td>
<td>Cerys Jones</td>
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<td>URSS students</td>
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<td>Moya Anne McCaskill</td>
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<td>Cindy Rinehart</td>
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Collaborators

Professor Alan Lopez, Associate Professor Chris Doran, Professor Neville Owen and Professor Andrew Wilson, School of Population Health, The University of Queensland

Dr Louisa Degenhardt, National Drug and Alcohol Research Centre, University of New South Wales

Dr Rick Harwood, National Institute on Drug Abuse, USA

Dr Jeff Dunn and Dr Joanne Aitken, Queensland Cancer Fund

Dr Susan Treloar, Ms Kellie Chenoweth and Dr Sandy Taylor, School of Social Work and Applied Human Sciences, The University of Queensland

Publications


Hall, W., Degenhardt, L. (2003) Medical marijuana initiatives: are they justified? How successful are they likely to be? *CNS Drugs* 17:689-97.


Research presentations


Hall, W. (2003), *Ethical issues in neuroscience and genetic research on addiction.* Canadian Institutes of Health Research, Jackson’s Point, Ontario, Canada.


Community Engagement and Awareness

IMB OFFICE OF PUBLIC POLICY AND ETHICS – OPPE

The OPPE Lecture program is aimed at those with an interest in bioscience, ethics and public policy. The program ran throughout 2003 with a series of eight lectures attended by a diverse audience—academics from myriad disciplines, representatives of government departments, lawyers, policy makers, students, teachers and members of the general public.

- 'Attack of the Clones': Patent Law and Stem Cell Research
  Dr Matthew Rimmer,
  Faculty of Law, Australian National University

- Patently Justified? Gene Patents, Ethics and Public Policy
  Prof Wayne Hall,
  Director, Office of Public Policy and Ethics, IMB

- A Bigger Voice? Engaging Citizens with Life Science Questions
  Dr Tom Shakespeare,
  Director of Outreach, PEALS Research Institute, UK

- Biotechnology, genetics and tobacco control: an ethical and policy analysis of some feasible scenarios
  Prof Wayne Hall,
  Director, Office of Public Policy and Ethics, IMB

- Better People Through Better Technology
  A/Prof Carl Elliott,
  Center for Bioethics, University of Minnesota

- What are the Key Messages in Genetics and how can we Broadcast them?
  Dr Kristine Barlow-Stewart,
  Director, Centre for Genetics Education, NSW Genetics Service

- The Popular Press and Genetics Policies: The Nature and Impact of "Genohype"
  A/Prof Timothy Caulfield,
  Canada Research Chair in Health Law and Policy, University of Alberta, Canada

- Genetic Risk Information – Can it motivate behaviour change?
  Prof Theresa Marteau,
  Professor of Health Psychology and PDirector of the Psychology and Genetics Research Group, King’s College, London
Further underlining the Institute's commitment to research excellence, IMB Group Leaders are core partners and participate in several Cooperative Research Centres (CRC), a major National Research Facility, Australian Research Council (ARC) Centres of Excellence (COE), an ARC Special Research Centre, and a new ARC Centre.

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 benefit to the country.

Involvement in these ventures reflects very highly on the participating researchers, indicating the high 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 the latest technologies to enable internationally competitive research in the field of genomics. The SRC comprises an integrated network of core technologies including computational biology, structural biology, proteomics, animal transgenics service, as well as a microarray facility.

The relocation of the IMB to the Queensland Bioscience Precinct brought together groups previously dispersed through several buildings on the St Lucia campus and provided opportunities for the recruitment of new research groups adding significant depth to the SRC.

A particular highlight was the recruitment of Jeff Gorman to head a joint CSIRO/IMB proteomics unit. Jeff successfully applied for funding from the ARC for a ToF-ToF mass spectrometer, which will massively enhance the throughput and sophistication of proteomic tools available to researchers.

In terms of scientific outcomes, SRC affiliates provided the largest foreign group in the international consortium that provided functional annotation to the
mouse transcriptome project (FANTOM2) and subsequent analyses that made a major contribution to a special issue of *Genome Research* providing an overview of the FANTOM2 project. The close collaboration with Japanese colleagues at the RIKEN Genome Sciences Centre will continue with our strong involvement in FANTOM3 in 2004.

The new resources and common location provide a powerful foundation for the SRC to fulfil its aim of providing all of the links in the pipeline from gene discovery to functional assignment and application. The future will see the coordinated application of these resources 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**

This major national research facility based at the Australian National University enables Australian and international researchers to define the mammalian phenome: how the estimated 40,000 genes in the genome sequence of humans and other mammals regulate the phenotype or behaviour of cells, tissues and the body.

The completion of human and mouse genome sequences catalysed an international race to harness more efficient methods of disrupting gene function in the mammalian genome so as to illuminate phenotypic consequence and practical use for human and animal health, industry and environmental conservation.

The Australian Phenomics Facility (APF) builds upon and provides wide access to a new technology pioneered in Australia allowing high throughput analysis of all mammalian genes for their phenotypic effects by inducing mutations in mice, looking for specific changes to traits of medical importance and then isolating the genes responsible.

It includes researchers from John Curtin School of Medical Research, The Australian National University, Monash Institute of Reproduction and Development, Monash University, Dairy CRC, Garvan Institute, IMB, University of Queensland.

The facility keeps Australia at the cutting edge of international efforts to advance human and animal health by defining the phenome. The APF is a leading facility of its kind, and in high demand nationally and internationally, generating international recognition, key intellectual property, new skills, and represents a prime opportunity to build new industries.

**COOPERATIVE RESEARCH CENTRE FOR THE DISCOVERY OF GENES FOR COMMON HUMAN DISEASES**

The basal cell carcinoma research conducted by Brandon Wainwright and Carol Wicking contributes to the Cooperative Research Centre for the Discovery of Genes for Common Human Diseases’ (GeneCRC) research portfolio to unravel the genetic causes behind many common human diseases.

Many of the diseases affecting humans have both genetic and environmental components. In some cases the genetic component is distinct enough to allow identification of the responsible genes by genomic experimental techniques. These discoveries have important applications as diagnostics and possible development as therapeutics.

In addition to its research focus the GeneCRC has a strong education and ethics program committed to engaging the Australian community in an informed debate on the applications of human genetic technology, to which the IMB’s Office of Public Policy and Ethics makes contributions.
COOPERATIVE RESEARCH CENTRE FOR CHRONIC INFLAMMATORY DISEASES

The Cooperative Research Centre for Chronic Inflammatory Diseases (CRCID) focuses on two diseases that together contribute to a massive community burden, rheumatoid arthritis and chronic obstructive pulmonary disease.

The research activities of the CRC are focused on developing innovative therapies for these chronic inflammatory diseases through understanding their basic biology.

In 2004 the disease focus of the CRC will expand to include osteoarthritis as a result of a successful grant for supplementary funding. This will enable development of new methods to treat debilitating joint disease and generate synthetic tissues to repair injured joints.

The Queensland node headed by David Hume makes up approximately 40% of the CRC activity with a focus on therapeutic target gene identification and validation.

The CRC seeks to identify genes that are regulated in inflammatory disease processes, and determine which of those genes is absolutely required for disease progression. From here, we will develop ways of screening for potential therapies that interfere with the function of the targeted gene.

NANO

The Nanoscale Analysis Network Organisation is an Australian Major National Research Facility and the peak facility for nanometric analysis of the structure and chemistry of materials in both physical and biological systems.

Spread across five different universities in four states, NANO operates and maintains state-of-the-art facilities for the characterisation and manipulation of matter at the atomic and molecular scale.

With a primary focus on microscopy and microanalysis, this network organisation will create collaborations to explore and define the structure-function relationships which enable innovation in nanotechnology and biotechnology. NANO will develop and support a commercial arm so as to provide a vehicle for the rapid commercialisation of results.

ARC CENTRE OF EXCELLENCE IN BIOTECHNOLOGY AND DEVELOPMENT

Solving human fertility disorders, fighting testicular cancer and controlling feral pests are the main targets of the Centre of Excellence in Biotechnology and Development (CBD).

Composed of researchers from the University of Newcastle and IMB, the team is focussing on decoding the complex genetic messages that drive the production of male germ cells (cells that form sperm cells) to broadly apply the research to people, pets and pests, as well as other targets.

The incidence of testicular cancer has doubled in the last 30 years while the rates of other cancers (eg ovarian, uterine and cervical) have remained constant. It is therefore imperative scientists find out more about the complex genetic processes involved in this cancer, as well as identifying any environmental factors that may be implicated in its occurrence.

IMB’s Peter Koopman is searching for new genes involved in the development of male germ cells and establishing the function of these genes.

CENTRE OF EXCELLENCE: THE NATIONAL STEM CELL CENTRE

The National Stem Cell Centre (NSCC) is a major Australian collaborative initiative uniting many of the country’s leading academic researchers with the biotechnology industry to develop innovative therapeutic products to treat a range of serious injuries and debilitating diseases.

The Centre will build on Australia’s existing expertise in stem cell and related platform technologies to lay the foundations for delivering stem cell therapies.

IMB’s Melissa Little, Head of the NSCC’s Scientific Management Advisory Committee, is particularly interested in renal disease and understanding the developmental processes involved in normal and diseased kidneys. Using stem cell technologies this will lead to new treatments of kidney disease and possibly renal regeneration.
ARC CENTRE IN GENOME/PHENOME BIOINFORMATICS

Headed by Mark Ragan, the Centre for Genome-Phenome Bioinformatics is investigating how all the information encoded in the human genome actually ‘comes to life’.

The primary focus is to understand the transformation of genomic information into cellular form and function, enabling researchers to model and visualise complex molecular processes in mammalian cells.

Understanding the progression from genome to phenome is pivotal to understanding what makes humans function at the cellular level, and understanding human health and our susceptibility to disease.

The COE will also develop new computer software and experimental techniques broadly applicable to biotechnology all the while building a critical mass of bioinformatics researchers providing human expertise and intellectual property vital to Australia’s internationally competitive research in advanced bioscience and biotechnology.

Involvement in these ventures reflects very highly on the participating researchers, indicating the high value of their work in both scientific and commercial terms.
The AGRF is recognised as a truly national facility through the establishment of successful and complementary nodes at the University of Queensland, the Walter and Eliza Hall Institute and now at the Waite in South Australia.
AUSTRALIAN GENOME RESEARCH FACILITY

The past twelve months have witnessed further consolidation of the Australian Genome Research Facility as the premier national genomics research facility.

Financially, the status of the organisation as a Major National Research Facility (MNRF) has been renewed by the Federal Government with a $14 million award through the MNRF Program over the next five years (2002-2006) to upgrade its equipment and expand into new services such as Single Nucleotide Polymorphism (SNP) genotyping.

This has been leveraged with grants from the Victorian State Government, the South Australian Government and Adelaide University to enhance the outputs of the MNRF in each respective state. Recognition of AGRF support for the development of biotechnology in Australia was clearly evident when AGRF hosted the signing of the Three State Alliance between the Premiers of Queensland, NSW and Victoria.

A clear example of the evolution of AGRF has been the revision of the organisational structure from a geographic to a functional focus. This has not only provided a more effective point of contact for users, but has significantly improved our financial management of existing and new activities.

The AGRF is particularly proud to have been associated with the successful completion of the first genome to be sequenced in Australia, that of *Leptospira borgpeterseni* with Professor Ben Adler and colleagues from Monash University funded through the NHMRC Program in Medical Genomics.

Another exciting achievement for the year was our co-authorship in the prestigious journal, *Science*, of the results of a study aimed at finding genes associated with the debilitating mental illness, schizophrenia. The well designed and implemented fine mapping study of a segment of chromosome 1 was finally able to prove conclusively that there are no schizophrenia genes in this region. This study has opened up a number of opportunities for collaboration with other international scientists within the consortium. In addition to this landmark study, our clients have published genetic studies that have located gene regions relevant to hypertension and bipolar disorder.

Despite growing international competition, the AGRF has continued to be able to provide a high quality service at competitive prices. The recent introduction of new equipment has significantly enhanced the sequencing and genotyping services and through productivity gains has allowed the savings to be passed through to AGRF users. Several new initiatives important to the future growth of AGRF were brought to fruition, including successful implementation of the SNP analysis service, which was launched at the International Congress of Genetics in July, 2003.

Plans were also completed for co-localisation of a new AGRF node with the Plant Functional Genomics Centre in Adelaide. This will significantly enhance AGRF’s ability to play a vital role in enhancing the uptake and utilisation of genomic technologies in the agricultural arena.

The AGRF is recognised as a truly national facility through the establishment of successful and complementary nodes at the University of Queensland, the Walter and Eliza Hall Institute and now at the Waite in South Australia.
The IMB Graduate program, established in 2000, came to fruition in 2003, when the first PhD students fully enrolled through the IMB graduated alongside a number of their IMB colleagues, enrolled through other University departments. Additionally, the total number of enrolments in the Graduate Research Higher Degree programs of the IMB swelled to 80 students throughout 2003. The Program is now widely recognized in Australia and around the world and is attracting high quality students.

The year saw a number of changes, with the Graduate Program’s inaugural Graduate Administrative Officer, Ann Day, moving onto other challenges at the University of Newcastle and Dr Amanda Carozzi taking over this role. She is now the very busy administrator and mentor for the diverse student cohort at the IMB.

In 2003, increased numbers of undergraduate students gained valuable laboratory experience at the IMB through several new initiatives. The Graduate Program instigated the IMB Undergraduate Research Scholarship Scheme in which third year students worked eight hours per week on a mini research project in an IMB research lab. The students were actively involved in all aspects of the research laboratory to which they were assigned. Of the 14 students that participated in this scheme, six intend to undertake their Honours year at the IMB, a very positive outcome.

The IMB also became more actively involved in the ‘Introduction to Research’ scheme. This course, run by UQ’s School of Molecular and Microbial Sciences, involves third year students undertaking a mini-project in a research laboratory as part of their BSc program. In yet another positive outcome, over a dozen students undertook their projects at IMB, with more than half intending to undertake Honours with an IMB Group Leader in 2004.

Both schemes not only proved beneficial in recruiting top quality students to the IMB but also fulfilled our mandate to make bioscience more widely accessible and gave talented undergraduates an early introduction to research.

The Graduate Program continued to run workshops designed to assist our students in their overall career development through the year. These included IMBcom’s “Introduction to Bio-Business” workshop for first year students, covering issues such as intellectual property, patenting and commercialization. This was supplemented by a second workshop catering for the unique needs of research students in the fields of bioinformatics and computational biology.

IMBcom also conducted a three day Bio-Entrepreneurism Retreat for third year PhD students, covering topics such as technology transfer, business planning, legal issues and communication (including people management, negotiation skills and dealing with the media). Wayne Hall and the Office of Public Policy and Ethics (OPPE) team ran a workshop for the first year students, discussing the topic of gene patenting. Particular attention was given to the implications of Genetic Technologies Ltd patent on non-coding DNA sequences prompting open discussion on the issues associated with the purpose and conditions of patents, IP and the ramifications for affordability of public health and medical research.
Melissa Little conducted an information session about applying for NHMRC Postdoctoral Fellowships, with a focus on the more popular fellowships such as the CJ Martin. This was greatly appreciated by students in the latter phases of their PhDs. It is intended that this information session become a regular feature of the IMB Graduate Program.

Another highlight for 2003 was the appointment of our Graduate Coordinator, Jenny Stow, to the Graduate Studies Committee of the University’s Academic Board, the committee responsible for the formulation of University policy on issues concerning Graduate students. A recent decision of direct relevance to IMB students was the amendment to thesis format allowing inclusion of bound manuscripts as part of a thesis.

Relocation of the IMB into the Queensland Bioscience Precinct saw, for the first time, all of the staff and students housed in the same building. This proximity prompted a resurgence of the IMB student association, SIMBA, which had effectively gone into hibernation during the busy months leading up to the relocation. Elections for a new Executive were held in the second half of the year and new President Fred Martinson eagerly embraced the challenge of re-establishing a cohesive and active student body in the IMB. The results have been impressive with several popular social events and the new monthly newsletter, SIMBAzine.

The IMB Graduate Program has grown to become an active and important part of the ongoing research and training at the IMB. It is extremely gratifying to see our graduates progress on to top research and science postings around the world. Examples include:

- Asanka Kararatne - Molecular Neurobiology, Salk Institute for Biological Studies, San Diego, USA
- Nicole Walsh - Rheumatology Division, Harvard Medical School, Boston, USA
- Melissa Edeling - Cambridge Institute for Medical Research, UK

**IMB GRADUATE FAST FACTS**

Scholarships awarded to IMB for studies commencing 2004:

- 11 Australian Postgraduate Award/University of Queensland Postgraduate Research Scholarships (of which 9 were accepted)
- 8 IMB Scholarships
- 2 National Health and Medical Research Council Dora Lush Scholarships
- 2 International Postgraduate Research Scholarships (one with additional stipend scholarship)
- 2 University of Queensland Graduate School Scholarships
- 1 Australian Rotary Health Research Fund Scholarship
### Honours Students

<table>
<thead>
<tr>
<th>Student</th>
<th>Supervisor</th>
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<tbody>
<tr>
<td>Katie Baldwin</td>
<td>Paul Alewood and Ian Gentle</td>
</tr>
<tr>
<td>Ming-Kang Chang</td>
<td>David Hume and Stuart Kellie</td>
</tr>
<tr>
<td>Louise Dempster</td>
<td>David Craik</td>
</tr>
<tr>
<td>Elizabeth Holliday</td>
<td>Mike Waters</td>
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<tr>
<td>Eugene Huang</td>
<td>Peter Koopman</td>
</tr>
<tr>
<td>Jack King-Scott</td>
<td>Brandon Wainwright</td>
</tr>
<tr>
<td>Genevieve Kinna</td>
<td>Melissa Little</td>
</tr>
<tr>
<td>Sheryl Maher</td>
<td>Mike Waters</td>
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<tr>
<td>Stephanie Martell</td>
<td>Brandon Wainwright</td>
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<tr>
<td>Tessa Nall</td>
<td>David Fairlie</td>
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<tr>
<td>Ashley Rossiter</td>
<td>Melissa Little</td>
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<tr>
<td>Samantha Stehbens</td>
<td>Alpha Yap</td>
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<tr>
<td>Elizabeth Westbury</td>
<td>Jennifer Martin</td>
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</tbody>
</table>

### New Research Higher Degree students for 2003

<table>
<thead>
<tr>
<th>Student</th>
<th>Supervisor</th>
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</thead>
<tbody>
<tr>
<td>Shannon Armstrong</td>
<td>Melissa Little</td>
</tr>
<tr>
<td>Rajith Aturaliya</td>
<td>Rohan Teasdale</td>
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<tr>
<td>Stephen Bradford</td>
<td>Peter Koopman</td>
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<tr>
<td>David Bryant</td>
<td>Jennifer Stow</td>
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<tr>
<td>Cheong Xin Chan</td>
<td>Mark Ragan</td>
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<tr>
<td>Hong Soon Chin</td>
<td>Jeff Gorman</td>
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<tr>
<td>Myrna Constantin</td>
<td>David Hume</td>
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<tr>
<td>Melissa Davis</td>
<td>Rohan Teasdale</td>
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<tr>
<td>Jennifer Fleming</td>
<td>Wayne Hall</td>
</tr>
<tr>
<td>Al Forrest</td>
<td>Sean Grimmond</td>
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<tr>
<td>Leith Fremlin</td>
<td>Rob Capon</td>
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<tr>
<td>Falak Helwani</td>
<td>Alpha Yap</td>
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<tr>
<td>Jason Kay</td>
<td>Jennifer Stow</td>
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<tr>
<td>Frank Lin</td>
<td>Jennifer Martin</td>
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<tr>
<td>Rebecca Pelekanas</td>
<td>Mike Waters</td>
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<tr>
<td>Daniel Sangermani</td>
<td>Jennifer Stow</td>
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<tr>
<td>Cas Simons</td>
<td>John Mattick</td>
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<tr>
<td>Stuart Stephen</td>
<td>John Mattick</td>
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<tr>
<td>Brendan Tse</td>
<td>David Hume</td>
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<tr>
<td>Thaningi Tun</td>
<td>Rohan Teasdale</td>
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<tr>
<td>Ong Wei Wooh</td>
<td>Mike Waters</td>
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<tr>
<td>Andy Wu</td>
<td>Ian Cassady</td>
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<tr>
<td>Ben Clark</td>
<td>Rob Capon University of Melbourne to IMB</td>
</tr>
<tr>
<td>Emma Millard</td>
<td>David Craik SBMS to IMB</td>
</tr>
<tr>
<td>Ranjala Ratnayake</td>
<td>Rob Capon University of Melbourne to IMB</td>
</tr>
<tr>
<td>Natalie Steen</td>
<td>Paul Alewood NRAV to IMB</td>
</tr>
</tbody>
</table>
PhD Completions 2003

1. Adolphe Christelle, *Examination of the in vivo effect or excess sonic in cuan and desc in hedgehog.* Brandon Wainwright
7. Kelly Loffler, *Molecular Genetics of Sex Determination in Mice.* Peter Koopman
9. Wendy Ingram, *Discovery of novel downstream target genes regulated by the Hedgehog Pathway.* Brandon Wainwright
10. Gabriel Kolle, *Functional studies of a novel gene, SS2 in the development of the central nervous system.* Melissa Little
13. Ayanthi Richards, *Endocytosis and retrograde transport of Simian Virus 40 (SV40) and cholera toxin – a comparative study.* Rob Parton
14. Johan Rosengren, *Twists, knots and rings -topological features of antimicrobial peptides.* David Craik
15. Tedjo Sasmono, *Regulation of the C-FMS gene in macrophages and transgenic mice.* David Hume
17. Annalese Semmler, *Biogenesis and function of Type 4 Fimbriae in Pseudomonas Aeruginosa.* John Mattick
19. Manuela Trabi, *Circular, disulfide rich peptides – sources, properties structures.* David Craik
20. Nicole Walsh, *The Function and Regulation of Tartrate-Resistant Acid Phosphatase (TRAP).* David Hume
## IMB Speakers

### IMB FRIDAY SEMINAR SERIES 2003

The IMB’s seminar series presented national and international speakers at the leading edge of the molecular biosciences.

A highlight of the 2003 seminar calendar was a talk from Nobel Laureate Sydney Brenner who spoke about the role and goals of computational biology.

<table>
<thead>
<tr>
<th>Speakers</th>
<th>Position</th>
<th>Seminar Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr David Manallack</td>
<td>Head of Applied Design&lt;br&gt;De Novo Pharmaceuticals, Cambridge, UK</td>
<td>Application of Quasi2 for drug discovery: an extended pharmacophore generation and database searching program</td>
</tr>
<tr>
<td>Professor Gottfried Otting</td>
<td>Research School of Chemistry&lt;br&gt;Australian National University, Canberra</td>
<td>Structural biology, NMR, and paramagnetically labelled proteins</td>
</tr>
<tr>
<td>Professor Ralph Bradshaw</td>
<td>Department of Physiology and Biophysics&lt;br&gt;University of California, at Irvine, USA</td>
<td>N-Terminal Processing: Role of Aminopeptidases and Transferases</td>
</tr>
<tr>
<td>Professor Nobutaka Hirokawa</td>
<td>Department of Cell Biology and Anatomy&lt;br&gt;University of Tokyo, Japan</td>
<td>The Kinesin Superfamily Motor Proteins, KIFs and Intracellular Transport: Structures, Dynamics, Functions and Diseases</td>
</tr>
<tr>
<td>Professor Mike Ostrowski</td>
<td>Department of Molecular Genetics&lt;br&gt;Ohio State University, USA</td>
<td>The microphthalmia transcription factor: coordinating signaling and transcription during osteoclast differentiation</td>
</tr>
<tr>
<td>Professor Nigel Laing</td>
<td>Centre for Neuromuscular and Neurological Disorders&lt;br&gt;Australian Neuromuscular Research Institute, Western Australia</td>
<td>Gene and protein defects in muscle disease</td>
</tr>
<tr>
<td>Professor Kevin Burrage</td>
<td>Department of Mathematics&lt;br&gt;The University of Queensland</td>
<td>Stochastic multiscale modelling of genetic regulatory networks</td>
</tr>
<tr>
<td>Professor Alok Mitra</td>
<td>School of Biological Sciences&lt;br&gt;The University of Auckland, NZ</td>
<td>Membrane protein channels and macromolecular complexes at the membrane interface studied by electron cryo-microscopy - what can structure tell us about function</td>
</tr>
<tr>
<td>Professor Bill Denny</td>
<td>Auckland Cancer Society Research Centre&lt;br&gt;The University of Auckland, NZ</td>
<td>Drugs that target tumour hypoxia: the promise and the challenge</td>
</tr>
<tr>
<td>Associate Professor Roger Daly</td>
<td>Cancer Research Program&lt;br&gt;Garvan Institute of Medical Research, Sydney</td>
<td>Adaptor and scaffolding proteins in receptor tyrosine kinase signalling</td>
</tr>
<tr>
<td>Dr Pritinder Kaur</td>
<td>Stem Cell Laboratory&lt;br&gt;Peter MacCallum Cancer Institute, Melbourne</td>
<td>Identification of a functional subset of dermal cells capable of regulating epithelial tissue regeneration</td>
</tr>
<tr>
<td>Professor Chris Goodnow</td>
<td>Medical Genome Centre&lt;br&gt;John Curtin School of Medical Research, Canberra</td>
<td>Elucidating cellular and molecular pathways for human health by genome-wide mutagenesis in mice</td>
</tr>
<tr>
<td>Speakers</td>
<td>Position</td>
<td>Seminar Topic</td>
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</tr>
<tr>
<td>Dr Charlie Bond</td>
<td>Division of Biological Chemistry and Molecular Microbiology, School of Life Sciences Wellcome Trust Biocentre, University of Dundee, Scotland</td>
<td>Structural Studies of Holliday Junction Resolution in the Archaea: the resolving enzymes Hjc and Hje.</td>
</tr>
<tr>
<td>Dr Archa Fox</td>
<td>Division of Gene Regulation and Expression, School of Life Sciences Wellcome Trust Biocentre, University of Dundee</td>
<td>New insights into nuclear organisation revealed by proteomic analysis of human nucleoli</td>
</tr>
<tr>
<td>Professor Ross Coppel</td>
<td>Department of Microbiology Monash University, Melbourne</td>
<td>Data, data everywhere, nor any chance to think</td>
</tr>
<tr>
<td>Professor Simon Eastal</td>
<td>Centre for Bioinformation Science and John Curtin School of Medical Research, Canberra</td>
<td>Complexity in diversity on the road to information-based medicine</td>
</tr>
<tr>
<td>Professor Halina Rubinsztein-Dunlop</td>
<td>Department of Physics/Centre for Biophotonics and Laser Science The University of Queensland</td>
<td>Catch, move and twist using optical tweezers</td>
</tr>
<tr>
<td>Associate Professor Vic Nurcombe</td>
<td>Department of Anatomy and Developmental Biology The University of Queensland</td>
<td>So long and thanks for all the fish; the answer is 42 ES cells. Reflections on UQ Developmental Biology; stem cell engineering; and the use of chopsticks for embryonic manipulation</td>
</tr>
<tr>
<td>Dr Ian Atkinson</td>
<td>Information Technology and Resources James Cook University, Townsville, Australia</td>
<td>Molecular self-assembly in supramolecular systems</td>
</tr>
<tr>
<td>Mr Adam Lowe</td>
<td>Genomic Applications Research and Development Applied Biosystems Pty Ltd</td>
<td>Combining content and technology in genomic research</td>
</tr>
<tr>
<td>Professor Edward Baker</td>
<td>School of Biological Sciences The University of Auckland, NZ</td>
<td>Targeting TB through structural genomics</td>
</tr>
<tr>
<td>Professor Chris Abell</td>
<td>Department of Chemistry University of Cambridge Chemical Laboratory, UK</td>
<td>Explorations in chemical and biological nanotechnology</td>
</tr>
<tr>
<td>Dr Helen Cooper</td>
<td>Neural Migration Laboratory, School of Biomedical Sciences The University of Queensland</td>
<td>Diverse roles of netrin receptors in central nervous system development</td>
</tr>
<tr>
<td>Dr Tim Bailey</td>
<td>Advanced Computational Modelling Center The University of Queensland</td>
<td>Searching for statistically significant regulatory modules</td>
</tr>
<tr>
<td>Professor Kathryn North</td>
<td>Neurogenetics Research Unit Children's Hospital at Westmead Clinical School, Sydney</td>
<td>The evolution of the <em>α</em>-actins and their role in human skeletal muscle muscle performance</td>
</tr>
<tr>
<td>Dr Steve Gerondakis</td>
<td>Immunology Division The Walter and Eliza Hall Institute of Medical Research, Melbourne</td>
<td>Mitogen-induced cell growth: B and T cells adopt different strategies in the exploitation of Rel/NF-κB</td>
</tr>
<tr>
<td>Dr Matthew Rimmer</td>
<td>Faculty of Law The Australian National University, Canberra</td>
<td>Myriad Genetics: patent law &amp; genetic testing</td>
</tr>
<tr>
<td>Speakers</td>
<td>Position</td>
<td>Seminar Topic</td>
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<tr>
<td>Dr Tom Garrett</td>
<td>Structural Biology</td>
<td>Structure and signalling in the epidermal growth factor receptor family</td>
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<td></td>
<td>Walter and Eliza Hall Institute of Medical Research, Melbourne</td>
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<tr>
<td>Professor David Vaux</td>
<td>Molecular Genetics of Cancer</td>
<td>Apoptosis - biology to die for</td>
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<tr>
<td></td>
<td>Walter and Eliza Hall Institute of Medical Research, Melbourne</td>
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<tr>
<td>Dr Sigrid Lehnert</td>
<td>Livestock Applications of Biotechnology Program</td>
<td>Transcriptional profiling of bovine muscle</td>
</tr>
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<td></td>
<td>CSIRO Livestock Industries, Brisbane</td>
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<tr>
<td>Professor Geoff McLachlan</td>
<td>Department of Mathematics and Institute for Molecular Bioscience</td>
<td>Classification of microarray gene-expression data</td>
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<td></td>
<td>The University of Queensland</td>
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<tr>
<td>Dr Peter Currie</td>
<td>Victor Chang Cardiac Research Institute Sydney</td>
<td>Specification, morphogenesis and differentiation of skeletal muscle cells</td>
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<td>within the zebrafish embryo</td>
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<tr>
<td>Professor Michael Johnson</td>
<td>Centre for Pharmaceutical Biotechnology University of Illinois at Chicago</td>
<td>Structural studies of spectrin - an ubiquitous protein</td>
</tr>
<tr>
<td></td>
<td>USA</td>
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<tr>
<td>Professor David Weisbrot</td>
<td>President, Australian Law Reform Commission, Sydney</td>
<td>Essentially yours: the protection of human genetic information in Australia</td>
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<tr>
<td>Dr Richard Bruskiewich</td>
<td>Bioinformatics</td>
<td>My genome is sequenced! So...what next?</td>
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<tr>
<td></td>
<td>International Rice Research Institute, Los Baños, Philippines</td>
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<tr>
<td>Dr Patrick Aloy</td>
<td>Biocomputing</td>
<td>The third dimension for protein interactions and complexes</td>
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<td></td>
<td>European Molecular Biology Laboratory – Heidelberg, Germany</td>
<td></td>
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<tr>
<td>Dr Martin Frith</td>
<td>Bioinformatics Program</td>
<td>Deciphering the Regulation of Human Genes: Motif Clusters in DNA and RNA</td>
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<td></td>
<td>Boston University, USA</td>
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<tr>
<td>Dr Nick Brown</td>
<td>Wellcome/Cancer Research UK Gurdon Institute and Department of Anatomy</td>
<td>Genetic dissection of the integrin-cytoskeletal link in Drosophila</td>
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<td></td>
<td>University of Cambridge, UK</td>
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<tr>
<td>Ms Anneliese Appleton</td>
<td>Accelys Inc.</td>
<td>Accelys Information Seminar</td>
</tr>
<tr>
<td>Dr Christine Vogel</td>
<td>MRC Laboratory of Molecular Biology Cambridge, UK</td>
<td>Domain duplication and recombination in the evolution of the protein repertoire</td>
</tr>
<tr>
<td>Dr Arnold Falick</td>
<td>Mass Spectrometry Laboratory</td>
<td>Protein identification with a MALDI Tandem Time-of-Flight mass spectrometer</td>
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<td>Howard Hughes Medical Institute</td>
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<tr>
<td>Professor Roger Tsien</td>
<td>Howard Hughes Medical Institute &amp; Department of Pharmacology</td>
<td>Breeding molecules to spy on cells</td>
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<td></td>
<td>University of California at San Diego, USA</td>
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</table>
### Speakers

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<tr>
<th>Speakers</th>
<th>Position</th>
<th>Seminar Topic</th>
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<tbody>
<tr>
<td>Dr Andrew Perkins</td>
<td>Monash University, Melbourne</td>
<td>Making blood and kidneys: transcriptional programming and ES cell differentiation</td>
</tr>
<tr>
<td>Professor Walter Birchmeier</td>
<td>Max-Delbrück Center for Molecular Medicine, Berlin, Germany</td>
<td>β-catenin and Wnt signaling: implications for developmental programming and cancer</td>
</tr>
<tr>
<td>Dr Margaret Frame</td>
<td>Beatson Cancer Center, Glasgow, Scotland</td>
<td>New insights into the regulation and action of Src kinases</td>
</tr>
<tr>
<td>Dr Matthew Cooper</td>
<td>Chief Scientific Officer Akubio Ltd, UK</td>
<td>Drugs, bugs and biotech</td>
</tr>
<tr>
<td>Dr Scott Weinberger</td>
<td>Director, Research Proteomics Ciphergen Biosystems Inc.</td>
<td>Proteinchip arrays: advances in SELDI technologies for the discovery in identification and characterisation of biomarkers of clinical interest</td>
</tr>
<tr>
<td>Professor Peter Roepstorff</td>
<td>Department of Biochemistry and Molecular Biology University of Southern Denmark</td>
<td>Current strategies in expression proteomics and modification specific proteomics</td>
</tr>
<tr>
<td>Dr Paul Trainor</td>
<td>Stowers Institute for Medical Research, Kansas, USA</td>
<td>Neural crest cells: patterning and development of a stem cell population during craniofacial development and evolution</td>
</tr>
<tr>
<td>Dr Anneliese Appleton</td>
<td>Accelrys Inc.</td>
<td>Accelrys information seminar</td>
</tr>
<tr>
<td>Dr Inke Nathke</td>
<td>School of Life Sciences University of Dundee, Scotland</td>
<td>Recent advances in understanding the fundamental biology of the tumor suppressor, APC</td>
</tr>
<tr>
<td>Dr David Sacks</td>
<td>Pathology, Brigham &amp; Women’s Hospital Harvard Medical School, Boston, USA</td>
<td>IQGAP1 - a fundamental regulator of Ca2+/calmodulin signalling and cytoskeletal architecture</td>
</tr>
<tr>
<td>Dr Irina Mineyev</td>
<td>Caliper Technologies California, USA</td>
<td>Caliper microfluidics technologies for drug discovery and genomics</td>
</tr>
<tr>
<td>Dr Al Reynolds</td>
<td>Department of Cancer Biology Vanderbilt University, Tennessee, USA</td>
<td>P120-catenin: a core regulator of cadherin function and potential tumour suppressor</td>
</tr>
<tr>
<td>Dr David Hansen</td>
<td>SRS Software Development LION Bioscience Ltd, UK</td>
<td>Providing integrated access to genomic data</td>
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</tbody>
</table>

### The IMB’s seminar series presented national and international speakers at the leading edge of the molecular biosciences.
Construction of the Queensland Bioscience Precinct (QBP) building was completed in early 2003 and followed by several weeks of systems testing and building cleaning prior to occupation by CSIRO and IMB.

Relocation of the IMB into the new facility began in late March and took four weeks to relocate all scientists and support staff. Delicate items of equipment such as the X-ray crystallography and the NMR machines remained behind until the manufacturer’s specialists were available to assist in relocation.

The titanic effort of Infrastructure Manager Chris Barnett, the newly appointed Floor Managers, Safety Officer Charles Nelson, the Information Technology team and the Workshop and Sterilisation staff ensured the move was executed as smoothly as possible. I also congratulate all support and infrastructure staff for their performance during 2003, which kept disruptions to IMB’s research to a minimum.

IMB researchers were again successful in attracting funds to purchase significant items of equipment facilitating IMB’s leading-edge research. The IMB took delivery of:

- Two new 600MHz Nuclear Magnetic Resonance (NMR) machines extending IMB’s ability to solve the three dimensional structures of biological molecules. The new magnets enable IMB to determine highly complex structures with greater confidence than ever before.

- Australia’s most powerful X-Ray Crystallography machine. The high resolution and exquisite sensitivity of the new machinery can only be bettered by a synchrotron, currently unavailable in Australia. These facilities enable the determination of high resolution structures of the most difficult proteins.

- P690 supercomputer equipped with DiscoveryLink software as part of the IBM’s Shared University Research program. This alliance provides an unparalleled level of excellence in an integrated research program combining the Institute’s world-class bioinformatics expertise and IBM’s state-of-the-art IT infrastructure for life sciences, as well as providing access to IBM’s own research resources.
A Sun fileserver greatly expanding IMB’s capacity to provide storage space for staff and students

Over $1 million high pressure liquid chromatography equipment to accelerate the effective exploration of Australian biodiversity as a means to discover new and improved drugs, with application in the areas of human and animal health, and crop protection.

The new IMB facilities are designed to meet the legislative regulations and government guidelines and standards, including those required by the Office of the Gene Technology Regulator, as well as the Workplace Health and Safety Act of Queensland. The IMB has implemented procedures to assist researchers in meeting these legal obligations. Comments received following an Environmental Management Systems audit conducted late in 2003 confirm the IMB’s systems are “functional more so than any other University area”.

Occupation of the new building resulted in increased demands on IMB support services due to the relocation of three research groups from other UQ departments, as well as the commencement of two new research groups. Consequently the sterilisation, workshop and animal house facilities have employed new staff to cope with the increased demand for services. A new central store facility has been set up to meet the day to day needs of all researchers in the Precinct.

Finally, the IMB was saddened by the sudden death of Level 7 Floor Manager, Dr Steve Tay in November. Steve joined the IMB as we took up residence in the new building and in his short time with the Institute he played a vital role in establishing the chemistry laboratories on Level 7. He will be sorely missed.
Some readers may be unfamiliar with some of the scientific terms used in this Annual Report. Please check below for a short explanation to some of the more common terms. More information about current issues in biotechnology can be downloaded from the Office of Public Policy and Ethics pages in the IMB website.

**Alzheimer’s disease** A disease associated with the breakdown of nervous tissue in the brain, giving rise to a dementia in the patient.

**Amino Acid** Amino acids are the building blocks of proteins. The sixty-four codons of the genetic code allow the use of twenty different amino acids (the primary amino acids) in the synthesis of proteins.

**Apoptosis** The normal process of programmed cell death. Disruptions to this process often lead to cancers.

**ARC** Australian Research Council. The ARC plays a key role in the Australian Government’s investment in the future prosperity and well-being of the Australian community. The ARC’s mission is to advance Australia’s capacity to undertake quality research that brings economic, social and cultural benefit to the Australian community.

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

**Cancer** Any malignant, cellular tumour. Cancers can be divided into two types carcinoma and sarcoma.

**Carcinoma** A malignant new growth made up of epithelial cells tending to infiltrate surrounding tissues and to give rise to metastases.

**Chromosome** A package of wound-up DNA in the nucleus of a cell. Humans have 23 pairs of chromosomes.

**Combinatorial chemistry** A technique for systematically assembling molecular building blocks in many combinations to create thousands of diverse compounds.

**Computational biology** The study of living systems using computation.

**Cryo EM** Cryo electron microscopy – an electron microscopy technique in which the sample is frozen rather than stained.

**Cystic fibrosis** A genetic disease with symptoms that usually appear shortly after birth. They include breathing difficulties and respiratory infections due to accumulation of sticky mucous problems with digestion and excessive loss of salt in sweat.

**Diabetes** A disorder characterised by excessive urine production. Commonly used when referring to diabetes mellitus (Type 1) a metabolic disorder in which there is inability to oxidise carbohydrates due to a disturbance of the normal insulin mechanism, producing hyperglycemia, glycosuria, polyuria. Also refers to non-insulin dependant diabetes (NIDD) an asymptomatic form of diabetes mellitus with onset after 40 years of age. Often brought on by a lifestyle of sedentary living with high intake of lipids in diet.

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

**EM** Electron microscope – a microscope that uses a beam of highly energetic electrons to examine objects on a very fine scale.

**Functional Genomics** The use of genetic technology to determine the function of newly discovered genes by determining their role in model organisms.
Gene **Considered** the basic unit of hereditary, a gene is a region of DNA encodes all the information to make a protein.

**Gene Expression** The actual production of the protein encoded by a gene.

**Genome** All DNA contained in an organism or cell.

**Genomics** The study of genes and their function.

**Genotype** Is the hereditary genetic constitute of an organism.

**Inflammatory disease** A disease characterized by inflammation. Examples studied at IMB include rheumatoid arthritis, chronic obstructive pulmonary disease.

**National Institutes of Health (NIH)** A large biomedical research organization that is part of the U.S. Public Health Service. NIH includes various institutes, centers and divisions including National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) which funds several groups in the IMB.

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

**NHMRC** National Health and Medical Research Council. A national organisation responsible for, among other things, fostering medical research and training and public health research and training throughout Australia.

**Peptide** Two or more amino acids joined by a peptide bond.

**Pharmacogenomics** The study of the interaction of an individual’s genetic makeup and response to a drug.

**Phenome** The physical characteristics of an organism.

**Protein** A large molecule composed of one or more chains of amino acids in a specific order; the order is determined by the base sequence of nucleotides in the gene that codes for the protein. Proteins are required for the structure, function, and regulation of the body’s cells, tissues, and organs; and each protein has unique functions. Examples are hormones, enzymes, and antibodies.

**Proteomics** The study of structure and function of all the proteins expressed in a cell.

**Recombinant DNA** Any new combinations of genes or gene parts spliced together to form a single DNA molecule.

**RNA** A chemical similar to a single strand of DNA. RNA delivers DNA’s message to the site of protein synthesis.

**Sarcoma** A malignant tumour made up of a substance like the embryonic connective tissue.

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

**X-ray Crystallography** A technique of determining a molecule’s three-dimensional structure by analysing the x-ray diffraction patterns of crystals made up of the molecule in question.
## Financial Statement – Statement of Operating Income and Expenditure

### Year Ended 31 December 2003

### INCOME:

<table>
<thead>
<tr>
<th>Note</th>
<th>Description</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>University of Queensland (Operating Grant)</td>
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<td>State Government</td>
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<td>6,000,000</td>
<td>8,500,000</td>
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<tr>
<td>3</td>
<td>SRC Grant (Australian Research Council)</td>
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<tr>
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<td>Australian Research Council</td>
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<td>1,688,000</td>
<td>1,599,576</td>
<td>3,218,103</td>
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<tr>
<td></td>
<td>Queensland Student Assistance</td>
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<td>2,500,000</td>
<td>6,000,000</td>
<td>8,500,000</td>
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<tr>
<td></td>
<td>Australian Research Council</td>
<td>1,131,271</td>
<td>1,688,000</td>
<td>1,599,576</td>
<td>3,218,103</td>
</tr>
<tr>
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<td>CRC for Discovery of Genes for Common Human Diseases</td>
<td>220,958</td>
<td>232,415</td>
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<td>CRC for Chronic Inflammatory Diseases</td>
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<td></td>
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<td>166,400</td>
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<td>Human Frontiers Science Program</td>
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<td>127,242</td>
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<td>Glaxo Welcome Australia</td>
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<td>Government Employees Medical Research Fund</td>
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<td>45,000</td>
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<td>Juvenile Diabetes Foundation International</td>
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<td>267,704</td>
<td>77,084</td>
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<td>Mayne Bequest Foundation</td>
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<td>60,000</td>
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<td></td>
<td>The Merck Genome Research Institute</td>
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<td></td>
<td>National Institute of Health (US)</td>
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<td>45,000</td>
<td>45,000</td>
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<td></td>
<td>Novartis</td>
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<td>641,790</td>
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<td></td>
<td>Post Graduate Scholarships</td>
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<td></td>
<td>QIMR</td>
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<td>53,908</td>
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<tr>
<td></td>
<td>Queensland Cancer Fund</td>
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<td>92,750</td>
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<td>Sylvia and Charles Viertel Charitable Foundation</td>
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<td>165,000</td>
<td>165,000</td>
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<td></td>
<td>Wellcome Trust</td>
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<td>23,829</td>
<td>204,763</td>
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<td>Commercial Income</td>
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<td>2,589,861</td>
<td>2,127,649</td>
<td>2,127,649</td>
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<td>Cross-Institutional contributions to LIEF</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>University of Newcastle (re ARC Centre)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>GBP recoveries</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td></td>
<td>Shared Grants</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Conference Income</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>Miscellaneous Income</td>
<td>415,591</td>
<td>272,136</td>
<td>392,822</td>
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<td></td>
<td><strong>TOTAL INCOME:</strong></td>
<td>18,556,004</td>
<td>21,121,405</td>
<td>24,565,049</td>
<td>33,878,069</td>
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<tr>
<td></td>
<td>Funds brought forward from previous year</td>
<td>1,009,031</td>
<td>3,843,597</td>
<td>3,594,479</td>
<td>7,545,101</td>
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<tr>
<td></td>
<td><strong>TOTAL FUNDS AVAILABLE:</strong></td>
<td>19,565,034</td>
<td>24,965,002</td>
<td>28,159,528</td>
<td>41,423,169</td>
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</tbody>
</table>

### EXPENDITURE:

<table>
<thead>
<tr>
<th>Note</th>
<th>Description</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Salaries-Research</td>
<td>6,549,841</td>
<td>7,809,255</td>
<td>9,066,745</td>
<td>12,338,779</td>
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<td></td>
<td>Administration</td>
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<td>1,117,375</td>
<td>1,342,620</td>
<td>1,365,120</td>
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<tr>
<td></td>
<td>Infrastructure</td>
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<td>813,527</td>
<td>1,012,400</td>
<td>1,735,158</td>
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<tr>
<td></td>
<td>Research Services</td>
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<td>6,034,733</td>
<td>4,865,433</td>
<td>6,938,972</td>
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<td></td>
<td>Education Programs</td>
<td>4</td>
<td>317,726</td>
<td>378,436</td>
<td>500,399</td>
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<tr>
<td></td>
<td>Administration</td>
<td>5</td>
<td>937,703</td>
<td>558,574</td>
<td>452,021</td>
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<tr>
<td></td>
<td>Infrastructure</td>
<td>6</td>
<td>357,436</td>
<td>928,651</td>
<td>786,009</td>
</tr>
<tr>
<td></td>
<td>Capital Equipment</td>
<td>7</td>
<td>2,307,116</td>
<td>3,152,769</td>
<td>1,840,464</td>
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<td></td>
<td>IMBcom</td>
<td>984,608</td>
<td>605,214</td>
<td>746,896</td>
<td>1,176,785</td>
</tr>
<tr>
<td></td>
<td><strong>TOTAL EXPENDITURE:</strong></td>
<td>15,721,437</td>
<td>21,370,523</td>
<td>20,614,427</td>
<td>34,676,171</td>
</tr>
<tr>
<td></td>
<td>Funds carried forward:</td>
<td>3</td>
<td>3,843,597</td>
<td>3,594,479</td>
<td>7,545,101</td>
</tr>
</tbody>
</table>
1. **In-kind Contributions**

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

<table>
<thead>
<tr>
<th>School</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Barker Molecular &amp; Microbial Sci.</td>
<td>80</td>
</tr>
<tr>
<td>D. Hume Molecular &amp; Microbial Sci.</td>
<td>20</td>
</tr>
<tr>
<td>J. Martin Molecular &amp; Microbial Sci.</td>
<td>10</td>
</tr>
<tr>
<td>S. Kelly Molecular &amp; Microbial Sci.</td>
<td>80</td>
</tr>
<tr>
<td>P. Koopman Biomedical Sciences</td>
<td>10</td>
</tr>
<tr>
<td>J. Rothnagel Molecular &amp; Microbial Sci.</td>
<td>80</td>
</tr>
<tr>
<td>B. Wainwright Molecular &amp; Microbial Sci.</td>
<td>20</td>
</tr>
<tr>
<td>M. Waters Biomedical Sciences</td>
<td>20</td>
</tr>
<tr>
<td>A. Yap Biomedical Sciences</td>
<td>20</td>
</tr>
<tr>
<td>B. Kobe Molecular &amp; Microbial Sci.</td>
<td>80</td>
</tr>
<tr>
<td>J. Stow Molecular &amp; Microbial Sci.</td>
<td>20</td>
</tr>
<tr>
<td>A. McDowall Microscopy &amp; Microanalysis</td>
<td>80</td>
</tr>
<tr>
<td>W. Hall Social Behavioural Sci.</td>
<td>20</td>
</tr>
<tr>
<td>G. McLachlan Mathematics</td>
<td>80</td>
</tr>
<tr>
<td>J. Hallinan ITEE</td>
<td>20</td>
</tr>
<tr>
<td>T. Bailey AMC</td>
<td>80</td>
</tr>
</tbody>
</table>

2. **Fellowship/Projects from Government Agencies**

   **Australian Research Council**
   
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Projects</td>
<td>2,707,459</td>
</tr>
<tr>
<td>Fellowships</td>
<td>510,644</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3,218,103</strong></td>
</tr>
</tbody>
</table>

   **National Health and Medical Research Council**
   
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Projects</td>
<td>5,936,844</td>
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<tr>
<td>Fellowships</td>
<td>824,559</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6,761,404</strong></td>
</tr>
</tbody>
</table>

3. **Funds brought Forward from 2002**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>University of Queensland Operating Grant</td>
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</tr>
<tr>
<td>University of Queensland Research Grants</td>
<td>69,686</td>
</tr>
<tr>
<td>Post Graduate Scholarships</td>
<td>4,371</td>
</tr>
<tr>
<td>State Government</td>
<td>346,758</td>
</tr>
<tr>
<td>SRC Grant</td>
<td>373,794</td>
</tr>
<tr>
<td>Fellowships (as approved by funding bodies)</td>
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<tr>
<td>Project Grants (as approved by funding bodies)</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>7,545,101</strong></td>
</tr>
</tbody>
</table>

4. **Education Programs**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Postgraduate scholarships</td>
<td>328,357</td>
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<tr>
<td>Postgraduate recruitment &amp; training</td>
<td>29,471</td>
</tr>
<tr>
<td>Public Policy &amp; Ethics</td>
<td>126,532</td>
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<tr>
<td><strong>Total Education Services</strong></td>
<td><strong>484,360</strong></td>
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</table>
## Explanatory Notes to Statement of Income and Expenditure

### Year Ended 31 December 2003

5. **Administration**

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Report</td>
<td>20,698</td>
</tr>
<tr>
<td>Marketing</td>
<td>48,102</td>
</tr>
<tr>
<td>Personnel Recruitment and Training</td>
<td>126,680</td>
</tr>
<tr>
<td>Visiting Scientists/Seminars</td>
<td>21,867</td>
</tr>
<tr>
<td>Fees</td>
<td>61,071</td>
</tr>
<tr>
<td>Entertaining</td>
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<tr>
<td>Equip Lease</td>
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<td>Photocopying</td>
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</tr>
<tr>
<td>Postage and Freight</td>
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</tr>
<tr>
<td>Printing &amp; stationery</td>
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</tr>
<tr>
<td>Telephone</td>
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<td>Travel Expenses</td>
<td>12,247</td>
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<td>Sundries</td>
<td>5,409</td>
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<tr>
<td>Cost Recovery</td>
<td>39,581</td>
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</table>

**Total Administration** | 519,046 |

6. **Infrastructure**

<table>
<thead>
<tr>
<th>Item</th>
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</thead>
<tbody>
<tr>
<td>Building Maintenance</td>
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<tr>
<td>Rental -Demountables/Storage</td>
<td>17,092</td>
</tr>
<tr>
<td>Safety Equipment</td>
<td>67,730</td>
</tr>
<tr>
<td>Laundry</td>
<td>1,953</td>
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<tr>
<td>Minor Equipment &amp; Furniture</td>
<td>32,378</td>
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<tr>
<td>Equipment Maintenance</td>
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<tr>
<td>Animals</td>
<td>72,950</td>
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<td>Computer Services</td>
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<tr>
<td>Glass washing and replacement</td>
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<tr>
<td>Reticulated gases, RO water &amp; dry ice</td>
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<td>Sundries</td>
<td>69,746</td>
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<td>Relocation Costs</td>
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<td>Stores</td>
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**Total Infrastructure** | 1,568,251 |

7. **Capital Equipment**

<table>
<thead>
<tr>
<th>Item</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Scientific Equipment</td>
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<tr>
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</table>

**Total Capital Equipment** | 8,649,700 |

8. **Funds carried forward to 2004**

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost</th>
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</thead>
<tbody>
<tr>
<td>University of Queensland Operating Grant</td>
<td>1,645,629</td>
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<tr>
<td>University of Queensland Research Grants</td>
<td>26,038</td>
</tr>
<tr>
<td>Post Graduate Scholarships</td>
<td>3,734</td>
</tr>
<tr>
<td>State Government</td>
<td>125,166</td>
</tr>
<tr>
<td>SRC Grant</td>
<td>374,734</td>
</tr>
<tr>
<td>Fellowships (as approved by funding bodies)</td>
<td>149,096</td>
</tr>
<tr>
<td>Overseas Grants funded mid year</td>
<td>1,705,903</td>
</tr>
<tr>
<td>Contract Research</td>
<td>1,270,789</td>
</tr>
<tr>
<td>Project Grants (as approved by funding bodies)</td>
<td>1,441,911</td>
</tr>
</tbody>
</table>

**Total** | 6,746,999 |

# Of this, $0.5m is the carry forward on IMB core accounts, $1.0m relates to outstanding 2003 commitments.