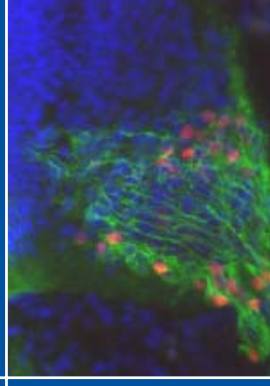

Institute for Molecular Bioscience
Annual Report 2001

Institute for Molecular Bioscience *2001 Annual Report*

The IMB Commitment

Contribute to world knowledge - human and animal biology, health and medicine

Create a platform for excellence in fundamental research and postgraduate teaching

Integrate the full spectrum of molecular bioscience from gene discovery to practical applications

Lead by example as an authority in public policy and ethics of new genetics, determining best outcomes for worldwide community

Develop Australia's biotechnology industry and attract international bioindustries to Queensland.

1901-2001
A Federation Fund Project
A Commonwealth Government Initiative

THE UNIVERSITY OF QUEENSLAND

Queensland Government

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About the IMB

The Institute for Molecular Bioscience (IMB) was officially established in 2000.

Based at The University of Queensland, the IMB incorporates the Centre for Molecular and Cellular Biology, the Centre for Drug Design and Development, the ARC Special Research Centre for Functional and Applied Genomics, and the headquarters and Brisbane division of the Australian Genome Research Facility, as well as significant components of the Advanced Computational Modelling Centre and the Centre for Microscopy and Microanalysis.

Recognised nationally and internationally, the IMB is already one of Australia's leading research institutes and a major centre for molecular bioscience research.

It links leading edge genomic discovery and bioinformatic facilities with state-of-the-art research to better understand human and animal biology, and to develop new pharmaceuticals, diagnostics, nanotechnologies and disease therapies.

Research at the IMB includes the genomic and genetic analysis of mammalian development and cell biology, as well as structural analysis of key proteins and the discovery of new chemicals that may interact with these proteins as the basis for new pharmaceutical development aimed at cancer, inflammatory and infectious diseases, and a range of common human diseases.

The IMB is a core partner in two Cooperative Research Centres, the CRC for the Discovery of Genes for Common Human Diseases and the CRC for Chronic Inflammatory Diseases.

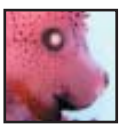
Creating operational synergies between research, industry and government, the IMB provides an integrated environment of excellence that capitalises on a spectrum of intellectual and physical resources, a multi-disciplinary approach and effective links between groups involved in discovery and those involved in developing practical applications.

The Institute's commercialisation arm, IMBcom Pty Ltd, was established in March 2000. IMBcom's mission is to provide a dedicated vehicle for the commercialisation and development of IMB's research and technologies.

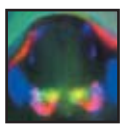
From 2002, the IMB will be housed in a new $105 million, state-of-the-art 35,000m^2 facility, currently under construction at The University of Queensland, together with the CSIRO and other research organisations, enabling greater scientific interaction and collaboration.

More than 700 scientists, research students and support staff from the IMB, CSIRO and Queensland Department of Primary Industries, will be working in the new complex, making it one of the largest and most innovative biological research centres in the Southern Hemisphere.

Exploring beyond traditional and narrow boundaries ensures the IMB continues to revolutionise emerging fields and new discoveries incorporating the full spectrum of molecular bioscience.







Leadership

The IMB is an innovative joint research and development initiative of The University of Queensland, the Queensland Government and the Commonwealth Government.

Artist impression of the UQ/CSIRO Joint Building Project currently under construction to house the IMB together with the CSIRO, Queensland Department of Primary Industries and other research organisations.

2001 Highlights

The IMB's research is a prime example of Australian minds leading the world, and these minds are the cornerstone of the future health and economic growth of Australia. Awards, discoveries and scientific grants further enhance the reputation and stature of our scientific endeavour, and recognise the dedication that these scientists bring to the quest for understanding. Following are highlights of some of the IMB's achievements during 2001:

People

Scholars stand out

Two IMB PhD graduates, Dr David Pennisi and Dr Michelle Hill, were recognised on the Dean's list for their watershed PhD theses.

This award recognises those few PhD graduates who receive unanimously outstanding reports from their examiners' reports which commend them on making genuine and substantial contributions to their field of research.

Co-Directors awarded

IMB Co-director Professor John Mattick was appointed as an Officer of the Order of Australia in the 2001 Queens Birthday honours list.

In presenting the award Queensland Governor Major General Peter Arnison AC recognised Professor Mattick's long and distinguished service to scientific research in the fields of molecular biology and genetics, as well as his role in the development of the IMB into an internationally recognised centre of bioscience research and discovery.

IMB Co-director and IMBcom CEO Professor Peter Andrews won the Entrepreneur of the Year Northern Region's Supporter of Entrepreneurship award.

Chosen for his innovative drive, ambition, ingenuity and basic hard work in an industry searching for firsts and discoveries, Professor Andrews is one of the leaders to nurture the IMB and stimulate our best young scientists to "take their discoveries further than the lab bench".

In Memory

The IMB was saddened by the unexpected passing of Dr Toshiya Yamada on 12 May 2001. Toshi's contributions to modern developmental neurobiology have now become standard textbook entries, a legacy very few scientists can claim. The IMB, with the assistance of the Australian Neuroscience Society, will establish an annual lecture in Toshi's honour, as well as dedicate a plaque and an area of the garden in the new Institute in his memory.

Dr Toshiya Yamada
15 October 1960 – 12 May 2001

World leader heads Public Policy & Ethics

The IMB appointed Professor Wayne Hall AM as Director of Public Policy and Ethics Unit at this important stage in molecular bioscience, biotechnology and genetic research. He brings to the IMB unparalleled experience in relation to ethical and social issues raised by the revolution in genomics, genetics, cell biology and biotechnology following his 12 years as Executive Officer of the National Drug and Alcohol Research Centre.

Research

Researchers scoop the gene pool

IMB researchers were awarded the AMP Biomedical Research Awards in both the pre- and post-doctoral categories for 2001.

PhD student at the IMB Delvac Oceandy won the pre-doctoral category for his research into the genetic control of Cystic Fibrosis (CF) lung inflammation disease. His results indicated that restoration of gene function in the lung epithelial cells can lead to easing of the disease and that gene transfer technologies may be useful in the development of new therapies for Cystic Fibrosis.

Dr Uwe Dressel, on a fellowship exchange at the IMB from the German Academic Exchange Service, won the post-doctoral category for his work investigating the mechanisms that regulate muscle development. Understanding the development of undifferentiated precursor cells into specialised tissues such as muscle provides cornerstones for the development of therapies to counter muscle-related diseases.

Awards for IMB researchers

The premier body for bioscience research in Australia, the Australian Society for Biochemistry and Molecular Biology (ASBMB), recognised the research excellence of two other IMB scientists.

Professor David Hume was awarded the prestigious 2001 Amersham-Pharmacia Biotechnology Medal for his distinguished contributions to the field of biochemistry and molecular biology. The Award is intended as a travelling Lectureship and carries an Honorarium and a Medal.

PhD student Julie Dutton was awarded a ASBMB Fellowship for her outstanding work on the structural biology of the toxins from marine snails and their potential as therapeutics for neurological disorders. Julie also won a Finn World Travel Award from the Protein Society and combined these awards to attend the 15th Symposium of the Protein Society in Philadelphia and visit the Wistar Institute at the University of Pennsylvania.

Another win for top research

Associate Professor Bostjan Kobe *(pictured above centre with the Prime Minister and other award winners)*, a joint appointment at the IMB and the Department of Biochemistry and Molecular Biology at UQ, was awarded the 2001 Minister's Prize for Achievement in Life Sciences at Parliament House.

The $35,000 award, presented at the Prime Minister's Prize for Science Dinner, recognised the ground-breaking contributions Associate Professor Kobe has made to world knowledge with his work on the 3-D structure of proteins.

Commercialisation development

Protagonist Pty Ltd, a new wholly Australian-owned biotechnology company, was one of four spin-out companies generated from IMB research in 2001.

Protagonist is gearing up as a major force to combat costly medical conditions and to benefit worldwide health following a $3 million investment from Start-up Australia.

The investment by Start-up Australia in Protagonist is tapping into a potential billion-dollar global market with significant social, health and economic benefits for Australians.

The other IMB spin-outs in 2001 were Mimetica Pty Ltd, Nanomics Biosystems Pty Ltd, and Kalthera Pty Ltd.

Amgen awards IMB honours student

IMB student researcher Emily McGhie was awarded the prestigious Amgen Australia Prize in Molecular and Cellular Biology in 2000.

During the course of her research, Ms McGhie investigated how changes in protein function can be achieved without altering the original genome sequence. The project was an example of the increasingly interdisciplinary nature of today's bioscience research.

(left-right) Amgen's Christine Culverhouse, Federal Member for Ryan Michael Johnson, and IMB's John Mattick presented Emily McGhie with her prize.

CRC up and running against inflammation

A new cutting-edge research centre with state-of-the-art technology started operating in July 2001 to help better understand and fight inflammatory diseases and thus improve the health of Australians.

The Cooperative Research Centre (CRC) for Chronic Inflammatory Diseases combines the formidable expertise of research groups from the IMB, the University of Melbourne, Monash University, and multinational drug company AstraZeneca. The focus of the Queensland node, headed by IMB's Professor David Hume, is "systems biology", in which researchers attempt to use the knowledge gained from the human genome project to identify all the components needed to make a biological system work.

Events

State of play

Biotechnology analyst Dr Daniela Bellomo from IMB's commercialisation arm IMBcom, made a presentation to Queensland Parliament about some of the commercial benefits of the bioscience revolution, including hundreds of new jobs.

The information in the genetic code will impact enormously on health and medical research but possibly the biggest gains will come in areas beyond these applications representing only the tip of the iceberg.

IMB hosts world's leading genomic scientist

The IMB hosted senior members of government, heads of research institutes, and key individuals from CSIRO, the biotechnology industry and the investment community from around Australia at various functions throughout 2001, including an event that featured President of Celera Genomics Dr J. Craig Venter.

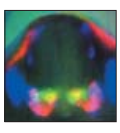
Dr Venter's event coincided with the publication of the human genome in the prestigious US journal *Science.*

The event was a rare opportunity to hear the world's foremost expert discuss the project that revolutionised bioscience research worldwide.

(left-right) IMB's John Mattick with Celera Genomics' Craig Venter.







Grants

IMB awarded $7.7 million

In the September 2001 round of ARC grants, IMB researchers were awarded over $7.7 million in competitive research funding. Spread over five years, the funding will support research projects and infrastructure costs across a broad range of inter-related research interests ranging from proteomics, to developmental biology.

Some of the successful projects in this round included:

- $735,000 to establish a world class proteomics facility allowing the investigation of how proteins control gene expression, the organisations of proteins in cells and identification of proteins that may be potential drug targets.
- $550,000 for a robotic nuclear magnetic resonance spectrometer that will aid the rapid characterisation of drug-protein interactions and in the discovery of new drugs or agrochemicals. This machine will accelerate the rate of discovery of the structure and function of proteins leading to the development of new bio-active molecules.
- $1.55 million over five years to create small molecules that mimic protein structure, with the potential to develop new drug leads and biological tools to better understand biological processes.
- $2.3 million over five years was earmarked for research into the development of potential drugs from the venom of Australian cone shells, particularly focussing on peptides that selectively affect the nervous system.
- $1.75 million over five years to continue research into genetic mechanisms controlling sexual development of embryos.

In brief:

The IMB Board was appointed and held first meeting in October 2001.

The IMB Scientific Advisory Board was appointed and their first meeting was scheduled for March 2002, coinciding with the inaugral IMB Scientific Symposium.

Construction of the UQ/CSIRO Joint Building Project, which will house the IMB together with the CSIRO from late 2002, continued during the year.

The IMB received notification in December that it had secured a major coup to host the prestigious Intelligent Systems in Molecular Biology 2003 conference. The Brisbane event will be the first time the ISMB conference has been held outside North America or Europe. It is anticipated that the conference will inject around $3 million into the Queensland economy over the four day event with more than 1800 world leaders in computational biology and bioinformatics attending.

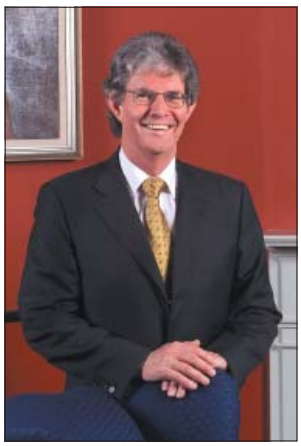
In 2001 PhDs were awarded to four students: Iain Sharpe, Gos Schepers, Ylva Strandberg and David Wilson and a Masters to Nikolai Sokolenko.

Several IMB staff were recognised with fellowships or promotions in 2001:

- *ARC Australian Professorial Fellowships to David Fairlie and Peter Koopman*
- *NHMRC Fellowships to Sean Grimmond, Michael Waters and Carol Wicking*
- *Rick Sturm promoted to Principal Research Fellow*
- *Greg Bourne, Robert Reid and Stephen Love promoted to Senior Research Officer*

The IMB Board was appointed in 2001 and is comprised of senior members of the University, IMB Directors and a majority of independent external members who are prominent individuals from research, industry, the professions, and the community who will guide the progress and support the mission of the IMB. Members of the Board held their first official meeting on 1 October 2001.

Chair's Report



The Institute for Molecular Bioscience (IMB) has enjoyed another remarkable year. Established in 2000 by the merger of two major University of Queensland research centres, the IMB has built a strong international reputation for excellence in research and productive industry collaboration.

The Institute was set up with financial support from the Queensland and Australian Governments as well as a private donor, and in 2003 will be based in a new $105 million complex at St Lucia, Brisbane, together with Commonwealth Scientific and Industrial Research Organisation (CSIRO) laboratories.

Apart from generous financial assistance, the key to the IMB's success has been its dedicated and talented staff, and I would like to give particular praise to the Institute's co-directors Professor John Mattick and Professor Peter Andrews. Under their leadership, the Institute has developed a spectrum of research from genomics through developmental and structural biology to medicinal chemistry and preclinical biology.

This has been underpinned by major University investments in bioinformatics and computational biology, including the establishment of a new supercomputing facility on the St Lucia campus.

The Institute is also committed to contributing towards the economic growth of Brisbane and Australia, and has helped in the formation of a number of significant spin-off companies.

The broad strategic direction of the Institute is overseen by an IMB Board, comprising key international scientists and industrialists, as well as the IMB's co-directors, senior University of Queensland executives and representatives of the Queensland Government. The board, which is assisted by high-level Scientific and Business Advisory Committees, held its inaugural meeting on 1 October 2001 and will meet twice per annum.

In welcoming board members to this first meeting, I noted that the IMB was the single most important initiative in the recent history of The University of Queensland. Furthermore, the IMB is paving the way for related initiatives in the new sciences in the fields of bioengineering and nanotechnology.

Through its high-quality research, industry collaboration and links to other important initiatives, the IMB is consolidating its position as a leader in the biosciences.

Professor John Hay
University of Queensland Vice-Chancellor
Chair, IMB Board

Co-director's Report

This year is the second of the IMB, in which we have seen further integration of the research interests of the Centres that came together to form the Institute. The IMB is unique in Australia in that it is a systems biology institute which brings together genomics, genetics, developmental biology, cell biology, structural biology and chemistry, with a strong underpinning of bioinformatics and computational biology. Our intention is to create a multidisciplinary environment that can attack the future challenges in biology, especially to understand how genotype affects phenotype, and to use this information to generate new understanding and new applications.

Biological science is undergoing rapid change. The advent of the genome sequences of the human, mouse, fruitfly, nematode and yeast, and of a large number of bacteria and archaea, is revealing the genetic programming and molecular components that underlie the diversity of life, and which will need to be understood and re-built into an increasingly coherent picture of how life works, and what affects individual variation, including susceptibility to disease. We not only need to understand the molecular details of different cellular processes and functions, but also start to integrate this information into a larger framework of the genetic and molecular networks that operate in the differentiation and development of complex organisms. This is a huge challenge, and one that will occupy at least the next generation of biological scientists. It will also require new engagement with the physical and informational sciences. The IMB is building its infrastructure and linkages to enable it to address these issues. Through the ARC Special Research Centre for Functional and Applied Genomics, and in partnership with other laboratories at UQ and other institutions, we have established a range of facilities that will allow an increasingly seamless and efficient analysis of the information. We have expanded our bioinformatics infrastructure and transgenic facilities, and established new microarray and proteomics facilities, with some of the most advanced equipment in Australia. We have also established large-scale protein expression facilities, which will vastly improve the numbers of proteins that we are able to characterise, both structurally and functionally. We have also, among other things, become a partner in a new Cooperative Research Centre for Chronic Inflammatory Disease. Most importantly, we have made a number of important discoveries during 2001, many of which are described in the research profiles and in the publications listed in this report.

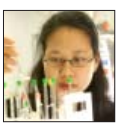
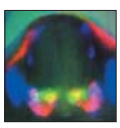
The IMB's new building will be completed later this year, and will form part of a large complex being constructed in conjunction with CSIRO. The facilities within it are outstanding and I would like to take this opportunity to congratulate our Deputy-Director, Ian Taylor, as well as Peter Sampson from the University's Property and Facilities section, and Mark Roehr from Daryl Jackson Architects, for having planned an outstanding research facility, which will become one of the most important in Australia. I would also like to once again thank the University of Queensland, the Federal Government, CSIRO, our private benefactor, and the State Government for their support for the construction of the complex, and the State Government for their provision of secure core operating funds that is allowing the Institute to develop innovative programs and to attract the best researchers in the world to Brisbane.

I would like to thank my Co-Director, Peter Andrews, who has taken responsibility for the commercial development of the Institute's activities while I oversee the research, and we jointly set strategic directions. This has been now a longstanding partnership of great strength and great enjoyment. I also commend our research staff, support staff and postgraduate students again for their efforts, support and achievements this year. We have now established the Board and Scientific Advisory Board of the Institute, whose members are all prominent and highly experienced individuals of international stature, and we are grateful for giving of their valuable time to provide governance and guidance.

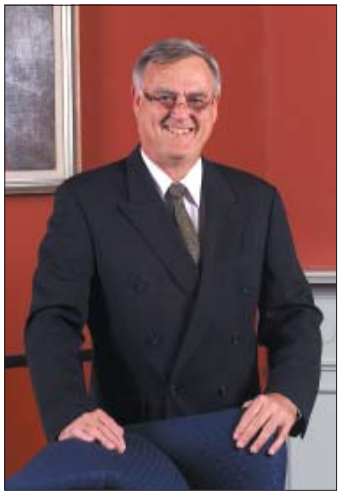
Finally, it is my sad duty to report the death in early 2001 of one of the IMB's Group Leaders, Dr Toshiya Yamada. Toshiya was one of the most influential neurobiologists of his generation, with an outstanding internationally reputation. His loss was a great shock. We will establish an annual lecture as well as a place in the Institute garden in his memory, and once again extend our heartfelt condolences to his family.

Professor John Mattick AO
IMB Co-director



Co-director's Report



Like John Mattick, I've given so many talks on IMB this year that I can do it in my sleep, and probably have. Colleagues throughout academia, industry, government and now the investment community are increasingly fascinated by our plans to span the spectrum from gene to drug, from bench to business, and most are keen to hear how we are going about achieving them.

Of particular interest to many is our thesis that by focussing on outstanding research, great development opportunities will follow. That thesis is already proving to be strongly supported by the facts.

During 2001 for example, three of our spin-out companies – Xenome, Promics and Protagonist – attracted first or second round venture capital investments of between $3 and $4.5 million. Xenome appointed Professor Tony Evans as its foundation CEO, and Dr Mark Smythe accepted a 50% appointment as CEO/CSO of Protagonist. Three other spin-outs – Nanomics, Mimetica and Kalthera – were established, and are currently considering offers of seed capital.

The Institute's external collaborations also continued to expand with the successful establishment of the new CRC for Chronic Inflammatory Diseases of which the Queensland node is led by our Professor David Hume, and the formation of a major alliance with Japanese trading house Itochu. Other key research alliances with CSIRO, QIMR and the Australian Institute of Marine Science have continued to progress, and have also proved to be key factors in our involvement in several biotechnology Centre of Excellence applications, the outcomes of which will be known in 2002.

All of these spin-outs and alliances are based on what was originally pure, curiosity-driven research, albeit undertaken by researchers with a strong interest in creating ultimate commercial outcomes. To that end, IMB's commercialisation arm IMBcom is working closely with the Institute's researchers to identify projects with commercial potential, and helping them to locate the capital and other resources required to further develop their research.

The upshot of all of this is that we are meeting and exceeding the various key performance indicators – jobs created, spin-offs established, income generated – that underpin the investments by the Queensland State Government in the capital and operating costs of the Institute. Those of you who live in Brisbane, or who have had the opportunity to visit us over the past year, will also have seen the most tangible evidence of this investment – the magnificent building under construction at the entrance to the University of Queensland.

Last, but far from least, congratulations to my friend and partner, John Mattick, on the award of the Order of Australia (AO) in 2001 for his long and distinguished service to scientific research in the fields of molecular biology and genetics, as well as his role in the development of the IMB into an internationally recognised centre of bioscience research and discovery.

The Institute that we are now building has been John's dream for the past seven years, and it is a delight to see it coming to fruition.

Professor Peter Andrews
IMB Co-director
IMBcom CEO

IMB Board

as at 31 December 2001

Chair

Prof. John Hay
Vice-Chancellor
UQ

Professor John Hay, Vice-Chancellor and President of The University of Queensland since January 1996, has extensive experience in Australian universities in academic, administrative and leadership roles.

The University of Queensland was named as Australia's 1998-99 University of the Year by the Good Universities Guides for outstanding outcomes for graduates.

Professor Hay has published widely in the fields of English literature, Australian literature, literary theory, scholarly bibliography and education with some 18 volumes and numerous research papers to his credit.

In 1987, he became Dean of Arts at Monash University where he also established the national Key Centre for Australian Studies. In 1988, he was appointed Senior Deputy Vice-Chancellor at Monash, with principal responsibility for strategic planning.

He also played a key role in Monash's major growth and mergers during 1989-91.

In 1992, Professor Hay was appointed Vice-Chancellor and President of Deakin University in Victoria and directed the transformation of a small, regional institution into a large, multi-campus university with 30,000 enrolments.

In 1995, Deakin was named University of the Year by the Good Universities Guides for use of technology in teaching undergraduate education.

In 1997, Professor Hay was appointed to the Board of the Queensland Performing Arts Trust by the Queensland Government.

Deputy Vice-Chancellor

Prof. Paul Greenfield
Deputy Vice-Chancellor
UQ

Professor Paul Greenfield was appointed Deputy Vice-Chancellor (Research) at The University of Queensland in October 1997. He has wide professional and academic experience both in Australia and overseas. He has worked as a consultant for numerous national and international companies and government agencies in the fields of biotechnology, wastewater management, environmental management and project evaluation. In addition, he has served on a number of national and international committees, including the National Greenhouse Advisory Panel which he joined in 1994, and the DETYA High Performance Computing Interim Executive Board of Management. He is also currently chair of the Scientific Advisory Committee overseeing the $5.2 million Moreton Bay and Brisbane River Wastewater Management Study.

Professor Greenfield's research is internationally recognised, in terms of ability to attract funding and publish significant output. He has authored over 180 journal publications, 120 conference publications, 3 patents and over 20 invited international (keynote/plenary) addresses. He continues to be an active supervisor for PhD students.

Professor Greenfield is currently a Fellow of the Australian Academy of Technological Sciences and Engineering (FTSE), the Institution of Chemical Engineers (FIChe), a Member of the Institute of Engineers, Australia (MIEAust), and a Member of the American Institute of Chemical Engineers (MAIChE). In 1995, Professor Greenfield's contribution to his field was recognised when he was presented the Chemeca Medal, awarded jointly by Institution of Chemical Engineers & Institute of Engineers Australia for Outstanding Contribution to the Profession, and again in 1998, when he was named as the Institute of Engineers 'Engineer of the Year'.

IMB representative

Prof. John Mattick AO
Co-Director IMB
Director AGRF
Director ARC SRC for Functional and Applied Genomics

Professor Mattick was responsible for the development of the IMB and is Co-Director of the Institute 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, with its primary focus being the molecular genetics of mammals and their diseases, including genome mapping, gene regulation, developmental biology and cell biology.

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. His current research interests are in the genetics of bacterial pathogenesis, and the role of non-coding RNAs in the evolution and development of complex organisms. He has published over 100 scientific papers.

Professor Mattick is also, among other things, 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. He is a member of the Queensland Biotechnology Advisory Council and on the Scientific Advisory Boards of several institutes nationally and internationally. He was appointed as an Officer in the Order of Australia in June 2001.

IMBcom representative

Prof. Peter Andrews
Co-Director IMB
CEO IMBcom

Professor Peter Andrews is Co-Director of the IMB at UQ, and CEO of its commercialisation arm, IMBcom Pty Ltd.

He is also a Director of Alchemia Pty Ltd, Xenome Ltd and Protagonist Ltd, a Fellow of the Australian Academy of Technological Sciences and Engineering, and President of the Asian Federation of Medicinal Chemistry.

Professor Andrews is an active promoter of the benefits of closer interactions between public sector research organisations and industry, and has been at the forefront of initiatives to foster the development of new industries based on Australia's high quality research.

Professor Andrews has worked in the field of drug design for over 25 years, establishing research laboratories at ANU, Victorian College of Pharmacy, Bond University and University of Queensland.

Outcomes from these laboratories include the delineation of the structural requirements of many classes of CNS-active drugs (ANU, VCP), the design of the Biota flu drug, Relenza (VCP), the development of heuristic methods for the analysis of drug-receptor interactions (VCP), and the discovery of potential antiviral and analgesic drugs currently in preclinical and clinical development (UQ).

His personal research interest is in the structure and function of biologically active substances, with a particular focus on the computer-aided design of novel pharmaceuticals.

International Scientist

Prof. Frank Gannon
Executive Director
European Molecular Biology Organization (EMBO)

Since 1994, Frank Gannon has been the Executive Director of the European Molecular Biology Organisation (EMBO) in Heidelberg, Germany, and also Senior Editor of EMBO Reports, Associate Editor of the EMBO Journal and a member of the Governing Body of E-Biosci. He serves on a number of scientific advisory boards at institutes throughout Europe.

Prior to his appointment to EMBO in 1994, he obtained a Bachelor of Science from the National University of Ireland, Galway in 1970, a PhD from the University of Leicester, England in 1973, was a post-doctoral fellow at the University of Madison Wisconsin from 1973 to 1975, and Chargé de Recherche in the University of Strasbourg from 1975 to 1981.

From 1981 to 1994, he was Professor of Microbiology, Director of the Biotechnology Programme and Director of the National Diagnostics Centre at the National University of Ireland, Galway.

He maintains an active laboratory that carries out research on the Estrogen Receptor Gene and is increasingly involved in the overall topic of electronic publication in the Life Sciences.

Among other positions, Professor Gannon is an Advisor to the Asia Pacific Rim International Molecular Biology Network (IMBN); Member of the Scientific Council of the Stazione Zoologica, 'Anton Dohrn', Naples; Member of the International Advisory Board on the International Institute for Molecular and Cell Biology, Warsaw; Advisory to Ibero-American Molecular Biology Organisation; and Coordinator of European Biotechnology Node for Interaction with China.

Biotechnology Industry Representative

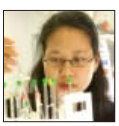
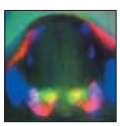
Dr Russell Howard
CEO
Maxygen, Inc. USA

Russell J. Howard is the Chief Executive Officer and a co-founder of Maxygen, Inc. At Melbourne University, Victoria, Australia, Dr Howard received his bachelors' degree in Biochemistry with honours in 1972 and his PhD on the biochemistry of marine algae in 1975. Dr Howard began his 18 year career in the field of molecular pathogenesis of malaria in 1976 with post doctoral studies with the immunoparasitology laboratory of Dr GF Mitchell, Walter and Eliza Hall Institute, Melbourne. These studies continued in 1979 with work as a visiting Associate at the National Institute of Allergy and Infectious Diseases at the National Institutes of Health in Bethesda, Maryland. Dr Howard received tenure at the NIH. In 1988 he created the Laboratory of Infectious Diseases at the DNAX Research Institute of Molecular and Cellular Biology and continued work on antigenic variation in malaria.

In 1992 Dr Howard joined Affymax Research Institute as Vice President and Director of Cell Biology, and in 1994 he became President and Scientific Director. During this period he led the interdisciplinary team of 200 scientists working on the Affymax combinatorial chemistry and drug discovery platform while continuing to lead studies on malaria molecular pathology.

In 1996 Dr Howard became President and Chief Operating Officer of Maxygen during its incubator phase. In 1997 Maxygen was spun-out of Affymax. Dr Howard became President and Chief Executive Operator of Maxygen in 1998. Dr Howard retains his interest in infectious diseases and vaccine discovery and serves currently as Chairman of the USAID Malaria Vaccine Development Program as well as a member of NIH/NIAID malaria vaccine development committee.



Business Representative

Ms Helen Lynch AM

Helen Lynch is a Non-Executive Director of Coles Myer Limited, Southcorp Limited, Westpac Banking Corporation and Deputy Chair of OPSM Protector Limited.

She is Chair of the Sydney Symphony Orchestra and a director of CRI Australia Holdings Limited.

From 1995-2000 she was the Chair of the Superannuation Funds Management Corporation of South Australia.

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 she was the Bulletin/Qantas Business Woman of the Year. She was made a Member of the Order of Australia in 1994 for services to the Banking and Finance Industry.

Ms Lynch has always been committed to the community, serving as a director of a number of arts and charitable organisations.

Her current appointments include Director, Centre for Independent Studies, member of the Board of the Garvan Medical Research Institute and a member of the New South Wales Rhodes Scholarship Selection Committee.

Executive Dean (rotating)

Prof. Mick McManus
Executive Dean
Faculty of Biological & Chemical Sciences
UQ

In 1992, Professor McManus was appointed Foundation Professor of Pharmacology at the University of Queensland and from 1993-97 was Head of the Department of Physiology and Pharmacology. He was appointed Executive Dean of the Faculty of Biological and Chemical Sciences in April of 1998. Before moving to Brisbane Professor McManus was a National Health and Medical Research Council (NH&MRC) Principal Research Fellow in the Department of Clinical Pharmacology at Flinders University in Adelaide. He was initially trained as a pharmacist at Curtin University of Technology and then earned his PhD. in biochemical pharmacology from the University of Western Australia in 1978. Following his PhD, Professor McManus spent two years as a postdoctoral fellow at the Royal Postgraduate Medical School in London and approximately four years as a Fogarty International Fellow/Associate at the National Cancer Institute (NIH) in Bethesda, Maryland USA.

On returning to Australia in 1983 he was first an Anti-Cancer Foundation Research Fellow of the Universities of South Australia and subsequently a NH&MRC Senior/Principal Research Fellow. His research interests include xenobiotic metabolism (sulfotransferase, cytochromes P450, and flavin-containing monooxygenases) and mechanisms of chemical mutagenesis and carcinogenesis. He is currently a member of the Editorial Board of Pharmacogenetics and the International Journal of Biochemistry & Cell Biology.

From 1993-96 Professor McManus was a Member of the Board of the Brisbane North Regional Health Authority. He has served on a number of NH&MRC panels: Grant Assigners Panel, CJ Martin and Douglas Wright Fellowship Assessors panels and Regional Grant Interviewing Committees, and has undertaken a number of toxicological consultancies for both the federal and local governments.

State Government representative

Mr Ross Rolfe
Director-General
Queensland Dept of State Development

Ross Rolfe was appointed the Director-General of the Department of State Development on 27 August 1998 and Co-ordinator General on 20 August 1998.

In 1996, he was the Director-General of the Department of Environment and Heritage, under the previous Labour Government.

Mr Rolfe has a background in issues relating to land management, the energy industry and the environment.

During the period between 1996 and 1998, 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.

Community Representative

Sir Sydney Schubert

Sir Schubert had more than 40 years career with the Queensland State Government, including Co-ordinator General and Director General of Premiers Department between 1976 to 1988.

He was also Chief Executive and Chairman of Daikyo Group of Companies, Australia and New Zealand from 1988 to 2000.

Sir Schubert is currently Chairman for a number of Boards, including CRC for The Great Barrier Reef World Heritage Area (since 1999), and International Marine Projects Activity Centre (since 2000).

He is also a Fellow with the Australian Academy of Technological Sciences and Engineering Honorary Fellow of the Institution of Engineers.

State Government Representative

Mr Kevin Yearbury
Director-General
Queensland Dept of Innovation and Information Economy

Kevin Yearbury has some 20 years experience in public administration working in the State Government and with Local Governments.

In 1998 as Director-General of the Queensland Department of Communication and Information, Local Government, Planning and Regional Communities, he oversighted the preparation of Queensland's first Communication and Information Technology Strategic Plan, the roll-out of a second broadband cable in coastal and regional Queensland, and the development of an IT architecture for the on-line delivery of Government Services.

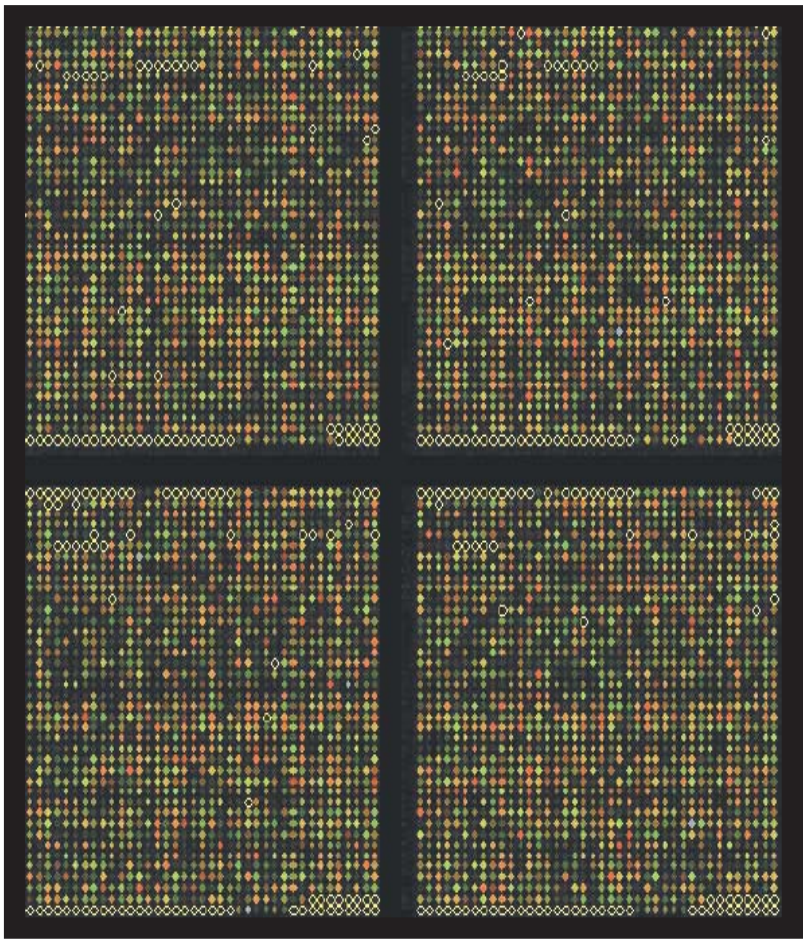
In February 2001 Mr Yearbury was appointed Director-General of the new Queensland Department of Innovation and Information Economy.

In this capacity he has responsibility for facilitating the development of science and technology infrastructure to attract new knowledge based industries, co-ordinating public sector investment in Research and Development (R&D) and promoting innovation and the application of technology to generate economic opportunities and social benefits for Queenslanders.

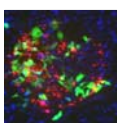
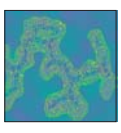
Kevin Yearbury is Chair of i.Lab, the Queensland Government sponsored IT incubator, and a Director of CITEC, the fully commercial IT&T and information services business owned by the Queensland Government.

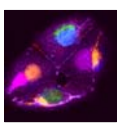
The IMB Board will meet biannually and have obligations to ensure the Institute remains viable and effective for the future.

Genomics and Bioinformatics



The interface of biology with mathematics, computer science, and information technology promises a more-quantitative understanding of the complexities of living organisms, and new models for advanced computation. In the IMB's Genomics and Bioinformatics Division, we apply computer-based methods to problems in molecular biology and genomics, and develop new approaches and software to investigate complex cellular processes.

Comparative and Computational Genomics

We use advanced computer 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.

Group Leader
Mark Ragan

Senior research assistant
Ian Bailey-Mortimer

Postdoctoral fellow
Josef Panek

Honours student
Steve Mayocchi

Student researcher
Brendan Tse

Automated inference of vertical and lateral gene transmission in bacterial genomes

For more than 130 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 structure-sensitive multiple sequence alignments, infer phylogenetic trees and find statistically supported instances of incongruence among them.

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.

Applications of Bayesian phylogenetic inference

Relationships among proteins within a family can be depicted as a branching tree. The best algorithms for inferring these trees from sequence data are NP-hard, *i.e.* as more sequences are added to the analysis, we can eventually no longer be sure of finding an optimal solution – and the ongoing high level of international activity in genomic sequencing ensures a continual supply of new sequences.

An exciting new approach based on Bayesian statistics appears able to postpone this point of incomputability.

We have carried out extensive comparisons of classical and Bayesian methods using real protein-sequence data, and are applying both approaches to a particularly difficult question concerning the origins of animals, fungi and a recently recognised group of parasites called Ichthyosporea.

Archaeal genomics

In July 2001, the *Sulfolobus solfataricus* genome-sequencing consortium (of which I was a founding member) reported in *Proceedings of the National Academy of Sciences USA* the complete 2.99-Mbp sequence of this therophilic archaean.

Its highly plastic genome contains 200 diverse insertion sequence elements, non-autonomous mobile elements, evidence of integrase-mediated insertion events, and long clusters of regularly spaced tandem repeats.

Relational database structures for sequence data

The continuing flood of new gene and protein sequences, together with the appearance of novel data types (*e.g.* from expression arrays), make it increasingly important that we use advanced tools from information science to organise and query genomic and other molecular sequence data.

In collaboration with Xiao-feng Zhou (Information Technology, UQ), I supervised undergraduate student Brendan Tse in mapping the data structures underlying GenBank.

We will continue this work during 2002, focusing on the human and mouse genomes.

Rnomics

Group Leader
John Mattick

Research officers
Derek Kennedy
Rhonda Perriman

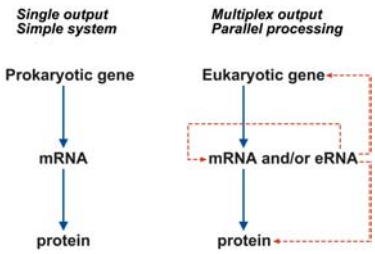
PhD students
Juliet French
Khairina Tajul Arifin
Larry Croft
Stefan Stanley
Budi Utama

Research assistant
Ke-lin Ru

Our group is interested in the role of RNA, especially that derived from introns and noncoding RNA genes, in regulating gene expression in mammals. The vast majority of the transcriptional output of the human genome is noncoding RNA. We are examining the systemic role of noncoding RNA in the networking and integration of genomic activity, as well as studying different classes of proteins that are involved in RNA metabolism.

Noncoding RNAs: the architects of eukaryotic complexity?

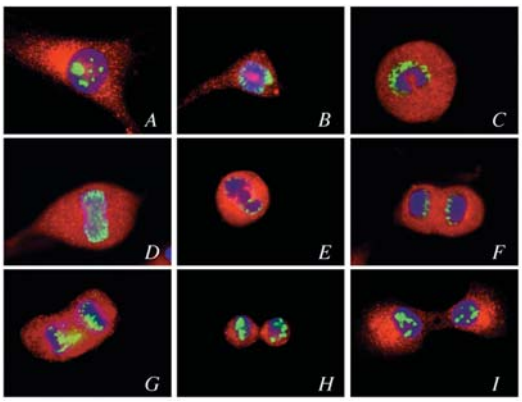
Around 98% of all transcriptional output in humans is noncoding RNA, derived from introns that are transcribed and processed from protein coding genes, and from other genes that only produce noncoding RNA, all of which appear to be developmentally regulated. RNA-mediated gene regulation is widespread in the higher eukaryotes and complex genetic phenomena like RNA interference, co-suppression, transgene silencing, imprinting, methylation, and possibly position-effect variegation and transvection, all involve intersecting pathways based on or connected to RNA signalling. We have suggested that the central dogma is incomplete, and that intronic and other noncoding RNAs have evolved to comprise a second tier of gene expression in the eukaryotes which enables the integration and networking of complex suites of gene activity. If this is correct there are three types of genes in the higher organisms – those that encode only protein (which are rare), those that encode both protein and eRNA (efference RNAs derived from introns), and those that only encode eRNA (derived from the introns or exons of noncoding RNA genes). Thus, although proteins are the fundamental components and effectors of cellular function, the basis of eukaryotic complexity and phenotypic variation may lie primarily in a control architecture composed of a highly parallel system of trans-acting RNAs that relay state information required for the coordination and modulation of gene expression, via chromatin remodeling, RNA-DNA, RNA-RNA and RNA-protein interactions. This system has interesting and perhaps informative analogies with scale-free and neural networks, as well as with dataflow computing.



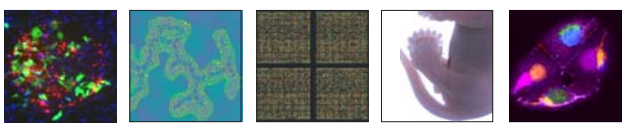
We are exploring this hypothesis by a variety of approaches, including structural analysis of major classes of RNA-binding proteins, sequence analysis to identify potential subnetworks of RNA transmitters and RNA or DNA receivers by homology matching, experimental analysis of such subnetworks and of the large numbers of yet unstudied noncoding RNAs identified in EST databases, and by computational modelling of genetic networks and operating systems, particularly comparing the conventional model with the parallel system that we have proposed.

RNA binding proteins

We recently reported the tissue specific expression of G3BP, an RNA-binding protein that was originally discovered in this lab. Our data also show that G3BP is involved in signal transduction through interactions with rasGAP120. This is one of the first RNA-binding proteins, shown to connect signal transduction pathways to RNA metabolism. We have also identified a novel nucleolar protein which is concerned in all eukaryotes, named Nucleolar RNA-associated protein (Nrap) because of its *in vivo* association with rRNA. Our results suggest that Nrap is involved in the early steps of 45S rRNA processing.



Localisation of Nrap during mitosis. The protein is associated with nucleoli during interphase, but redistributes to the condensed chromosomes during mitosis.



Expression genomics

Microarray based gene expression profiling has proven very successful in screening large sets of genes (up to 20,000 per experiment) and identifying those that display differential expression in response to a given stimuli. When a large number of expression profiles are compiled, data-mining tools can be used to infer the biological role of differentially expressed genes as well as surmise what biological events were taking place within a sample.

Group Leader
Sean Grimmond

Research officer
Joanne Redburn

Research assistants
Alistair Forrest
Chris Johns
Rowena Cecil
Darrin Taylor

UROP student
Jessica Mar

Recording transcriptional programs promoting angiogenesis

Vasculature is essential for all tissue maintenance and repair.

We are using microarray-based temporal expression profiling to define the transcriptional programs driven by endogenous promoters of angiogenesis (hypoxia, VEGF family, bFGFs) with the hope of identifying key regulators of the process. Such molecules are keenly sort as potential targets for controlling pathological angiogenesis such as ischaemia and tumour angiogenesis.

Reverse transfection: Microarray based assays of gene function in living cells

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. Briefly, the method works as follows: adherent mammalian cells are cultured on a glass slide that has been printed in defined locations with different liposome –cDNA expression vector complexes.

Cells are then grown on the surface of the array, creating regions of localized transfection throughout a lawn of non-transfected cells. The effect of each expression construct can be gauged by studying the cluster of living cells present at each spot location.

Pilot efforts using this technology at the IMB (in collaboration with Rohan Teasdale and Jenny Stow) have successfully assayed sub-cellular localization of full length cDNAs from the RIKEN mouse clone encyclopedias (see figure 1).

We are now expanding these studies to systematically test gene function and sub-cellular localization *in silico* predictions.

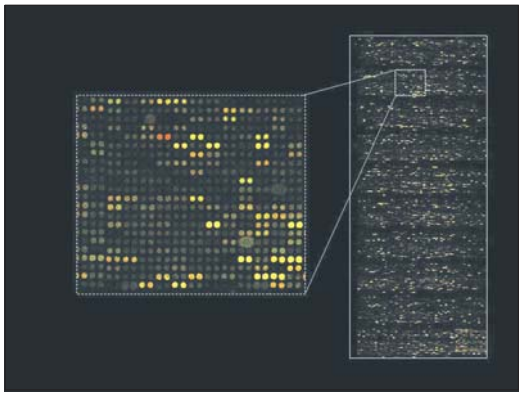


Figure 1: Two colour overlay of 32,000 element IMB-V2 microarray.

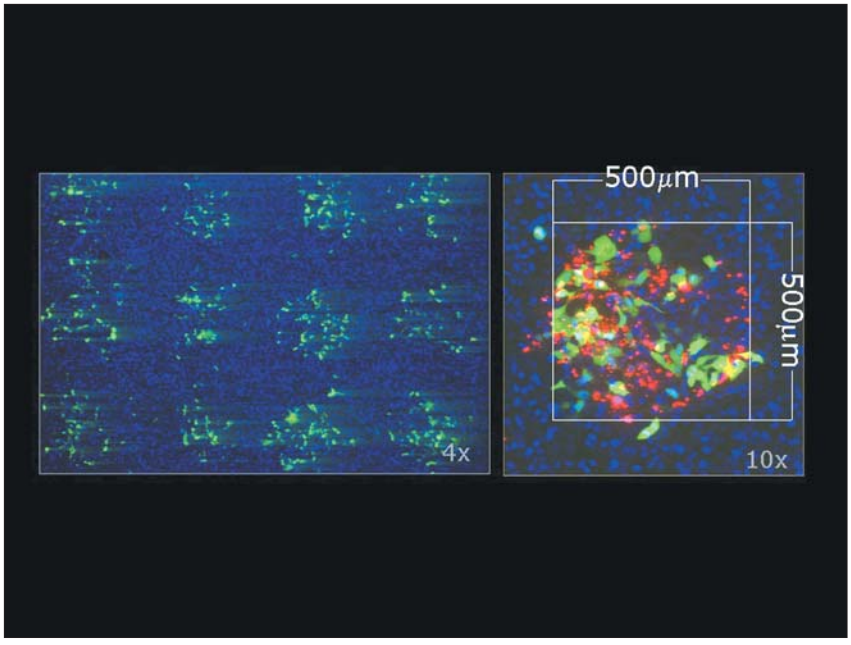


Figure 2: Left panel: 3 x 4 Reverse transfection microarray showing localized expression of Green Fluorescent Protein (Green) in HEK293 cells. Nuclei have been counter stained blue to show monolayer of cells over the array. Right panel: Close up of a spot from a reverse transfection array: Reverse transfected cells expressing green fluorescent protein (green), HEK cell nuclei counterstained with DAPI (blue) and carrier showing location of DNA-liposome complex spotted onto the array (red).

Pseudomonas aeruginosa genomics and pathogenesis

Group Leader
John Mattick

Research officers
Cynthia Whitchurch
Ben Huang

PhD students
Scott Beatson
Andrew Leech
Shannon Walsh

Masters student
Claire Wade

The research programs in the Pseudomonas aeruginosa group are concentrated on studying the genes required in the biogenesis and function of type IV fimbriae, control of twitching motility and virulence factors. The role of extracellular DNA secretion in biofilm formation of P. aeruginosa and the genes involved in this DNA production are also being investigated.

Characterisation of novel genes required for biogenesis and function of type IV fimbriae

Type IV fimbriae of *P. aeruginosa* are filaments up to several micrometres in length emanating from one pole of the bacterial cell.

One of the functions of type IV fimbriae is to mediate flagella-independent bacterial movement on a solid surface called twitching motility.

From characterisation of a high density transposon mutant library in our lab, over 40 genes have been identified to involve in the biogenesis, function and regulation of type IV fimbriae in *P. aeruginosa*.

Many of the characterised genes are homologous to genes involved in type II protein secretion and DNA uptake, revealing that each of these is an evolutionarily and structurally related subset of a supersystem which places multimeric complexes on the cell surface.

Additional characterisation of the remaining mutants in the library has found that two novel genes are required for the assembly and function of type IV fimbriae.

One is FimX, a DUF1/DUF2 containing protein, which connects environment signals to twitching motility. The other is TonB3, which is an iron uptake transporter, but is also involved in fimbriae transport from cytoplasma to cell surface.

We are also continuing to analyse and annotate the *P. aeruginosa* genome sequence which can be reviewed at http://pseudomonas.bit.uq.edu.au.

Characterisation of functional sites of ChpA in fimbrial biogenesis and virulence factor production

The expression and function of type IV fimbriae are regulated by a number of signal transduction systems, including pilS/R, fimS/algR, Vfr (virulence factor regulator) and a complex chemosensory system whose central component is chpA.

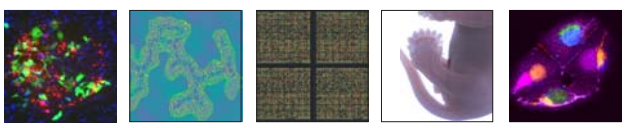
ChpA is the most sophisticated signal transduction protein yet described in nature, which has seven CheA-like phsphorylation domains and a CheY like regulator domain. The eight possible sites have been point-mutated to study functionally the role of the possible individual site in the type IV fimbrae biogenesis and virulence factor production.

Proteomic techniques such as 2D electrophoresis and Ciphergen technology are also being employed to characterise the signal transduction pathways controlling virulence factor regulation in *P. aeruginosa*.

The role of extracellular DNA secretion in biofilm formation

It has been estimated that biofilms are responsible for 65% of all infections. Bacteria in biofilms are more resistant to antibiotics resulting in recurring infections.

A recent finding in this lab has shown a novel role for extracellular DNA in biofilm formation. We are in the process of developing molecular genetic approaches such as transposon mutagesesis to identify the genes regulating secretion of the extracellular DNA and further characterising its role in biofilm formation.



Complex systems networks

Our research is focused upon understanding cells as complex systems. We use computational modelling and analysis to study the networks of biomolecular interactions which occur within cells, and the way in which the structure, function and dynamics of these networks are related.

Group Leader
Jennifer Hallinan

The reductionist approach to molecular biology has generated large amounts of detailed data about the structure and function of living cells at the level of DNA, RNA and proteins, and the interactions between these molecules.

Recent developments in automated sequencing, high-throughput protein-protein interaction detection and large-scale gene expression determination have increased the amount of data available to researchers exponentially over the last decade.

In parallel with the explosive growth in molecular data has been an increase in the computational power that is cheaply and easily available.

The combination of detailed data and powerful computers has led to the emergence of the new field of systems biology.

Systems biology attempts to understand and model cells, organisms and ecosystems as complex dynamic systems, with behaviour and emergent properties which cannot be predicted from an examination of the system components.

A particularly interesting area of complex systems research is the study of biological interaction networks.

Interactions between biomolecules within a cell take many forms, including protein-protein interactions and interactions between enzymes and their substrates.

The entire system of interactions forms a discrete network within the cell, which can be reconstructed computationally, enabling researchers to investigate the properties and behaviour of the network quickly, easily and repeatedly.

Our research focuses upon characterizing the structure, function and dynamics of intracellular interaction networks, using a combination of computational modelling and real biological data.

We model networks as graphs. Each interacting individual in the system, such as a protein or other biomolecule, becomes a vertex of the graph, and the interactions are edges between the vertices.

Edges may be directed or undirected, weighted or unweighted, depending upon the system being modelled.

The pattern of connectivity in the network, whether it is ordered, random, or somewhere in between, has been shown to affect its behaviour.

It has recently been shown that many naturally occurring, large, complex networks are characterized by a pattern of connectivity between nodes in which the probability $P(k)$ of a node having a particular number of connections, k, follows a power-law, $P(k) \sim k^{-g}$, often over many orders of magnitude.

Such networks are referred to as *scale-free* or *small-world* networks.

A major problem with extrapolating theoretical and computational results about network behaviour to real biological systems is caused, ironically, by lack of biological data.

Although large amounts of data have been collected about various aspects of cellular structure and functioning, the data collection effort has not been targeted towards use in the computational modeling of complex systems.

Consequently, the type of data which could be used to construct biologically plausible network models – for example, data on protein-protein interactions – is incomplete for most organisms, and the data which does exist are concentrated on specific molecules and biochemical pathways suspected to be of biological and/or medical importance.

We are currently investigating what proportion of an entire network must be available in order for useful inferences to be drawn.

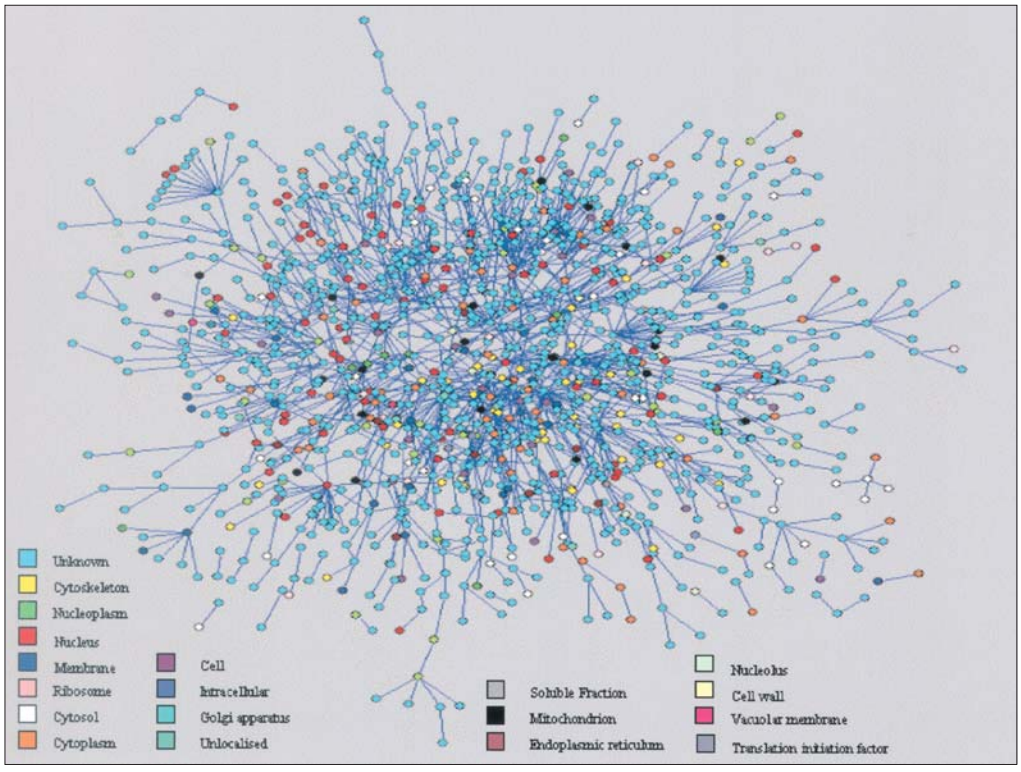
Biological networks tend to have a modular organization, with clusters of genes or gene products forming relatively highly interconnected modules, and fewer connections between modules.

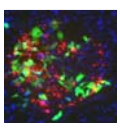
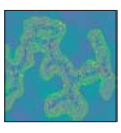
Such modularity arises in the course of evolution, and probably has significant implications for the functional dynamics of the network. Particularly for networks organized as a collection of such functional modules, it is possible that individual modules could be studied more-or-less in isolation.

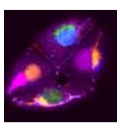
This is an attractive idea, since biological data for a small number of complete modules may be much easier to assemble than data for an entire network.

We are currently developing algorithms for the objective detection of modules within complex networks

The illustration shows the protein-protein interaction network of the yeast Saccharomyces cerveisiae. The subcellular location of the proteins is colour coded.



Computational discovery in cellular biology

A major advance in the biological sciences over the last decade is the sequencing of the genomes from different organisms including the human genome. "Database mining" allows for the prediction of the functional properties of a new protein based on the information contained within these genomes. The goal of my research is to extract this information to open up new avenues of scientific exploration predominantly within cell biology.

Group Leader
Rohan Teasdale

Research assistants
Cameron Flegg
Elaine Thomas

Honours students
Markus Kerr
Jenny Bennets
Calle Wibom

PhD student
Kevin Miranda

Post-doc student
Zheng Yuan

Bioinformatic discovery of new genes, proteins and pathways

The challenge today for medical scientists is to utilise the mass of nucleotide sequence to expand their knowledge of the biological processes they are currently researching.

I have over five years experience at "mining" this wealth of information for novel sequences using various bioinformatic approaches.

These *in silico* observations have catalysed numerous new avenues of scientific exploration for researchers within my laboratory or my collaborators.

Recent examples of this include:

- defining the *Leishmania* major GPI biosynthesis pathway;
- analysing the mouse and human genomes for novel members of the SOX, SLIT, and SNX protein families;
- prediction of the function of novel genes isolated in subtracted cDNA libraries enriched for developmentally regulated mRNAs; and
- prediction of the function of novel genes identified using microarray technology.

Computational prediction of Golgi localised proteins

The known functions of the Golgi complex include the sorting, packaging, post-translational modification and transport of secretory proteins, membrane proteins and lipids.

Other functions still remain elusive to cell biologists.

With the goal of identifying novel Golgi proteins, a computational prediction method was developed that can distinguish the transmembrane region of a Golgi resident enzyme from that of a protein which transiently moves through the Golgi.

Subcellular localisation signals

A major issue in cell biology today is how 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-resident proteins allows passage through them. Individual proteins have "signals" that are responsible for their intracellular localisation.

My research group is 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. Recent examples of this include:

- basolateral targeting of E-cadherin in polarised epithelial cells;
- identification of a Golgi Localisation Domain (GLD) on a novel family of peripheral membrane proteins; and
- identification of an endosomal targeting domain, termed SNX-PX.

Characterisation of novel human proteins involved in the endosome to Golgi membrane trafficking pathway: 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 sub-compartments 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.

We are currently characterising a number of such proteins using a range of cellular and biochemical techniques.

Recently, we defined the protein composition of human retromer complex and showed it was associated with endosomal membrane.

The characterisation of this protein complex represents the major focus of the cellular biology aspect of my research group.

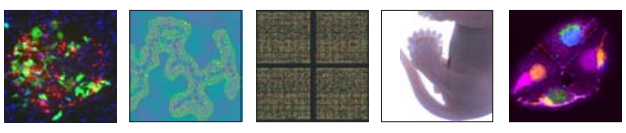
Identification of proteins involved in the membrane trafficking in parasites

The Trypanosomatidae comprise a large group of parasitic protozoa, some of which cause important diseases in humans. These include *Trypanosoma brucei* (the causative agent of African sleeping sickness), *T. cruzi* (the causative agent of Chagas disease in Central and South America) and *Leishmania*.

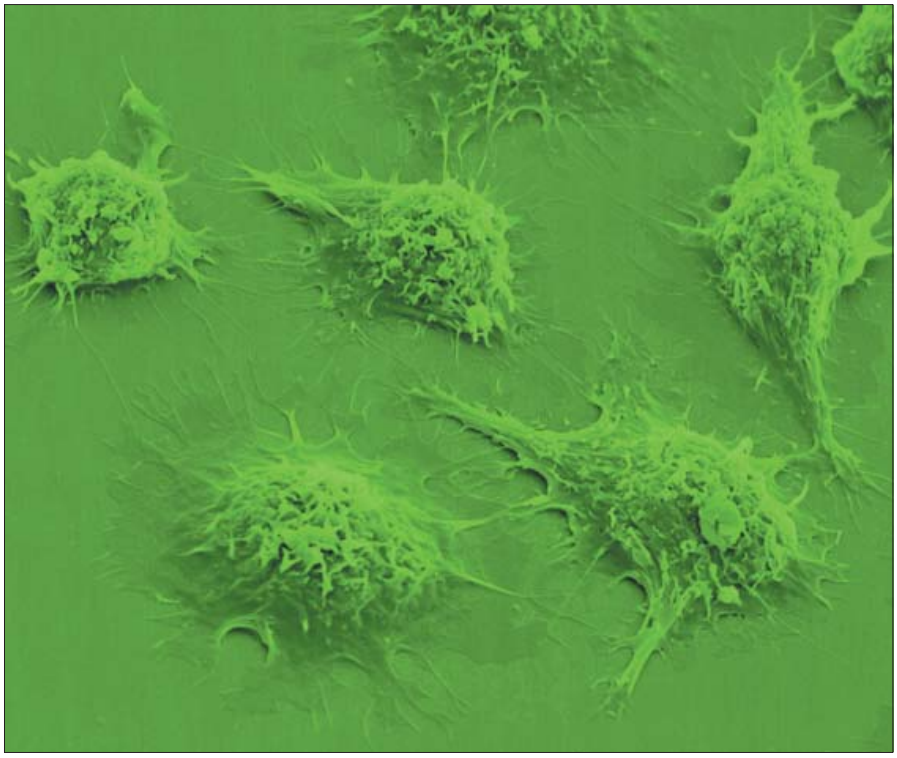
Parasite survival requires the surface expression of specific molecules that form protective surface coats, mediate specific host-parasite interactions and allow the parasite to take up essential nutrients. The biosynthesis, processing and surface transport of these molecules that occurs within the intracellular organelles of the parasite secretory pathway is poorly understood.

A recent effort to sequence the genomes of these parasites provides us with an opportunity to identify parasite homologues of proteins that function in membrane trafficking.

A recent collaboration between my laboratory and Dr Malcolm McConville (University of Melbourne) has been established to characterise these proteins.



Cellular and Developmental Biology



In order to understand the workings of the cell we have a need to bring together genetics and genomics with an understanding of how cells interact with each other to form an organism (differentiation and development) along with an insight into how the cell responds to its environment (cell biology). The research of this Division covers that spectrum and forms a powerful continuum of approaches, model systems and key scientific questions. Our programs in genetics focus on the use of genetic approaches to identify genes involved in cystic fibrosis, basal cell carcinoma, sex determination, angiogenesis and melanoma. Studies of differentiation and development have focussed on the development of the central nervous system, cranio-facial structures, muscle, kidney and gonads. The programs also focus on understanding molecular signalling within and between cells, and in particular the targeting and trafficking of proteins to specific cellular compartments, including investigating novel subcompartments and their roles in transducing signals such as the RAS pathway. As the number of mammalian genomes which are sequenced begins to climb the challenge now is how to use such information to derive function. In order to do so an integrated program of research bringing together genetics, cell biology, differentiation and development will provide an outstanding platform upon which to generate significant insights.

Macrophages and osteoclasts

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Macrophages are large white blood cells that play a central role in host defense, recognising and engulfing potential pathogens and also removing damaged tissue and dying cells in normal development and wounds. Osteoclasts, a macrophage related cell type, are the major cell type able to decalcify bone. Improved understanding of macrophage and osteoclast function could be used not only to boost their normal functions but also to limit the pathology caused by these cells when their destructive capacity is unleashed inappropriately in inflammatory and infectious diseases.

Comprehensive Gene Expression Profiling

In a collaborative program involving our laboratory, the RIKEN Genome Sciences Center in Japan, the Institute for Systems Biology in Seattle, and the ARC Special Research Centre for Functional and Applied Genomics, we have assembled a very large set of mouse macrophage-expressed genes for comprehensive gene expression profiling. The set of genes expressed in macrophage populations is complex and is influenced by many different variables. Our studies have also revealed that the genotype of the mouse also profoundly alters the gene expression profile under any particular condition, probably reflecting the divergence in innate immunity between individuals (see Figure 1).

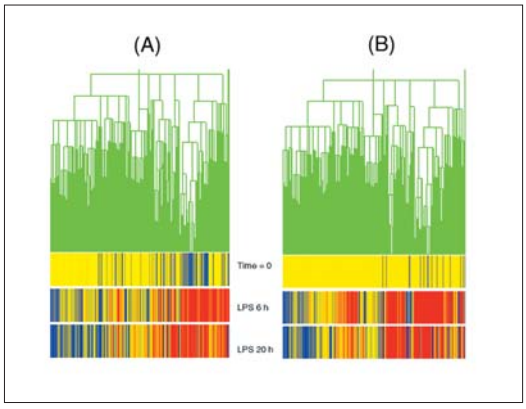

Figure 1. Macrophage gene trees from (A) BALB/cJ and (B) SJL/J strain macrophages treated with Interferon gamma and LPS

Computational methods are used to identify sets of genes that always track together; so-called clusters that contain genes that act in the same pathway, or contribute to the same overall biological response. Macrophage/osteoclast specific genes, or those that are induced in an informative manner, many of which have no known function, are selected for further study as part of a structural genomics program in collaboration with Associate Professor Jenny Martin and Associate Professor Bostjan Kobe.

Transcription control in the macrophage lineage

We have worked on delineating the characteristics of macrophage-specific promoters that direct transcription solely in the macrophage lineage. Our major focus has been on *c-fms*, which encodes the receptor for macrophage colony-stimulating factor (CSF-1), the major growth factor for cells of the mononuclear phagocyte lineage.

We have identified the minimal elements, the proximal promoter and a highly-conserved intronic enhancer, required to direct expression of a transgene specifically to the macrophage lineage. Using this information, we have produced mice which express green fluorescent protein (GFP) in all cells of the mononuclear phagocyte lineage (Figure 2).

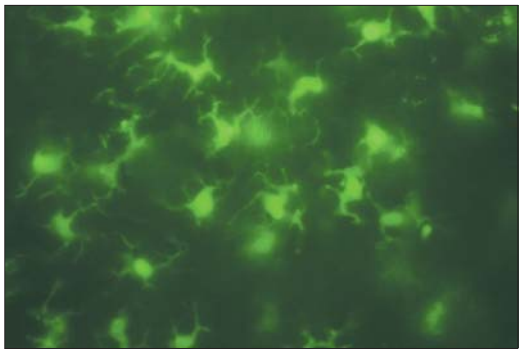

Figure 2. Macrophages expressing green fluorescent protein (GFP) in the skin of a c-fms-EGFP transgenic mouse

In collaboration with Dr Connie Bonifer in Leeds, and Dr Mike Ostrowski in Columbus, Ohio we have identified a series of candidate regulators that interact with PU.1, a macrophage specific transcription factor, such as the leukaemia-associated AML1 transcription factor complex, and members of the microphthalmia transcription factor family.

Differentiation of osteoclasts

Osteoclasts derive from a progenitor shared with other mononuclear phagocytes, and share the major growth factor, CSF-1 (Figure 3).

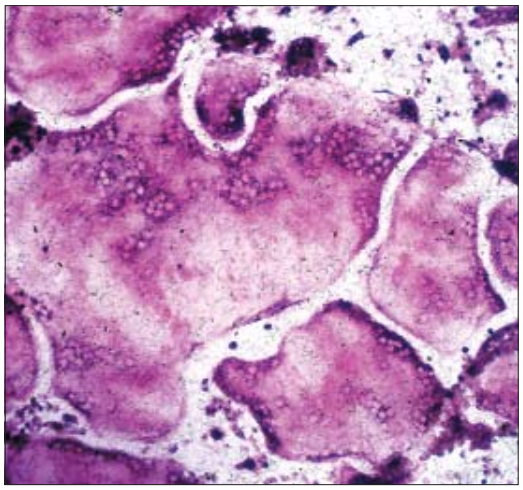

Figure 3. Large multinucleated osteoclasts stained for tartrate-resistant acid phosphatase (TRAP) expression

We have carried out detailed analysis of the promoter of the osteoclast marker gene, tartrate-resistant acid phosphatase (TRAP), as a model for understanding transcription control during osteoclast-macrophage divergence.

Amongst the transcription factors that interact with the TRAP promoter, the microphthalmia transcription factor (MITF) interacts with the macrophage-specific PU.1 factor.

In collaboration with Mike Ostrowski at Ohio State, we are searching for other targets of MITF expressed in osteoclasts.

Detailed gene expression profiling using cDNA clone sets derived from purified osteoclasts is being used to identify candidate regulators and genes restricted to osteoclasts.

These studies have been expedited by the recent discovery of cell line systems in which phenotypic transformation towards an osteoclast-like phenotype can be induced.

This system will also allow further characterisation of the role of members of the nuclear hormone receptor superfamily in osteoclast differentiation.

Response of macrophages to CpG DNA and LPS

Bacterial cell wall products such as lipopolysaccharide (LPS), activate macrophages to become cytotoxic to the pathogen and to secrete a range of cytokines which recruit and activate other immune cells.

Microbial DNA is another product capable of stimulating the immune system.

The ability of the host to discriminate foreign from self DNA relies on the presence of unmethylated CpG motifs in bacterial but not mammalian DNA.

Our ongoing studies address many aspects of the response of macrophages to bacterial DNA including identification of proteins that interact to form the recognition complex for CpG DNA. We have also examined why self DNA does not activate immune cells.

The lack of activity of self DNA appears to result from a combination of CpG suppression, methylation of CpG motifs that are present, and the presence of inhibitory motifs within self DNA that suppress responses to activating sequences.

We are defining the differences between LPS and CpG DNA that may account for the differential toxicities of these two stimuli.

Analysis of global gene expression profiles in response to LPS and CpG DNA stimulation has identified genes that are both LPS- and CpG DNA-specific in macrophages.

In addition we have demonstrated that CSF-1 enhances the LPS-induced inflammatory response but suppresses the same response to CpG DNA. Thus CSF-1 may contribute to the differential toxicities of LPS and CpG DNA *in vivo*.

Molecular transport

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Following a meal, sugar enters the body and sends a message to the pancreas causing the secretion of insulin, which then travels to fat and muscle cells instructing them to store the sugar for later use. Disruption of this process leads to major diseases such as diabetes and obesity. These types of diseases are growing at an alarming rate in Australia and our research will help curb this increase.

Our group is primarily interested in the complex processes involved in stimulation of glucose transport in muscle and fat cells.

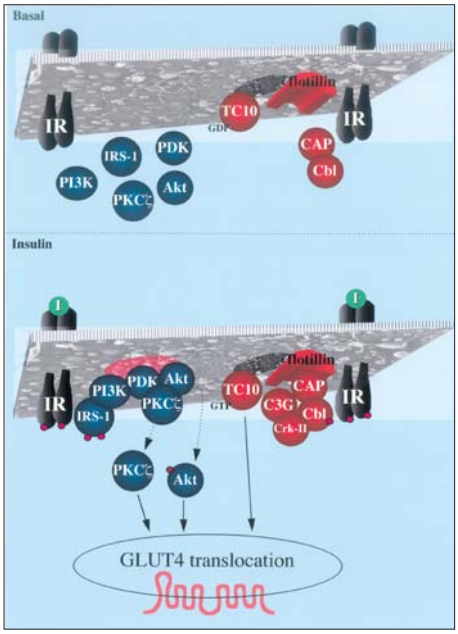
The major glucose transporter in muscle and fat cells is GLUT4, which is stored inside the cell in small vesicles, or GSVs, in the absence of insulin.

The presence of insulin stimulates the movement of GSVs to the plasma membrane (PM).

We have attempted to define the intracellular trafficking routes employed by GLUT4 that keep it inside the cell and allow it to move to the PM when insulin is present.

In the absence of insulin GLUT4 carefully negotiates its way between multiple intracellular compartments including endosomes (EE and RE in Figure 1) as well as the trans Golgi (TGN).

Figure 1



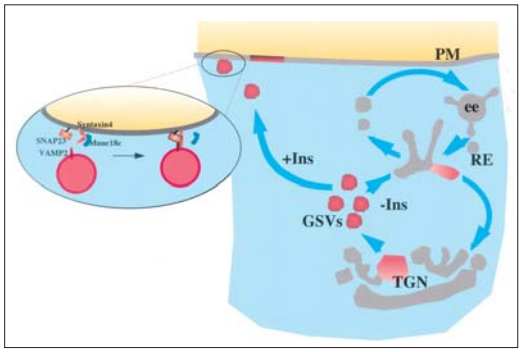
This cycle serves to prevent GLUT4 from moving up to the PM. Insulin somehow overrides this intracellular routing, pushing GLUT4 into a circuit that takes it to the PM.

Our group has identified a series of molecules known as SNAREs, (depicted in the diagram) that usher the intracellular GLUT4 vesicles into the surface membrane allowing them to fuse.

In this way GLUT4 now becomes incorporated into the surface membrane where it can mediate its transport function.

Another area we are interested in is the signal transduction process (Figure 2).

Figure 2 (Bryant et. al.)



There are two major pathways that are triggered when insulin binds to its receptor on the plasma membrane. One involves the serine threonine kinase Akt and the other involves a dimeric complex containing Cbl/CAP.

We are focussing our efforts on trying to establish what is downstream of these molecules in the hope that we will find other molecules that specifically regulate some of the trafficking steps displayed in Figure 1.

Molecular genetics of organ development

Work in my laboratory is aimed at isolating genes involved in cell differentiation and morphogenesis, and studying their expression, regulation and function in the mammalian embryo. We are particularly interested in the foetal period when the major organs of the body are established. These studies will reveal how the complexity of embryonic development is regulated at the molecular genetic level, as well as how genetic controls go awry in disease states.

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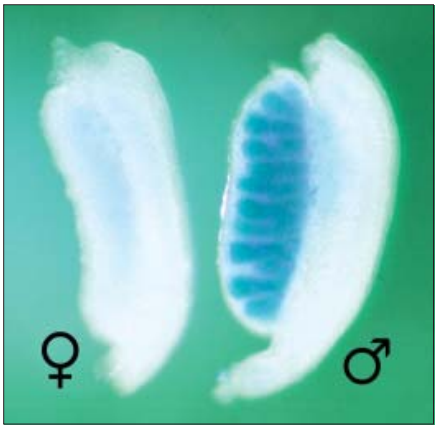
Molecular genetics of sex determination

A major area of interest is the genetic control of mammalian sex determination. Sex determination is regarded as a paradigm for the study of how genes control mammalian development, involving a pathway of gene regulation under the control of a "switch" gene on the Y chromosome, *Sry*.



Our group is continuing to study the molecular biology of *Sry* in order to understand its role in male sex determination and the defects that can result in sex reversal.

We discovered a gene, *Sox9*, which plays a critical role in male sex determination and acts downstream of *Sry*; current studies are aimed at understanding the molecular and cellular role of *Sox9* in this pathway.

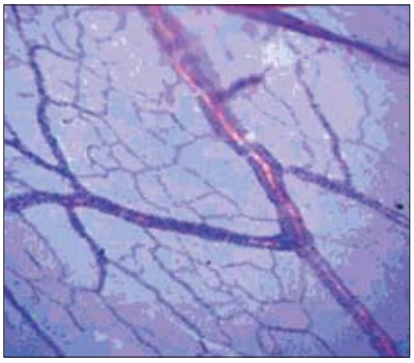
We are also searching for other genes downstream in the sex-determining pathway, using expression screening approaches such as microarrays.

Several novel genes have been identified, and we are developing assays to study the functions of these genes in the regulation of gonadal development.

Molecular genetics of vascular development

In collaboration with George Muscat's group, 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* in vascular development, and exploring the possibility that angiogenesis can be modulated – for example to slow the growth of tumours, or promote wound healing - by enhancing or suppressing *Sox18* activity.



Sox gene function in mammalian development

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 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 of these genes, how they evolved, how they came to assume different roles in the embryo, and how the different SOX proteins achieve their specific functions biochemically.

Kidney development and disease

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The kidney is a complex but vital organ. It not only filters the blood to produce urine but also regulates blood pressure, red blood cell production and produces various hormones and growth factors, including vitamin D. If your kidneys fail, current treatment involves long term dialysis or organ transplantation, both of which have considerable side effects. The projects under way in my laboratory focus on understanding how the kidney arises in the first place and what goes wrong to give you renal disease.

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.

Annually, 1500 patients reach end-stage renal failure (ESRF); 3 times the number of renal transplant operations performed.

Dialysis is expensive (~$25-45,000/yr/patient) and only substitutes for the filtration function of the kidney.

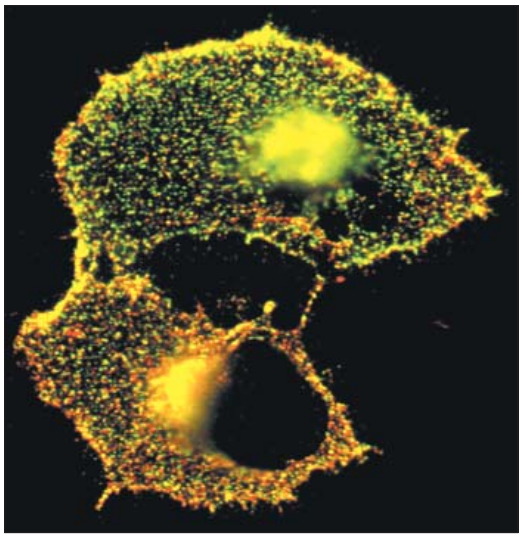
The most common cause of ESRF is glomerulonephritis, however the current steady rise in ESRF rates is primarily due to an increase in the number of people with Type II diabetes.

One in four Australians will get Type II diabetes during their life and this will ultimately result in nephropathy.

In addition, there is growing evidence that persons with a lower number of nephrons per kidney, which is determined before birth, are more likely to suffer CRF.

Hence, a greater understanding of the processes involved in normal kidney development and CRF are critical to the development of new therapeutic strategies.

This laboratory is focussing on the isolation of novel and important genes involved in kidney development. To do this we are using the genomic technique of expression profiling where glass



microarray chips are used to simultaneously analyse the overall expression patterns of tissues and identify those genes that change during development.

Novel genes isolated from such screens are then assessed for their importance in kidney development using the organ culture assays we have now established.

These organ cultures allow us to screen novel proteins for their ability to direct or hinder normal branching of the ureteric tree within the kidney or affect the formation of new nephrons.

There are several key gene projects which have grown out of this screen. We have isolated several members of the Slit gene family from developing kidney.

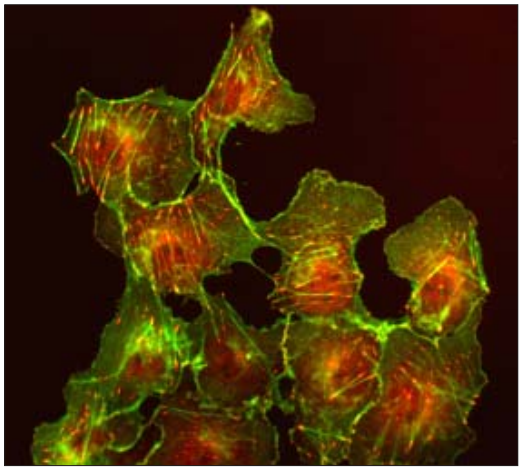
Previously known to be important in development of the central nervous system in everything from flies to mammals, we have shown that these genes also play a role in mesoderm development and are all expressed in specific areas of the kidney.

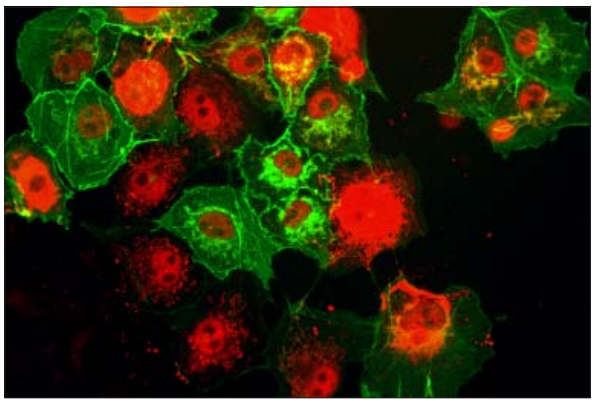
We have also isolated a completely novel gene, *Crim1*, from the developing kidney which encodes a large membrane protein with an ability to interact with members of the TGFbeta growth factor superfamily.

We are now investigating the ability of this protein to control kidney development and also lens, spinal cord, brain and tooth.

We also focus on the childhood renal tumour, nephroblastoma or Wilms' tumour. This is one of the most common solid tumours of childhood.

Like many cancers, the inappropriate overgrowth of cells in the tumour is due to a loss of genes whose role in normal development is to direct differentation rather than cell growth. One of the critical genes mutated in Wilms' tumour is the *WT1* gene.





This laboratory has long worked on the analysis of the role of *WT1* mutation in Wilms' tumour and several other conditions.

We have shown that while mutated in sporadic Wilms' tumours, *WT1* is not mutated in all such tumours.

While mutated in renal disease, normal function of *WT1* is critical for both kidney development and the ongoing function of the kidney after birth. Hence, *WT1* is also mutated in several rare renal failure conditions, including Denys Drash syndrome, WAGR syndrome and Frasier syndrome.

We have been involved in understanding how the timing and type of mutation results in these different conditions.

The *WT1* gene encodes many related proteins which must interact to regulate other genes within the cell.

We are investigating how this regulatory protein works to create a kidney and keep it functioning by examining what genes it regulates, what proteins and nucleic acids it interacts with and to what end.

Muscle and nuclear hormone receptors

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My research interests focus on the regulation of mammalian differentiation by protein-protein interactions involving nuclear hormone receptors and cofactors, and tissue specific transcription factors. These factors mediate the link between genome and phenome, by operating at the nexus of pathways that control tissue specific transcription, cell signalling and cellular differentiation. Specifically, we seek to understand the hierarchical genetic control of tissue specific gene expression and signal transduction during muscle differentiation, and disease.

One asks why study muscle differentiation at the molecular level, in particular the transcriptional and mechanistic regulation by nuclear hormone receptors?

Nuclear hormone receptors (NRs) and the associated cofactors function as ligand activated transcription factors that regulate gene expression involved in reproduction, development and metabolism.

NRs function as the conduit between physiology and gene expression. Consequently, they regulate cell fate, spatio-temporal gene expression and differentiation during development.

Moreover, NRs and cofactors, when misregulated and/or mutated result in the onset of disease, which emphasizes the need for achieving a high resolution view of their function in tissue differentiation.

Furthermore, the importance of NRs in human physiology is underscored by the pharmacopeoia that has been created to combat disorders associated with dysfunctional hormone signalling.

Twenty of the 100 top selling drugs in the USA are directed at nuclear receptor targets and have annual sales in excess of $5 billion. NRs affect every field of medicine, including reproduction, inflammation, asthma, cancer, diabetes, and cardiovascular disease.

Secondly, skeletal muscle is a major mass peripheral tissue which accounts for ~40% of total body weight and is a primary site of glucose metabolism and fatty acid oxidation. Consequently, it plays a very significant role in insulin sensitivity and the blood lipid profile. The heightened occurrence of cardiovascular disease, obesity and diabetes is associated with lipid disorders.

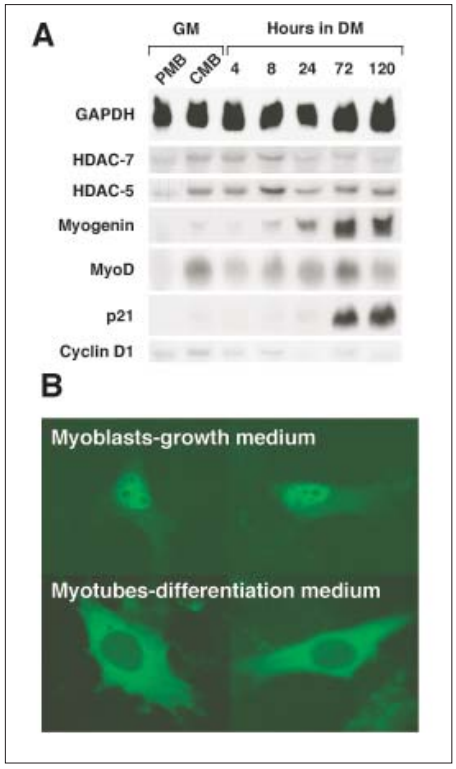

Figure 1. HDAC7 is constitutively expressed and shuttles into the cytoplasm during cell cycle withdrawal and myoblast differentiation

Moreover, age and wound-induced muscle wasting, cachexia, etc reflect a malfunction in the balance between regeneration and decay.

The impact of muscle wasting on therapeutic tolerance (e.g. 'statin' treatment of hypercholesterolemia patients), morbidity and mortality in patients with AIDS, cancer and chronic disease further underscores the importance of this tissue. Accordingly, our work explores the regulatory crosstalk between the hierarchical transcription factors (e.g. myoD, myogenin & Mef2) and nuclear receptor cofactors.

Specifically, we study how the recruitment of nuclear receptor cofactors that control histone acetylation, deacetylation, methylation and chromatin remodelling orchestrates the growth and differentiation of muscle.

We have demonstrated how nuclear receptor cofactors that mediate acetylation and methylation of specific proteins regulate the transcriptional control of skeletal myogenesis and contractile protein specific transcription.

This study demonstrated that protein-protein interactions involving nuclear receptor cofactors, and muscle specific regulators that modify histones operate at the nexus of pathways that control tissue specific gene expression and hormone signalling.

Secondly, we have also demonstrated how the class I and II Histone deacetylases (targets of anti-cancer drugs) suppress the activity of MyoD and MEF2 in myoblasts, and provided a potential explanation for the paradoxical findings that these transcription factors are present in undifferentiated muscle (myoblasts).

Thirdly, our studies have elucidated the molecular basis of transcriptional regulation by the 'orphan' nuclear hormone receptors in the context of muscle development and differentiation.

Current projects include:

- Regulation of mammalian differentiation by lysine and arginine methyltransferases.
- Molecular mechanism and structure/function aspects of orphan nuclear hormone receptor action and transcription (e.g. ROR, Rev-erb, Nur77, etc).
- Functional analysis of the oxy-cholesterol dependent liver X receptors (LXR a/b), and the fatty acid regulated Peroxisome Proliferator Activated Receptors (PPAR a, g and d) in skeletal muscle. LXR and PPAR are the major regulators of lipid and cholesterol metabolism.
- Sox 18 and cardiovascular development and differentiation.

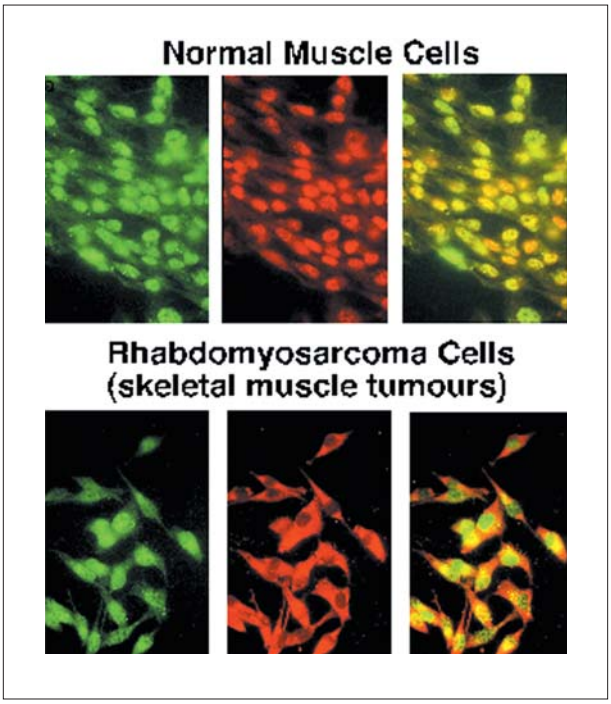

Figure 2: Defective sub-cellular localisation and cytoplasmic accumlation of MEF2 in rhabdomyosarcoma cells. Immunofluorescent staining with MEF2-red and SRC2-green images highlighting aberrant cytoplasmic MEF2 expression in Rhabdomyosarcoma cells.

Cell biology of the plasma membrane

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Our research interests focus on the organisation, dynamics, and functions of the plasma membrane. These studies have shown that the plasma membrane is organised into microdomains with essential functions in signal transduction and lipid regulation. We are studying the function of domains termed caveolae and their exploitation by viruses.

Caveolae, small pits in the surface of many mammalian cell types, have been implicated in regulation of cell proliferation, endocytosis, and lipid transport. In addition, caveolae and caveolins, the major proteins of caveolae, have been implicated in a number of disease states including tumour formation, Alzheimer's disease, and Muscular Dystrophy. Caveolins are involved in regulation of specific signal transduction pathways. It is a fatty acid and cholesterol-binding protein which has been implicated in regulation of cellular lipids. All cells maintain a delicate balance of cholesterol, through regulation of influx, efflux, synthesis, and esterification, which is crucial to the correct functioning of the cell. Caveolins have been suggested to be vital components of cholesterol regulation with a role in cholesterol efflux. Our studies have shown that cholesterol is involved in organising plasma membrane signalling domains termed lipid raft domains, and that this process may be regulated by caveolins. Our studies are aimed at understanding the role of caveolae in mammalian cells. We have used a number of tools to dissect caveolae function including dominant negative caveolin mutants, caveolin-1 knockout mice, and novel Ras assay systems (in collaboration with John Hancock). In addition, we have utilised lower eukaryotic systems, such as Zebrafish (in collaboration with Brian Key, School of Biomedical Sciences), to understand the role of caveolae and caveolins in development and in normal cellular function. *In vitro* studies show that caveolin mutants perturb very specific cholesterol-dependent signalling pathways and disrupt lipid metabolism. Our *in vivo* studies have shown a role for caveolins in evolutionarily conserved developmental pathways.

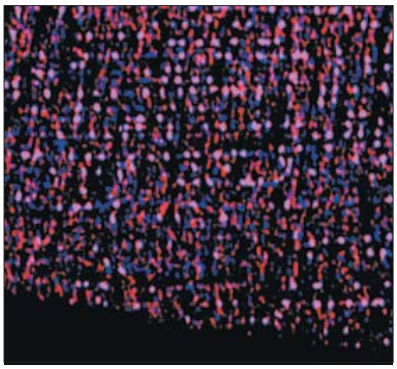

Figure 2. Isolated mature muscle fibre treated to remove surface cholesterol and labelled in red and blue.

Our laboratory is particularly interested in the role of a muscle-specific caveolin family member, termed caveolin-3, which we discovered in 1995. Mutations in caveolin-3 cause a number of different muscle diseases including rare forms of Limb Girdle Muscular Dystrophy. We are presently analysing caveolin-3-interacting proteins and a novel compartment with which caveolin-3 associates in differentiating muscle cells. We are also studying caveolin-3 point mutations occurring in muscular dystrophy. We recently showed one particular dystrophy-associated mutant of caveolin-3 inhibits signalling through lipid raft domains and this could underly the disease condition. Caveolae have also been exploited by pathogenic agents. We have shown that Simian Virus 40, SV40, a non-enveloped oncogenic virus, exploits caveolae to enter mammalian cells. SV40 binding activates specific signalling pathways to recruit cytoplasmic proteins and cause caveolae budding. SV40 is internalised and then enters an apparently novel trafficking pathway which culminates in virus reaching the endoplasmic reticulum, the cytosol, and finally the nucleus where replication occurs.

By a combination of electron microscopy, light microscopy and microinjection of living cells, we have identified some of the compartments and molecules involved in this unusual trafficking pathway. Understanding this pathway could lead to novel strategies for drug delivery or gene therapy.

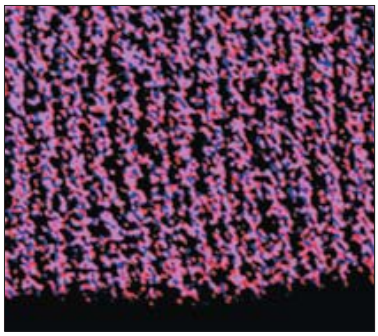

Figure 1. An isolated mature muscle fibre labeled with antibodies to two forms of the caveolar protein, caveolin-3. The different forms of the protein are labelled in red and blue. The image shows the organised distribution of caveolae over the fibre surface.

Molecular genetics and cellular biology of keratinocytes

The skin and in particular, the epidermis provides a barrier that protects us from harmful radiation, environmental toxins, and infection as well as preventing desiccation. We are studying the contribution of individual genes and proteins to the maintenance of healthy skin. An understanding of the molecular processes involved will permit a more targeted approach to the treatment of inherited and acquired skin diseases such as eczema, psoriasis and cancer.

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A major focus of our group is identifying the signals and messages involved in specifying the formation of the integument. We are studying several genes and their protein products including, *Smoothened, Frizzled-3 and Gli1*.

Analyis of the *Gli1* oncogene revealed alternatively-spliced exons that generate 5' leader sequences with differing translational capacities.

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.

A primary function of the epidermis is to protect us from environmental assault as well as preventing desiccation.

A major keratinocyte protein involved in both these functions is profilaggrin. This large (>600kDa), abundant protein is expressed late in epidermal differentiation and is thought to regulate skin water content, have innate anti-microbial activity, modulate the skin's response to UV damage and act as a calcium sink.

We have cloned the mouse profilaggrin gene as well as related genes in both human and mouse that form a large protein family which has not been previously described.

Keratinocytes are characterised by their extensive arrays of keratin intermediate filaments which form the cytoskeleton of these cells.

Intermediate filament proteins consist of a highly conserved central alpha-helical domain flanked by non-helical domains of varying size and composition.

While the function of the helical domain has been known for several years, the role of the end domains has yet to be fully elucidated.

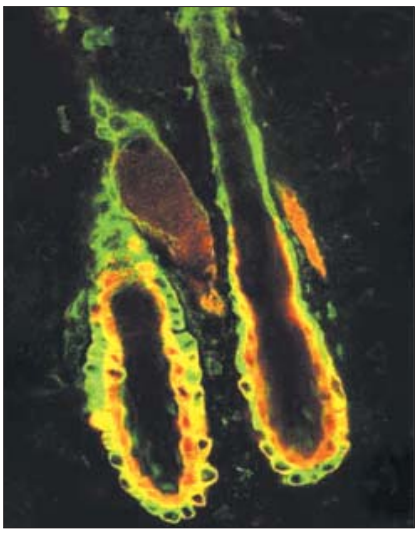
We used fluorescent tags to determine that a subset of these end domains contain motifs that specify cytoplasmic localization probably through interactions with intermediate filaments near the nucleus and microfilaments at the cell periphery.

In a related project we have investigated the motor protein complement of keratinocytes and determined that kinesin is not involved in transporting intermediate filaments.

KRT6a has an unusual expression characteristic for an intermediate filament gene. The *KRT6a* gene encodes keratin K6a, which is normally expressed in the companion layer of the hair follicle but is induced in outer root sheath and epidermal keratinocytes in response to wounding.

Because of the utility of an inducible promoter for applications such as gene therapy we have examined the promoter of the mouse *KRT6a* gene in transgenic mice.

We found that deletions into the promoter resulted in constitutive expression of the transgene but did not alter cell type specificity. We have localized the cis-elements that mediate inducibilty to region 1.5kb upstream of the transcription initiation site.



Protein trafficking

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Our research is on the sorting, trafficking and secretion of proteins in epithelial cells and macrophages. This work provides insights into how polarized epithelial cells, in normal tissues and in cancers, deliver proteins to their different membrane domains. In macrophages we are identifying the molecules that regulate the secretion of inflammatory cytokines.

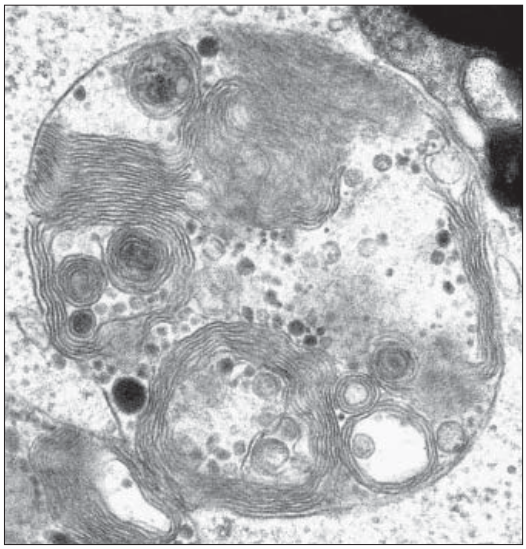
E-cadherin is a membrane protein on the basolateral surface of epithelial cells with essential roles in cell polarity and cell-cell adhesion. It is also a powerful tumour suppressor and its loss or dysfunction is an early event in many metastatic tumours.

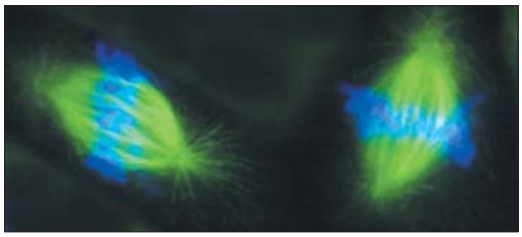
Our studies aim to show how E-cadherin is sorted and delivered to and from the cell surface in kidney epithelial cells and in tumour cells.

We have shown (in collaboration with Alpha Yap), that surface E-cadherin is endocytosed and recycled via a novel pathway.

Trafficking of E-cadherin between the surface and endosomes in this recycling pathway is regulated, in both directions, by protein kinases.

This work has major implications for how cell-cell adhesion may be regulated in development, in mature epithelial tissues and in cancer.





We have also examined how sorting in the trans-Golgi network of epithelial cells allows E-cadherin to be trafficked in a polarized fashion.

In collaboration with Rohan Teasdale's group, we have identified the targeting signal in E-cadherin that orchestrates its sorting and basolateral membrane delivery.

This is the first, conserved targeting signal formally identified in cadherins and our findings foretell how cadherins in many cell types are sorted and trafficked.

There are also implications for how other protein cadherins interact with the E-cadherin cytoplasmic tail and this is currently being investigated.

We are interested in how transport vesicles bud off Golgi membranes to transport membrane and soluble proteins to the cell surface.

This process has been reconstituted in an *in vitro* assay and from this we have identified different classes of transport vesicles and we have examined the roles of specific proteins in regulating vesicle budding.

This work also makes use of real time imaging to follow fluorescently-labelled carrier vesicles in live cells.

Most recently we have shown that regulators of G protein signaling (RGS) family proteins have an essential role in regulating vesicle budding.

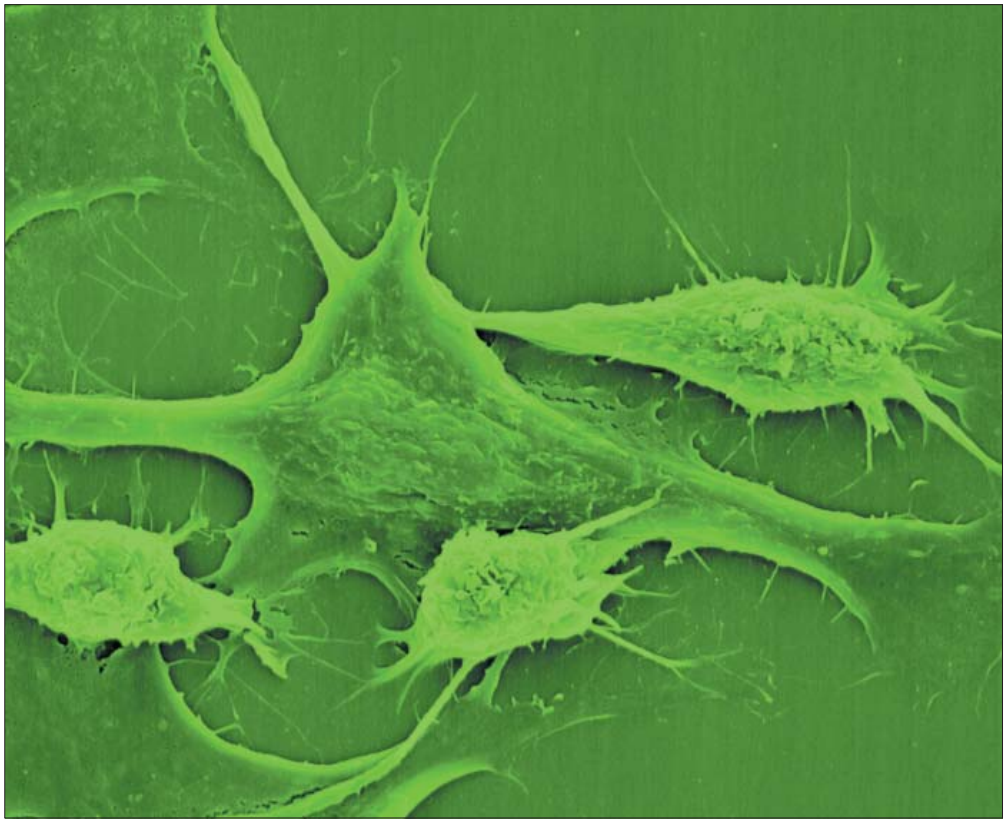
This work contributes to our understanding of basic cell processes and also provides means to experimentally or therapeutically manipulate secretion in cells. Macrophages are professional secretory cells with finely-tuned but little-studied secretory pathways.

Our work has focussed on the mechanisms for secretion of tumour necrosis factor (TNFa) in immune-activated macrophages.

We have developed a detailed understanding of the intracellular trafficking of TNFa.

We have employed novel approaches and assays to identify immune-responsive trafficking proteins that regulate the post-Golgi transport of TNFa.

The regulatory molecules we are identifying are potential drug targets for the future development of anti-TNF therapies.



Molecular genetics of pigmentation

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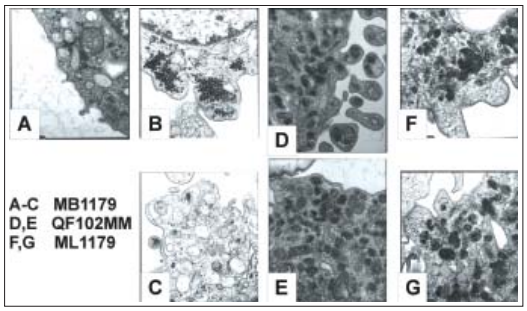
Melanocytes produce the melanin pigments responsible for skin, hair and eye colour. Darker forms of melanin protect the skin from solar radiation exposure, however melanocytes are also the cell-type from which malignant melanoma can originate. We are studying the human pigmentation system to understand the genetic basis of cellular differentiation, tissue-specific gene expression and cellular transformation induced by solar UV light.

MC1R alleles determine skin phototype and skin cancer risk

Pigmentary traits such as red hair, fair skin, lack of tanning ability, and propensity to freckle have been identified as genetic risk factors for both melanoma and non-melanocytic skin cancers in high UV conditions. The human melanocortin-1 receptor (MC1R) is a key determinant of the pigmentation process and can account in large part for the diverse range of variation in human pigmentation phenotypes and skin phototypes. We have examined MC1R variant allele frequencies in the general population and a collection of adolescent dizygotic and monozygotic twins. MC1R allele association studies have also been performed using several case-control studies of sporadic melanoma, Basal Cell Carcinoma, Squamous Cell Carcinoma, and familial melanoma kindreds collected within Australia. These studies have shown that three alleles Arg151Cys, Arg160Trp and Asp294His were associated with increased risk of all forms of skin cancer and with penetrance and age of onset of CDKN2A mutation carriers in familial melanoma, with a significant heterozygote carrier effect on skin phototype and skin cancer risk. Ultimately, it is the genetic and chemical assessment of melanin synthesis not skin colour that will be the best indicator for skin cancer risk.

Culture of human melanocyte and melanoblast strains from skin

Melanocytes isolated from human skin demonstrate a limited life span of up to 25 passage doublings before arrested growth and cessation of further division. We have genotyped a large number of independent neonatal melanocyte cell strains to study their growth characteristics and to functionally test the effects of MC1R receptor variants on cell physiology in primary cell culture. Melanoblasts are the neural crest derived precursors of melanocytes and have not previously been characterised in culture. We have established cultures of human melanoblast cells from neonatal foreskins. These cells typically are non-pigmented, and have a triangular cell body with three dendrites,



similar to the morphology seen for murine melanoblasts. When transferred to a medium routinely used for melanocyte culture, the cells take on morphology identical to that of normal melanocytes and become pigmented.

b3 integrin induction of osteonectin in metastatic melanoma

Cell adhesion is a reversible process required for tissue remodelling but is disrupted during the process of tumour cell metastasis. Expression of the b3 integrin protein has been found to be critical for melanoma cell progression to metastasis, however, the genetic determinants that drive the metastatic process remain to be determined. A search for gene expression changes between b3-subunit positive and negative melanoma cell populations, using a highly efficient subtractive hybridization method revealed that b3 integrin overexpression upregulates molecules associated with both adhesion and de-adhesion. We have found that the counter adhesion protein osteonectin is induced during the progression of melanoma cells from non-tumourigenic radial growth to tumourigenic vertical growth. Expression of osteonectin was also associated with reduced adhesion of melanoma cells to vitronectin, suggesting that melanoma cells can readily detach from the extracellular substrate despite expression of the vitronectin receptor avb3 integrin. Since melanoma cells also secrete vitronectin, it appears that the secretion of these two molecules establishes a balance of adhesion and de-adhesion during the invasive process.

Molecular genetics of human disease

Our research group is focused on elucidating molecular pathology of human genetic disease, primarily through the analysis of the single gene disoder, 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. 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.

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Structure/function of the patched tumour suppressor gene

The patched gene is part of a signalling cascade conserved from flies to mammals. We discovered the *Patched* gene was mutated in basal cell carcinoma of the skin and the common human brain cancer, medulloblastoma.

In order to further define the function of *patched* we modelled many mutations i*n vitro* in order to examine their localisation and binding to the ligand, sonic hedgehog. We also established that Patched function can be measured in transfection studies through its ability to downregulate a *Gli* reporter gene. In collaboration with Dr Gary Hime (University of Melbourne) some novel mutants have been over-expressed in the fruitfly *Drosophila melanogaster* and as a result we have identified a region of *Patched* which appears to be responsible for transmitting the *Shh* signal.

Cellular origin of basal cell carcinoma

Transgenic animal studies have indicated that patched mutant mice will develop BCC-like lesions. However, it is still not clear which cells of the skin give rise to basal cell carcinomas.Using a number of transgenic approaches we have shown, in association with Joe Rothnagal, that direct gene excision will specifically occur in the keratinocytes of the outer root sheath - the cell type which is a strong candidate for the cellular origin of BCCs. Also, Cre expression under the control of the keratin 14 promoter has been achieved and this directs gene excision throughout the epidermis. Gene targetted mice have been developed which excise the *Patched* gene in the presence of Cre recombinase so that we now know the necessary materials to examine the exact cell type which gives rise to basal cell carcinoma.

The downstream targets of patched/ hedgehog signalling

The downstream targets of patched/hedgehog signalling are largely unknown and play a key role in differentiation and development.

We have established that the mouse mesoderm cell line 10t1/2 differentiates in response to members of the hedgehog ligand family and so we have used this model system to identify a number of novel targets of patched/hedgehog signalling. These molecules potentially have application to common human cancer and also to studies of tissue growth and repair.

Regulation of the inflammatory response by CFTR

Individuals with cystic fibrosis suffer from life threatening lung disease caused by stimulated colonisation with the opportunistic pathogen, *Pseudomonas aeruginosa* (PA). Data now indicates that in addition to the known biochemical properties of the CF gene (CFTR), CF individuals have a CFTR mediated inflammatory defect such that they respond massively to inflammatory stimuli. The mechanism via which CFTR modulates the inflammatory response is not clear, and it is controversial as to which cells in the lung are contributing to the pathology. Our data has shown that macrophages from CF mice are sensitive to lipopolysaccharide (LPS) stimulation - overproducing a number of inflammatory mediators, including TNF-a and iNOS. We are identifying the lung epithelial genes regulated by PA infection, which are potential therapeutic targets to prevent the irreversible lung disease characteristic of CF.

Origin of the cystic fibrosis inflammatory response

The cytokine profile of the infected CF lung indicates that both epithelial cells and inflammatory cells may express cell autonomous CFTR-mediated defects in the inflammatory response. We have shown that the introduction of functioning CFTR into the airway cells is necessary and sufficient to restore the inflammatory and pathogen clearance defects characteristic of CF. These studies have given us an indication of what the true targets for successful gene therapy might be.

Molecular biology of cytokine hormones, growth hormone & prolactin

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Postnatal growth is a complex process involving cell commitment, differentiation, proliferation and apoptosis, and is driven primarily by growth hormone (GH). In the adult GH serves as a regulator for carbohydrate, lipid, nitrogen, xeno- and endo-biotic metabolism. We are studying the mechanistic basis for these divergent actions at all levels from activation of the GH receptor to the genome. We also study the actions of the homologous hormone, prolactin, which regulates breast and ovarian function.

Activation of the GH receptor

The conventional view of receptor activation by hormone is that it results from dimerization of receptor subunits by the hormone. However, we now have good evidence that the receptor exists in a predimerized state, and that the activation mechanism involves a conformational change. We have identified a particular structural motif which alters its shape in response to receptor activation, and which is required for signalling to the MAP kinase pathway within the cell. Furthermore, perturbing the transmembrane helix of the receptor with a range of modeled mutations has shown that there is a more stringent conformational requirement for MAP kinase activation than for other signalling pathways.

We have also fully epitope mapped the residues on the extracellular domain of the receptor which are targeted by an agonist antibody, the only one of 14 monoclonal antibodies to the receptor extracellular domain to act as an agonist. This information is being applied to the design of small mimics and antagonists of GH, and to the creation of more potent animal growth hormones.

In vivo signalling by the GH receptor and the nature of the signal for growth

In vitro studies have defined a number of signalling pathways used by the GH receptor, and the cytoplasmic domains of the receptor used to initiate these. However, the signalling pathways used for promoting postnatal growth are not known. We have a program to create targeted knock-in mice with particular receptor signalling domains debilitated so as to define the domains and pathways necessary for somatic growth. We currently have chimeras for four constructs and germline transmission for one of these. These will be used in conjunction with gene arrays to define sets of transcripts which are regulated by the different GH signalling pathways. We recently published the first documentation of protein/peptide hormone (GH) regulated genes using cDNA arrays.

Direct nuclear actions of the GH receptor

We have shown nuclear localization of the GH receptor in many cells, including cancers. Nuclear targeting of the GH receptor sensitizes the cell to the mitogenic actions of GH. We have shown that the extracellular domain of the receptor can act as a transcriptional activator, and have defined certain co-activators that bind to it.

We are in the process of identifying the genomic sequences which are associated with the receptor in chromatin complexes.

Osteogenic actions of GH and its role in tooth development

We have shown that GH acts to promote bone and tooth formation *in vitro* and *in vivo*, and that this correlates with the induction of bone morphogenetic proteins 2 and 4.

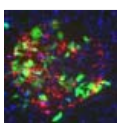
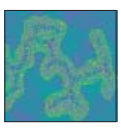
The *in vivo* roles have been delineated with GH deficient dwarf rats and GH receptor knockout and transgenic excess mice.

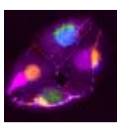
Signalling crosstalk and the role of SOCS proteins in regulating tissue sensitivity to cytokines

We have found that the sensitivity of the mammary gland to its trophic hormone, prolactin, decreases when the gland fills, and this correlates with the induction of suppressor of cytokine signalling (SOCS)-3, which we have shown blocks the ability of prolactin to signal.

Recently we have extended this to show that prostaglandin F2a, a GPCR which initiates luteolysis of the corpus luteum in rodents, appears to do this by inducing SOCS-3, hence blocking the luteotrophic actions of prolactin.

This represents a new view of how cell sensitivity to cytokines/hormones can be controlled by heterologous non-cytokine agents.

Developmental genes and human disease

Defects arising from abnormal embryonic development are a major cause of infant mortality and childhood disability. In the wake of the vast amounts of information generated by the large scale genome efforts, we are using genomics techniques to identify novel genes with a role in development and disease. In addition, we are further investigating the functional role of genes which are known to be pivotal to embryogenesis and human disease.

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The identification of genes involved in craniofacial development

A common feature of many human developmental syndromes is dysmorphology of the face, the major features of which derive from the pharyngeal arches during early embryogenesis. The aim of this project is to use a genomics approach to identify genes specifically expressed in pharyngeal arches and which are therefore likely to be important in the development and patterning of the face. Because facial dysmorphology is a common feature of human malformation syndromes, we anticipate that many of these genes will also play a more general role in the development of other organ systems, and will thus be implicated in a range of congenital disorders. Using the mouse as a model system, we are employing subtractive hybridisation and microarray technology to identify novel developmental genes. Access to human genome sequence information means we can more readily identify human homologues and investigate their role in human disease. To date we have identified a large number of novel and previously characterised genes whose expression in the developing embryo suggests a role in development of a range of systems.

Regulation of the hedgehog signalling pathway by intracellular trafficking and sterol levels

The hedgehog signalling cascade plays a pivotal role in embryonic development and tumour formation. There is mounting evidence to suggest that regulation of hedgehog signalling at the cell level involves complex trafficking events which are linked to cellular sterol levels. In collaboration with Rob Parton and Brandon Wainwright we have determined the fine subcellular localisation of members of the hedgehog pathway, in particular the hedgehog receptor molecule Patched. Employing both immunofluoresence analysis and immuno electron microscopy studies we have localised Patched to endocytic vesicles within the cell.

We are further investigating the effects of altered sterol levels and perturbed trafficking on subcellular localisation and signalling activity.

Microarray analysis in a mouse model of limb development

We are using microarray technologies to investigate large scale expression differences which result in the polydactyly phenotype seen in the limb of the extra-toes (Xt^J) mouse mutant. This mutant is a spontaneous mutant for the gene encoding the Gli3 zinc finger transcription factor which, together with Gli1 and Gli2, is involved in mediating the output of the hedgehog signalling pathway. By assessing the large-scale transcriptional consequences of dysregulation of hedgehog signalling in the limb of normal versus Xt^J embryos, we have the potential to uncover a wealth of molecules acting downstream of the hedgehog signal to determine the correct embryonic patterning of the limb. Since hedgehog signalling is central to the development of an array of vertebrate organs and systems, we anticipate that the results obtained in this study will contribute to our understanding of vertebrate development in a broader context.

Molecular genetics of neural development

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The central nervous system (CNS) is an incredibly complex organ system and is responsible for movement, sensation, memory and learning. In humans, the CNS is also responsible for higher functions such as language and consciousness. We are investigating molecules and genes that control the development of the nervous system in a number of animals. Discovering how genes and molecules function and interact in the nervous system during embryonic development will provide a fascinating insight into the processes that generate a functioning nervous system as well as a greater understanding of nervous system disease.

Our laboratory is interested in the molecular genetics of neural development in the mouse, chicken and zebrafish embryo.

During normal development, an embryo produces thousands of different types of neurons and glial cells.

As well as developing different functions and morphologies, neurons must develop at correct positions within the nervous system and connect precisely with other neurons or target cells.

We are studying how these processes are controlled at molecular and genetic levels during embryonic development.

Control of neuronal cell identity in vertebrate CNS by Sonic hedgehog signalling pathways

The diversity of neuron types in the developing spinal cord is thought to be partly determined by a gradient of a secreted signalling protein known as Sonic hedgehog.

Many aspects of this signalling process are, as yet, unknown.

This project investigates the roles of the signalling protein Sonic hedgehog and its downstream signalling pathways in neuronal precursors in the developing spinal cord.

Cell-type specification by transcription factors

In response to differentiation signals such as Sonic hedgehog, neuronal precursors and young neurons begin to express a variety of transcription factors which first act to “specify” the cells.

This specification causes the initiation of a genetic cascade that leads to differentiation.

In this project, we focus on several transcription factors whose expression defines unique classes of neurons in the developing spinal cord. We aim to elucidate their role in spinal cord development and to characterise the neurons that express them.

To identify the exact function of one these genes, *Sox14*, we are currently making a *Sox14* gene knockout mouse model.

For other genes, we are employing the modern and powerful technique of *in ovo* electroporation to study their function and regulation in the developing chicken spinal cord.

Functional analysis of vertebrate Slit genes in developing CNS

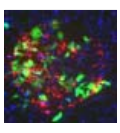
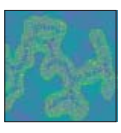
The formation of functional neuronal circuits is controlled by complex cell interactions mediated by a variety of secreted signals. We are investigating this process by studying the function of vertebrate Slit genes that are expressed in the floor plate and notochord, tissues known to be critical in the control of cell patterning and axon guidance in the CNS.

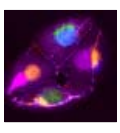
Characterisation of a novel cysteine-rich transmembrane protein *Crim-1* in vertebrate CNS development

Crim1 is a newly discovered gene expressed in the floor plate, notochord and developing motor neurons in the spinal cord. The protein product of *Crim1* is thought to regulate the functions of other growth factors in the developing CNS through its highly conserved cysteine-rich repeats.

In particular, we are testing potential interactions between *Crim1* and Bone Morphogenic Proteins and other members of the TGF-beta superfamily.

We aim to uncover the functions of *Crim1* in neuronal cell differentiation, cell migration and/or survival.

Cell adhesion and morphogenesis

My group is interested in how cell-to-cell contact regulates the patterning and organization of cells in tissues. We focus on the cell surface adhesion molecule, E-cadherin. E-cadherin plays in key role in organizing epithelial tissues, such as the lung, breast, and gastrointestinal tract. Abnormalities in E-cadherin's function are major contributors to processes by which epithelial cancers become invasive and metastatic. Our aim is to understand the basic mechanisms of E-cadherin's biological action, as a fundamental basis for elucidating its role in tumor control.

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E-cadherin determines processes as profound and diverse as epithelial polarity, cell-cell cohesion, motility, and three-dimensional patterning. Given its diverse functions, a key question is whether the biological function of E-cadherin is solely due to its contribution to cell surface adhesion, or whether E-cadherin may also signal to the cell interior upon cell-cell contact. Until recently it was difficult to find unambiguous evidence that addressed this question. In large part this was due to analytic difficulties in discriminating between primary signals that were activated by the cadherin molecule itself and secondary signals that were due to adhesion bringing together cell membranes that contained other contact-dependent signals. In the past 12-18 months we have made considerable progress in resolving this issue.

Using novel experimental systems that combined pure, specific cadherin ligands with a range of cell-based assays we have identified a primary cadherin-activated signalling pathway that regulates the actin cytoskeleton.

E-cadherin activates the Rac GTPase signalling molecule

We have now unequivocal evidence that E-cadherin acts as a signalling receptor. Upon adhesive binding, E-cadherin activates the Rac GTPase, a small signalling molecule that controls fundamental cellular processes, especially the actin cytoskeleton. In elucidating the sequence of molecular events leading from cadherin ligation to Rac activation, we identified the lipid kinase, phosphatidylinositide 3-kinase (PI3-K) as a key intermediate. PI3-K is recruited to the cadherin molecule upon adhesive binding, where it sets up a cascade of signals that are necessary for Rac activation. Importantly, activation of PI3-K may also control other cellular processes, such as apoptosis and cell growth.

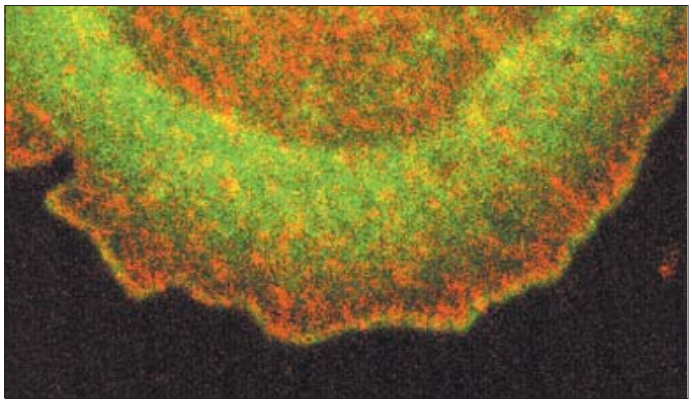
A major part of our work is now devoted to further analysing these signaling pathways, with particular attention to their potential to control cell movement and tumor cell invasiveness.

E-cadherin controls actin assembly

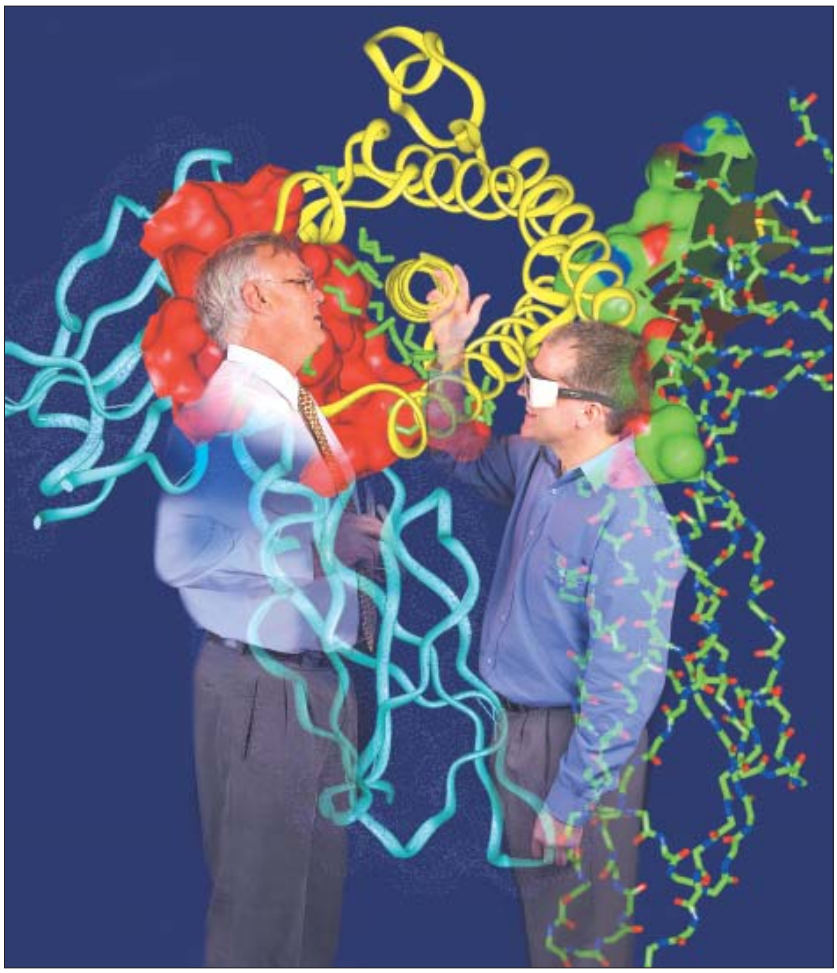
It has long been believed that cadherin adhesion molecules function in cooperation with the actin cytoskeleton. Generally, it was envisaged that cadherins would passive scaffold onto actin filaments, thereby stabilizing adhesion. In contrast, my group has now discovered that E-cadherin adopts an instructive, active role to itself regulate the actin cytoskeleton.

We found that adhesive binding of E-cadherin determines the site on the cell surface where actin filaments assemble and, indeed, we demonstrated the novel finding that E-cadherin interacts with the Arp2/3 complex of proteins, a major regulator of actin assembly. We envisage that this process of cadherin-directed actin assembly plays a key role in cell-cell recognition during development and tissue remodelling. We postulate that the cadherin-activated Rac signalling pathway acts to activate Arp2/3 and actin assembly.

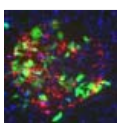
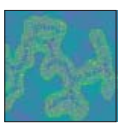
Members of my group are now pursuing the molecules that transmit the Rac signal to Arp2/3 and testing their function in cell adhesion and recognition.

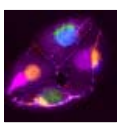


Structural Biology and Chemistry



Structure-based drug design depends on a thorough understanding of the three dimensional characteristics of important biological molecules, including venoms from Australia's deadliest creatures. Using this information advanced chemistries are harnessed to determine the roles of proteins and peptides, develop libraries of small molecule mimetics, design and synthesise reactive and bioactive compounds. Some of these compounds are drug leads that are developed through pharmacological studies into candidate drugs for clinical evaluation.

Bioactive peptides and proteins

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, heterocyclic chemistry, proteomics and bioorganic and medicinal chemistry. Special emphasis is placed on determining the structure-function relationships of natural and / or designed molecules.

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Toxins

In Australia, venomous creatures and their venoms regularly capture the public's imagination.

We are currently investigating novel components from the venoms of snakes, spiders, ants and cone snails all of which contain arrays of peptidic toxins.

Typically, these are cysteine rich, selective for a variety of ion channels and receptors, and contain 10-80 amino acids.

Some of the highlights in the past year include the structure and activity of novel omega conotoxins from *Conus Catus*, the discovery of a leucine switch in the alpha conotoxin PnIA, the discovery and structure of a new and highly specific blocker in insect calcium channels from funnel web spiders and the uncovering of two new pharmacologies from the discovery of two new conotoxin classes Chi and Rho.

These multidisciplinary programs are carried out in close collaboration with the IMB's Richard Lewis, David Craik and David Adams from UQ's Department of Physiology and Pharmacology.

Considerable new chemistry is being undertaken to further explore the nature and importance of these 'tight frameworks', control of disulfide bond formation and structure-function properties of circularised conotoxins.

Protein Chemical synthesis

The human genome project and other major sequencing projects have greatly accelerated the progress of biotechnology by providing scientists with a vast array of new amino acid sequences.

An outcome of these initiatives has been an explosion in the number of gene-encoded proteins that are considered novel or important drug targets.

In order to elucidate the biological function of this large number of protein sequences, it is necessary to produce both native and modified peptides rapidly and in high yield.

Although biological approaches, such as recombinant-DNA expression methods and native protein isolation are useful procedures for producing polypeptides, they are frequently time consuming and often result in insufficient quantities for further biological and structural studies. Furthermore, modifications are usually limited to the 20 naturally occurring amino acids.

Chemical protein synthesis provides a rapid and

efficient route for the production of homogenous proteins up to 200 residues that are free of biological contaminants.

Our laboratory has been a major player in this field and contributed significantly to the recent improvements in SPPS, together with the introduction of powerful ligation techniques.

In the past year we have reported the first chemical syntheses of Early Pregnancy Factor (related to Chaperonin 10) and the thyroid hormone binding protein, transthyretin through the introduction of a new cassette ligation strategy which employs a novel tunable functional group and subsequent thioether ligation – transthyretin was folded and assembled to its tetrameric structure in the presence of its native ligand, thyroxine, as shown by gel filtration chromatography, native gel electrophoresis, transthyretin antibody recognition and thyroid hormone binding.

We also described the first synthesis of human S100A12 (EN-RAGE) using native chemical ligation. The propensity of S100A12 to dimerise was examined by electrospray time-of-flight mass spectrometry which clearly demonstrated the prevalence of the non-covalent homodimer (M_r 20,890 Da).

Importantly, synthetic human S100A12 in the nanomolar range was chemotactic for neutrophils and macrophages *in vitro*.

Solid Phase Chemistry

'Difficult' sequences have plagued the history of peptide chemistry and continue to pose problems for syntheses today.

They are a phenomenon whereby unacceptably low coupling efficiencies are experienced for a series of residues during the synthesis, the occurrence of which is sequence dependent and often unpredictable.

They are usually a result of intermolecularly hydrogen bonded aggregates (beta-sheet formation) that do not allow acylation of the N-terminus.

Currently, we are exploring several ways to overcome difficult sequences. These include such techniques as the use of

1 highly activated *in situ* coupling reagents;
2 highly efficient coupling methods like *in situ* neutralisation;
3 polar solvents including dimethylformamide (DMF) or dimethyl sulfoxide (DMSO); and
4 very powerful reversible amide backbone substitution.

Recently, we described the use of an activated acyl transfer auxiliary for hindered 'difficult' peptide synthesis.

We found *ortho*-hydroxyl substituted nitrobenzyl (Hnb) groups were suitable *N*-auxiliaries for this purpose.

The relative acyl transfer efficiency of the Hnb auxiliary was superior to the 2-hydroxy-4-methoxybenzyl (Hmb) auxiliary with protected amino acids of varying size.

Significantly, this difference in efficiency was more pronounced between more sterically demanding amino acids.

The Hnb auxiliary is readily incorporated at the *N*-amine during SPPS by reductive alkylation of its corresponding benzaldehyde derivative, and conveniently removed by mild photolysis at 366 nm.

NMR in drug design

Our work focuses on the application of NMR spectroscopy in drug design and development. By determining the structures of biologically active molecules it is possible to identify functional regions of these molecules and use this information to design novel drugs. We have a particular interest in the concept of stabilising proteins by joining their ends to make circular molecules.

A major focus of our group is on the use of small disulfide-rich proteins as leads in drug design. Such proteins often have potent biological activities and, because of their cross-linking disulfide bonds, usually have well defined three-dimensional structures that can be determined using NMR spectroscopy.

The proteins we study come from animal and plant sources, as well as "designer" proteins we produce in the lab. In particular we have been exploring the bioengineering of circular proteins.

By cyclising proteins and creating embedded knots within the structures using disulfide bonds we are able to significantly enhance the stability of proteins.

Our goal is to overcome current limitations on the use of conventional proteins as drugs, i.e. their poor bioavailability and susceptibility to degradation *in vivo*.

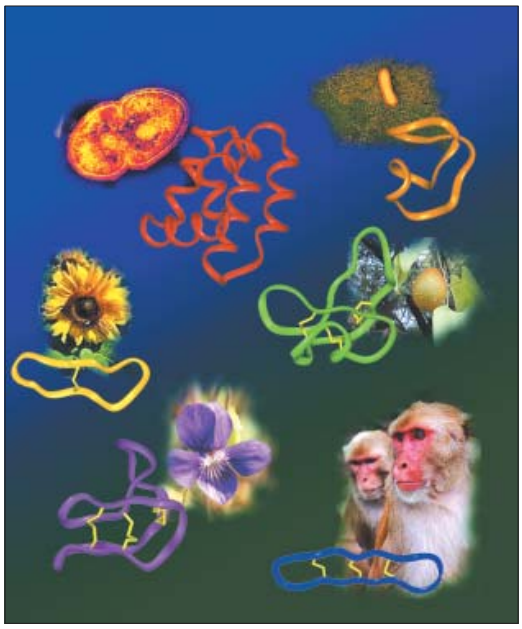
A company, Kalthera Pty Ltd, has been formed to commercialise research outcomes relating to a particularly stable protein motif that we discovered called the cyclic cystine knot.

Two figures illustrating recent structures of cystine knot proteins determined in our group are shown.

One is a trypsin inhibitor from the fruit of the tropical plant *Momordica cochinchinensis* and the other is a venom component from the Australian funnel web spider.

The cystine knot arrangement makes these proteins exceptionally stable and is a common structural motif found in defence molecules.

We are currently determining relationships between structure and activity in a wide range of cystine knot proteins, including those from plants, cone-snail venoms, snakes, spiders and frogs.



Our cystine knot discovery program involves fieldwork to many parts of Australia and included an interesting crossing of the Simpson Desert in 2001.

Cystine knot proteins have applications in agriculture as well as in the development of pharmaceuticals, and in collaboration with Dr Marilyn Anderson at La Trobe University we have been examining the insecticidal properties of a range of disulfide rich proteins.

The cyclotide proteins discovered in our laboratory show particular promise as "natural" insecticides against pest in a range of crop plants.

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We aim to better understand molecular mechanisms of chemical reactions, biological processes, disease development, and drug action. Understanding how molecules interact, how chemical reactions work, and how structure influences reactivity enables us to design and synthesize potent enzyme inhibitors and receptor antagonists as potential drugs for cancer, infectious diseases, inflammatory disorders and Alzheimer's disease.

A key strategic objective has been to mimic small bioactive protein surfaces that are recognized by other proteins-, DNA- or RNA- during disease processes.

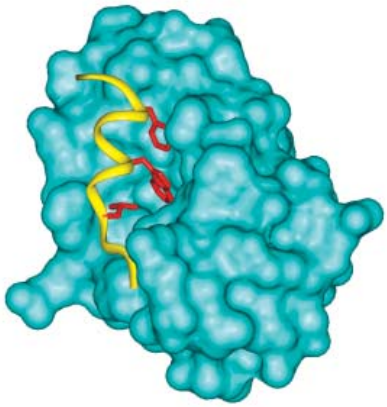

Figure 1. 2-helical turn of tumour suppressor p53 (yellow) bound to oncoprotein MDM2 (blue).

We have identified peptide conformations that are common recognition elements for protease enzymes, for classes of G protein-coupled receptors, and for transcriptional receptors.

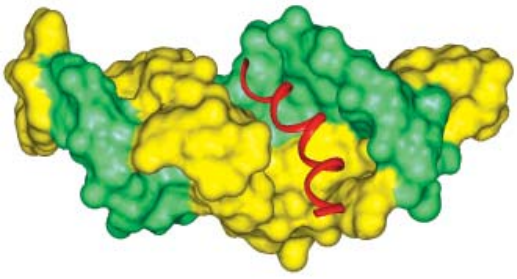

Figure 2. RNA-binding domain of HIV-rev (red).

One of our synthetic programs has been aimed at developing generic technologies for creating small organic molecules to mimic elements of protein structure (e.g. beta-strands, beta and gamma turns, beta-sheets, alpha-helices, helix bundles, multi-loop bundles).

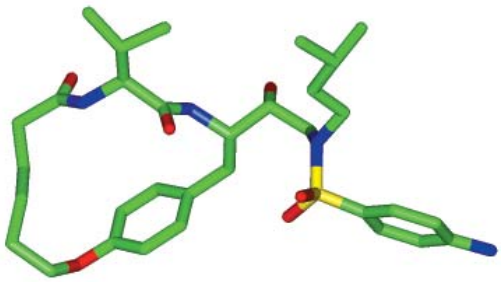

Figure 3. HIV-1 protease inhibitor, a strand mimetic.

These efforts have resulted in small organic molecules that are both structural and functional mimics of bioactive protein surfaces.

Figure 4. helix mimic of Zn-binding domain of thermolysin.

Another program involves the design and optimisation of new drugs using structure- and analogue- based approaches in conjunction with *in silico* screening and parallel synthesis methodologies.

This has been particularly important for our research on developing non-peptidic agonists/ antagonists of GPCRs.

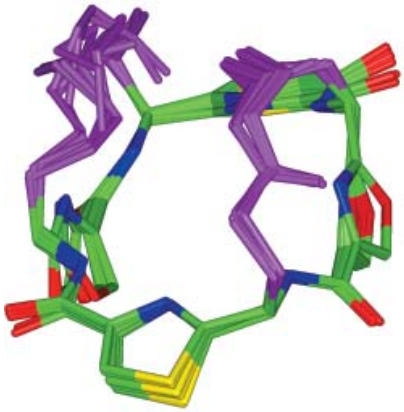

Figure 5. parallel loops (pink) on a rigid scaffold (green).

We are also using bioactive small molecules in pharmacogenomics approaches to identify aberrant gene regulation and protein expression related to untreated versus drug-treated diseased states.

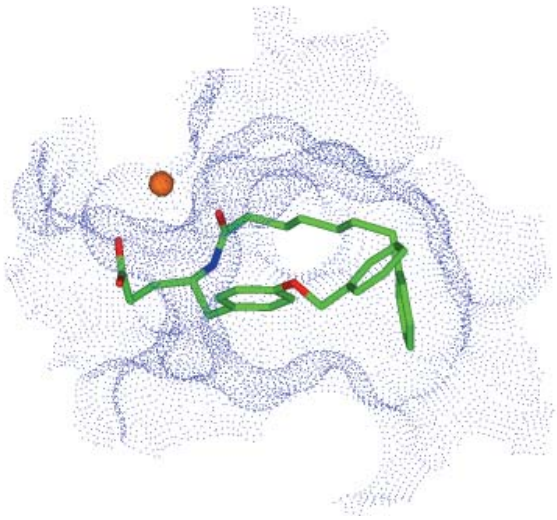

Figure 6. inhibitor bound in active site of sPLA2.

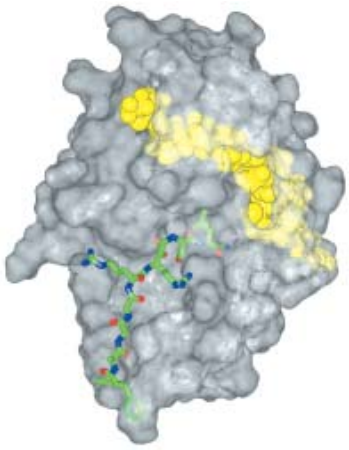

Figure 7. cofactor (yellow) and inhibitor bound to Dengue NS3 protease (grey).

The generic technologies that we have developed to date have led us to successfully create potent and selective inhibitors of aspartic, serine, metallo and cysteine proteases; as well as potent and selective antagonists and agonists of G protein-coupled receptors that span human cellular membranes and mediate cell signalling.

Figure 8. rigid cone-shaped scaffold.

In our labs multiple classes of small organic molecules are being developed with potent antitumour activity (inhibiting histone deacetylases), antiparasitic activity (against malaria, giardia, and schistosomal proteases), anti-inflammatory activity (against human cytokines, phospholipases, complement receptors), antiviral activity (low resistance inhibitors of HIV and Dengue proteins), and anti-Alzheimer's activity (against secretase enzymes). These compounds are in various stages of development.

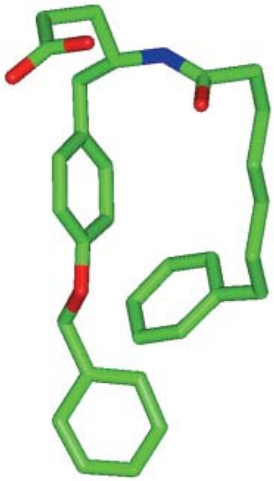

Figure 9. sPLA2 inhibitor

Structural basis of protein interactions

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The primary research theme in our laboratory involves understanding how the three-dimensional structure of a protein translates into its function, and in particular how proteins interact with each other. We combine methods of protein structure determination, particularly crystallography, with computational techniques, biophysical methods for evaluation of interactions, protein chemistry and molecular biology.

We are targeting several important biological areas with the aim of understanding the structural basis of molecular recognition processes and protein regulation.

Regulation of nuclear import

Nuclear proteins are synthesized 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 localization sequences (NLSs).

Importin-alpha is the nuclear import receptor that recognizes 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.

Regulation of phenylalanine hydroxylase

Phenylalanine hydroxylase is a highly regulated metabolic enzyme, mutations in which lead to the genetic disease phenylketonuria.

We are using a combination of mutagenesis, protein chemistry and structural biology techniques to understand the regulation and disease-causing mutations associated with this protein.

Specificity of signal transduction pathways

The specificity of signal transduction pathways stems from specific recognition and regulatory properties of proteins involved in these pathways.

The ongoing work involves both experimental structure-function studies of signaling molecules such as protein kinases, the phosphopeptide-binding FHA domains and a novel class of G-proteins, and computational work aimed at developing bioinformatic tools for functional annotation based on new protein sequences obtained by genome sequencing.

In particular, we have recently developed methodology to predict the substrate specificity of novel Ser/Thr kinases based on sequences alone, providing a powerful tool for genome-wide analysis of signaling pathways and identifying therapeutic targets.

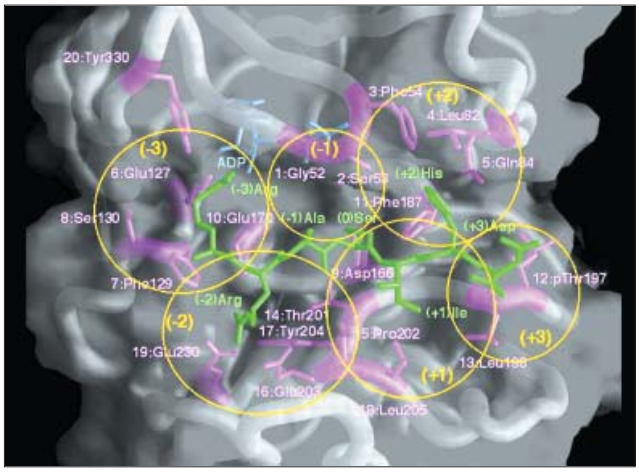

Figure 1. Substrate binding site in the crystal structure of protein kinase A. The main chain of the protein is shown in worm representation, and the determinant residues (magenta), substrate peptide (green, individual substrate residues are labelled (-3) to (+3)) and ADP (blue) are shown in stick representation. The protein kinase surface is shown in transparent representation, determinant residues are marked 1 to 20, and individual protein kinase subsites are marked with yellow circles.

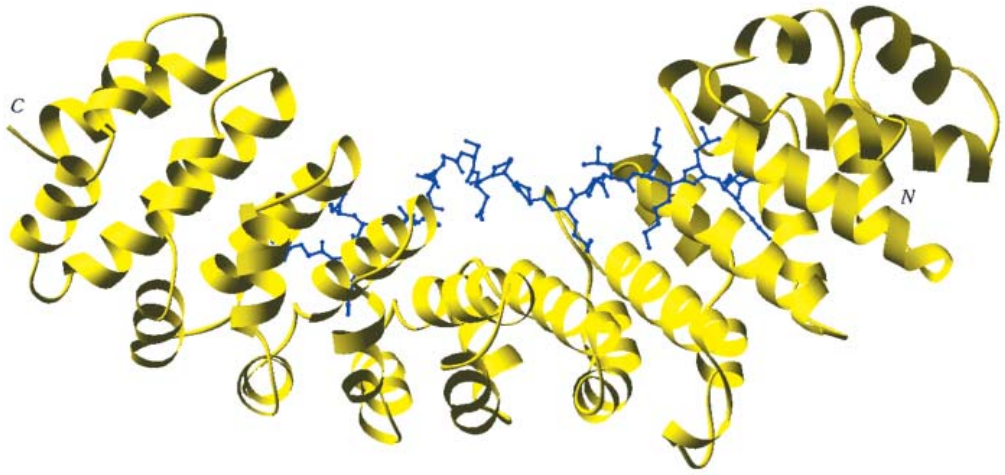

Figure 2. Structure of the complex between importin-alpha and a peptide corresponding to the nuclear localization sequence from the retinoblastoma protein. Importin-alpha is shown as a ribbon diagram (yellow), and the peptide is colored blue.

Solenoid proteins

Many proteins built from repetitive structural units are now known to exist, and they are usually involved in protein-protein interactions and other molecular recognition events.

We are using the armadillo-repeat protein importin-alpha as a prototype structural framework to attempt to engineer novel binding specificities.

Leucine-rich repeats are a dominant structural feature of proteins involved in plant disease resistance.

We are targeting several plant proteins trying to understand the molecular basis of plant disease resistance.

Targeted structural genomics of macrophage proteins

Structural genomics is a large-scale effort to determine 3D structures of all representative proteins. 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 will be 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.

Venom peptides to drugs

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Conotoxins are small peptides (mini-proteins) produced by cone snails to rapidly immobilise their prey. These toxins are highly selective modulators of a variety of membrane bound proteins, making them important research tools and potential therapeutics. Through a multidisciplinary research program we are further developing the potential of this interesting class of molecules.

Conus species from which conotoxins are derived, comprise a group of over 500 predatory marine snails whose venoms have evolved to target fish, worms or molluscs.

The venom of each species contains a unique mix of approximately 100-200 small, constrained peptides that typically contain 10-40 amino acids and 2-5 disulfide bonds. Conotoxins are injected into prey to cause rapid immobilisation, principally by targeting voltage-sensitive Na^+, Ca^{2+}, and K^+, and ligand-gated acetylcholine, serotonin (5-HT3), and *N*-methyl-D-aspartate receptors.

Importantly, most conotoxins are also potent and selective as mammalian isoforms of these targets, and the number of new pharmacologies continues to grow as more conotoxins are characterised.

Conotoxins can be divided into a number of major classes based on their pharmacological activity and cysteine frameworks. They are among the smallest bioactive peptides, and are unusual in containing a high density of cysteine residues and post-translation modifications, including hydroxylation, carboxylation, amidation, sulfation and bromination.

While these features often complicate chemical characterisation and occasionally chemical synthesis, they allow highly potent and specific interactions with ion channels, making them attractive leads in drug design programs.

Our group has broad-ranging expertise in the synthesis and structural and functional characterisation of these small disulfide-rich peptides that gives us an internationally competitive advantage in this field of research.

We conduct multidisciplinary research that integrates strengths in peptide discovery, functional characterisation and design approaches that take advantage of the breadth of opportunities offered by conotoxins and the diversity of channel types and subtypes being uncovered through the use of molecular biology.

The primary goals of this program are to:

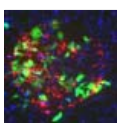
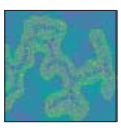
- define at a molecular level, the structural and functional determinants of ion channel/conotoxin interactions.
- develop new probes that advance neurophysiological research. This will be achieved by exploring interactions of existing conotoxins with ion channels, and through the discovery and design of new conotoxins using assay and structure guided approaches. The discovery and development of conotoxins with the right characteristics of potency and selectivity to be useful as therapeutics is of particular interest.

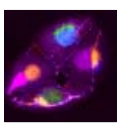
Programs within the group include studies of the molecular basis of interactions of: conotoxins with the NMDA receptor, mu conotoxins with the sodium channel, omega conotoxins with the calcium channel, chi conotoxins with the noradrenaline transporter, alpha conotoxins with the acetylcholine receptor, rho conotoxins with alpha1 adrenoceptor.

The discovery of new conotoxin pharmacologies is achieved by assessing the effects of crude venom or new synthetic toxins on a variety of cell and tissue assays.

The specific peptide and target are then dissected using a multidisciplinary approach.

This work has lead to the discovery of CVID (AM336) which is in clinical trials for the treatment of severe pain, and two new classes of conotoxins (chi and rho) which are the first peptide inhibitors of the noradrenaline transporter and alpha1 adrenoceptor respectively.

Protein structure and drug design

Our research focus is the determination of the structures of proteins by protein crystallography, the analysis of these to better understand protein evolution, function and folding and the use of these structures for structure-based design studies. We target the structures of medically relevant proteins, through collaborations within the Institute and with other research teams both in Australia and internationally. In this report, we focus on two of the several projects in the lab – the adrenaline-synthesizing enzyme PNMT and the SNARE proteins involved in insulin action.

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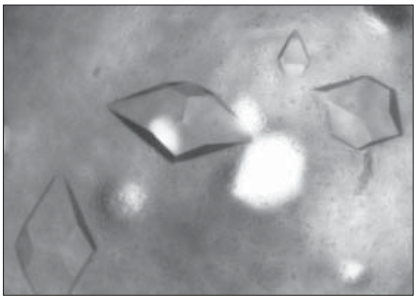
Adrenaline synthesis

Although adrenaline is best known for its adrenal hormone role in the body's stress response, it is also produced in significant quantities in discrete regions of the CNS where it functions as a neurotransmitter. The hormonal role of adrenaline is well known but the role of adrenaline in the CNS is not. It has been implicated in fundamental physiological processes including the central control of blood pressure and pituitary hormone secretion.

Other studies link CNS adrenaline with the physiological effects of ethanol intoxication and the neurodegenerative effects of Alzheimer's disease.



Concrete evidence that CNS adrenaline regulates any of these processes would make the neurotransmitter a prime candidate for therapeutic intervention. However the lack of a suitable pharmacological tool to probe adrenaline function without compromising other catecholamine processes has meant that adrenaline's CNS role remains unclear.

In collaboration with Prof Grunewald (Kansas University) and Dr McLeish (University of Michigan) we determined the crystal structure of PNMT, the adrenaline-synthesizing enzyme. This will be used to design specific inhibitors with which to probe the role of CNS adrenaline.The crystal structure of PNMT also allows us to investigate the function and evolution of this protein. Comparison with the structures of other small molecule MTases indicates that PNMT may have evolved from catechol O-methyltransferase (COMT), a methyltransferase enzyme that also binds catecholamines and which inactivates adrenaline and noradrenaline by methylating the catechol hydroxyls. The structural comparison also provides evidence for an evolutionary link to a third and much more complex enzyme, glycine N-methyltransferase (GNMT).

SNARE proteins

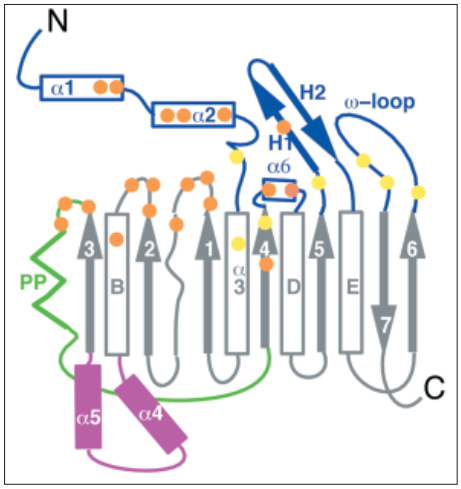
In collaboration with Prof. David James, we are investigating the SNARE proteins that participate in the insulin regulation of glucose transport in muscle and fat cells. Insulin stimulates glucose transport in these cells by triggering the exocytosis of intracellular vesicles containing the glucose transporter GLUT4 to the plasma membrane. To ensure that the contents of the storage vesicles are delivered to the correct destination, vesicular transport must be tightly regulated with high fidelity.

The exquisite specificity is controlled by SNARE proteins, a family of cytoplasmically oriented integral membrane proteins that mediate docking and fusion between the vesicle and its target membrane. SNARE proteins on the vesicle membrane (v-SNARE VAMP) form a SNARE ternary complex with SNARE proteins on the target membrane (t-SNAREs Syntaxin and SNAP). Formation of this complex begins a cascade of interactions resulting in membrane docking and fusion.

We developed protocols for producing in large quantities the purified forms of the three SNARE proteins involved in insulin regulated glucose transport, as well as a SNARE regulatory protein Munc18c.

We successfully produced stable complexes of the SNARE proteins and are developing a BIACORE assay to investigate the specificity and affinity of these interactions.

We intend to investigate the structures of the SNARE proteins and their complexes by protein crystallography. To this end, we recently produced crystals of the SNARE regulatory protein Munc18c.



Combinatorial chemistry and molecular design

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Many biological processes are carried out, or regulated, through protein-protein interactions. Despite their physiological significance, they remain one of the most difficult molecular recognition events to inhibit or mimic. Consequently there is a huge pharmaceutical demand for the discovery of small molecules that modulate protein function. We are developing methodologies for the discovery of small molecule protein mimetics by studying the chemical and conformational diversity of protein surfaces to provide better candidates for the development of leads for protein-protein interaction targets.

Conformational diversity of proteins

Protein structure is currently classified by the shape of the polymeric backbone.

Unfortunately this provides medicinal chemists with very little information as to the shape or topography of amino acid side-chains on protein surfaces.

We have developed the required algorithms and applied these to cluster continuous and discontinuous protein surfaces.

These privileged side-chain shapes serve as "screens" in an *in silico* "assay" to identify small molecules that match these shapes in a virtual screening of virtual library approach.

Virtual screening of virtual libraries

We are developing databases of compounds that encapsulate the wealth of chemical diversity available to synthetic chemists.

We are continually optimising a drug design environment that allows us to identify compounds in the chemical universe that match the shape of proteins.

New linkers for library synthesis

We have developed a backbone linker and a safety catch linker for the synthesis of libraries of macrocycles, in particular large arrays of peptidic macrocycles.

We are optimising chemistries for the solid phase synthesis of large arrays of macrocycles containing unnatural polymers and amide bond isosteres on these linkers.

We are developing new linkers for the synthesis of macrocycles.

Overcoming difficult macrocyclisation step

We have developed a novel ring contraction auxiliary that yields monocyclic products that are unobtainable using existing synthetic methods.

We are examining the combination of this strategy with new and existing linkers to provide the solid-phase avenues for the synthesis of highly strained and novel macrocycles.

Development of potent G-protein coupled receptor agonists & antagonists

We have synthesised a class of macrocycles that are unobtainable using existing chemistries.

This class of natural products has shown wide ranging biological activities including antitumour, herbicide, antimalarial, opiate agonist and tachykinin NK-2 antagonist activities.

We are exploring this class of macrocycles as orphan ligands for G-protein coupled receptors.

Cytokine Mimetics

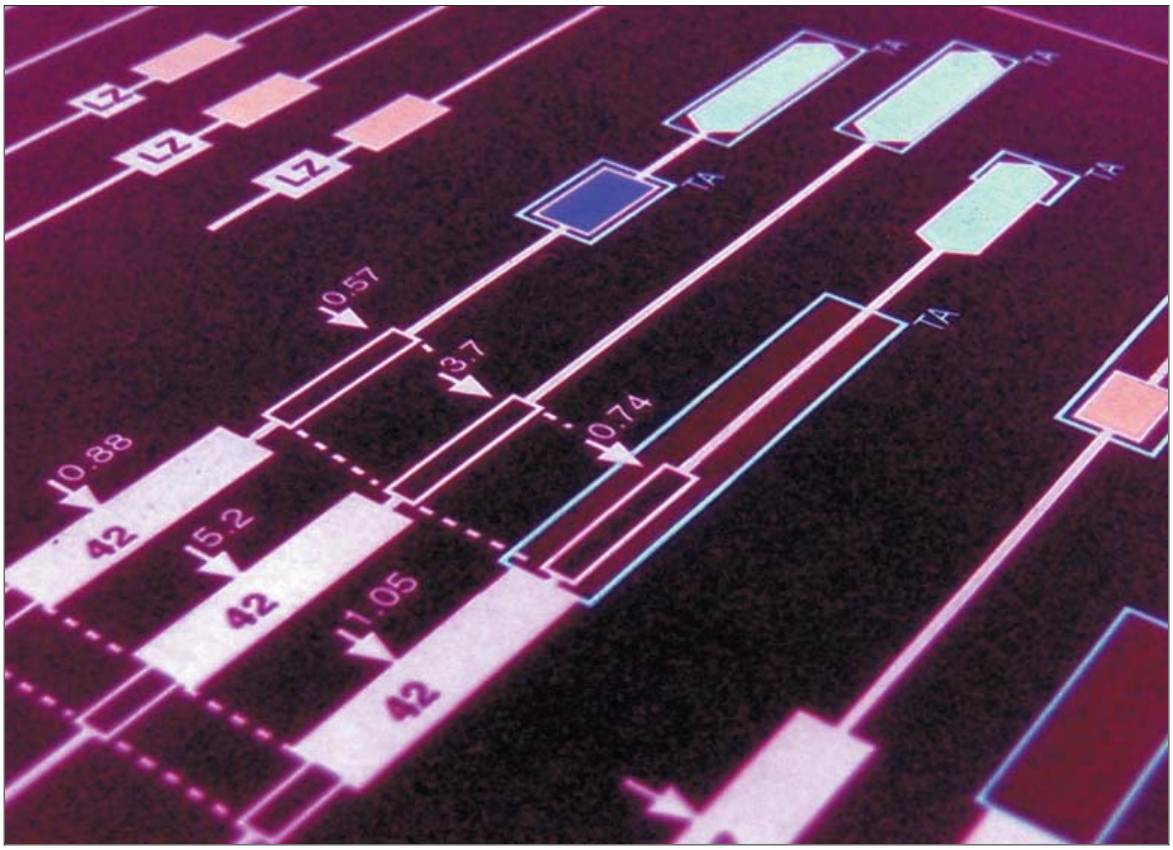
Cytokines are a broad class of proteins that regulate cell-cell interactions under both normal and physiological conditions.

Although the therapeutic use of cytokines is still at an early stage, current therapeutic indications include cancer, hepatitis C, multiple sclerosis, growth, asthma and arthritis, and several cytokines have achieved sales well in excess of $1billion/annum.

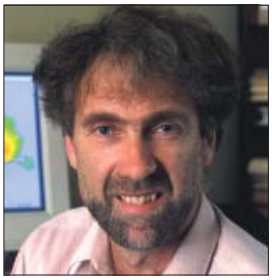
We are developing the required design and synthetic methodologies for the discovery of molecules that modulate cytokine function.

Using these structure-based design approaches we have developed an antagonist of Interleukin-4.

IMB Associates



Kevin Burrage: Computational biology



In 2001, the number of staff in the Advanced Computational Modelling Centre (ACMC) grew to 20 academics, specialising in high performance computing, advanced visualisation, bioinformatics and computational modelling. The ACMC also oversaw the establishment of a new 64 processor SGI supercomputer and a Virtual Reality Centre at the University of Queensland. Both of these facilities have strong use from researchers and students within the IMB.

Specific collaborative projects being undertaken by Kevin Burrage and researchers within the IMB that use the Virtual Reality Centre (VISAC) include:

- visual manipulations (including a 3-D fly-through) based on electron micrographic images with Francis Clark (ACMC);
- an immersive 3-D visualisation of genomic (mouse) microarray data – in collaboration with Sean Grimmond's micro array group and Steve Jeffrey (ACMC) ;
- immersive 3-D visualisation of a molecular motor (ATPase) based on PDB coordinates and atomic force-field calculations - in collaboration with Mark Ragan and Thomas Huber (COMBINE).

It is planned to extend this latter project to a collaborative project in 2002 with David Craik's group on knots and topologies in protein folding.

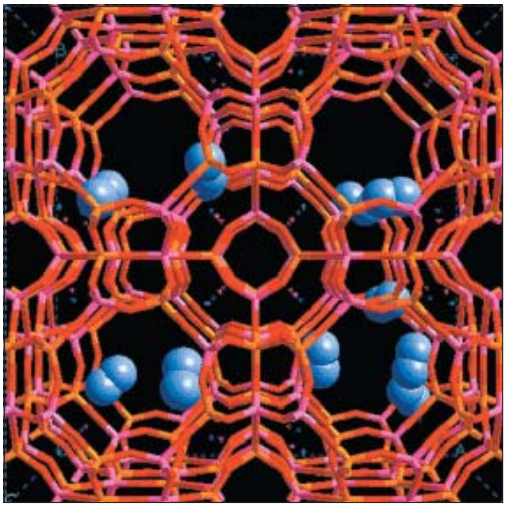
Matt Trau: Centre for Nanotechnology & Biomaterials

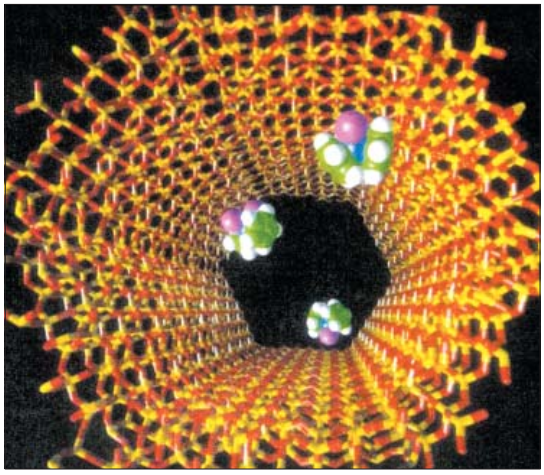
Nanotechnology and Biomaterials focuses on the formation of novel materials and devices for medical and diagnostic needs. Examples of these include devices for rapid DNA sequencing, genetic screening, and drug discovery. Other devices of interest are artificial tissue matrices for human bone, liver and pancreas tissue. Nanotechnology, the ability to control and manipulate nanometer-sized features of matter, is a fundamental tool which is used to fashion such materials & devices.

The overall goal of the research within our centre is to develop biologically related materials and devices which will ultimately improve human health. Our research work is divided into two main categories: (i) Genetic Screening & Drug Discovery devices, and (ii) Artificial tissue matrices for implants into the human body. Both of these areas require the preparation of novel materials and devices which have been fashioned to contain designed nanostructure.

Genetic screening and drug discovery devices

Rapid access to genetic information is central to the revolution occurring in the pharmaceutical industry, particularly in relation to novel drug target identification and drug development. Genetic variation, gene expression, gene function and gene structure are just some of the important research areas requiring efficient methods of screening DNA. Within our group we are currently developing colloidal devices (ie, devices that are comprised of microscopic particles) which can be used for rapid DNA sequencing, genetic screening and drug discovery applications.





Artificial tissue matrices

Many human ailments arise as a result of the body's inability to fully re-generate damaged tissue (eg, bone, liver, pancreas). Common medical therapies in these cases involve the use of autografts (implants from one's own body), allografts (implants from cadavers), or other synthetic (non-biological) materials, each of which have their associated problems. Our research focuses on developing novel biological, degradable and "living" implants for the human body.

Steve Barker: Evolutionary genomics of arthropods

Most animals are arthropods. Yet the genomes and evolutionary genetics of these animals are poorly understood. My research focuses on the ticks of cattle and the lice of humans - parasites that cause disease and economic burdens.

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 mitochondria of these animals has changed so many times it is difficult to reconstruct the evolutionary path of these mitochondria. By studying the exceptions, mitochondria that have changed a lot, we hope to learn about the rule (why the arrangements of genes in mitochondria evolve so slowly).

Nuclear genomics

We have begun to sequence the expressed genome of *Pediculus humanus*, a louse that infests people and transmits 3 bacteria that, together, have killed over 50 million people in the last 100 years.

Molecular epidemiology and evolutionary genetics of parasitic diseases

We study the epidemiology and genetics of four pathogens that cause diseases: the lice of humans, the scabies mite of humans and dogs, the paralysis tick of dogs, and a single-celled animal called *Perkinsus* that kills abalone.

John Hancock: Mammalian signal transduction

Cellular communication is vital for processes like cell division, movement, stasis and programmed death. The information used in these processes needs to be transmitted across the cell membrane to the nucleus. This transmission of information is referred to as signal transduction. Studying this is important because cancer cells have major problems with their signalling networks.

Ras genes encode small (21kD) guanine nucleotide binding proteins that operate as molecular switches in signal transduction pathways downstream of tyrosine kinase and G-protein coupled receptors. Ras is activated by guanine nucleotide exchange factors that catalyse exchange of GTP for GDP. The binding of GTP to Ras induces a conformational change that allows RasGTP to activate multiple effector pathways.

Some 25% of human tumours have point mutations in one of their Ras genes which render the GTPase activity of the mutant protein resistant to GAP stimulation. Oncogenic Ras is therefore fixed in the activated GTP bound state and constitutively activates its effector pathways. These include: the Raf/MEK/MAP kinase cascade, phosphatidylinositol-3-kinase (PI3K) and networks of other Ras-related proteins including Ral, Rac, Rho, and Cdc42. The consequences of these events is stimulation of cell proliferation.

In order to function Ras proteins must be localized to the inner surface of the plasma membrane. This is achieved by the addition of a C-terminal membrane anchor in the endoplasmic reticulum. From there Ras proteins must be trafficked to discrete regions or microdomains of the plasma membrane. How Ras proteins traffic to these domains and how Ras function is regulated by membrane interactions is a major focus of our work. This has major relevance in the design of new anti-cancer therapeutics.

Ian Frazer: Immunoregulation

Tumours are different enough from the person in which they grow that the body's defences against infection can recognise them as foreign, but unlike infections, tumours are poorly controlled by these defences. There are many reasons for this - some relate to the body's natural reluctance to attack itself, and this problem can be overcome through better vaccines. Our work focuses on understanding how the body chooses not to attack tumour cells, and on developing vaccines to reverse this reluctance.

Targeting immunotherapy to epithelial tumours

We use a model in which mice are transplanted with skin transgenic for the E7 protein of HPV16 to mimic the immunobiology of presentation of self antigen by tumours and normal tissue in the periphery. We observe that E7 transgenic skin is not rejected by immunocompetent animals even if immunised with E7 protein and adjuvant. However treatment of grafted animals with *Listeria* results in prompt graft rejection and acquisition of memory immune responses sufficient to allow subsequent rejection of further E7 transgenic grafts without further *Listeria* exposure. We are currently exploring the molecular and cellular mechanisms of self tolerance and of rejection using this model and developing surrogate markers for an effective immune response that could be applied to our clinical trials of E7 specific immunotherapy for cervical premalignancy. This work is being undertaken in collaboration with Dr Ranjeny Thomas' dendritic cell biology laboratory at CICR and Dr David Hume's macrophage biology centre at IMB.

Codon usage as a determinant of expression of papillomavirus genes

Many viruses including papillomaviruses utilise codons which are rarely used in mammalian genes. We have shown that papillomavirus capsid proteins are poorly expressed in undifferentiated epithelial cells but well expressed in their differentiated progeny, and that the block to expression in undifferentiated cells is overcome by modifying codon usage to the mammalian consensus. Current work is therefore addressing mismatches between codon usage and AA.

Bryan Mowry: Molecular genetics of schizophrenia

Schizophrenia is a brain disease characterised by psychotic symptoms such as hallucinations, delusional ideas, disordered speech and thinking, as well as deficits in emotional and social behavior. It is now generally accepted that schizophrenia is a brain disease with a predominantly genetic basis. Our work is aimed at identifying genes for this devastating disease that afflicts an estimated 1% of the world population.

While the causes of schizophrenia remain unknown, evidence from family, twin and adoption studies clearly demonstrates that it aggregates in families, with this clustering largely attributable to genetic rather than cultural or environmental factors. However, epidemiological data and molecular genetic studies demonstrate that susceptibility to schizophrenia is not the result of a mutation to a single major gene. Rather, it is likely that there is a number of interacting genes of small to moderate effect that interact with each other and with non-genetic risk factors to confer schizophrenia susceptibility.

Current candidate-gene and genome-wide linkage studies provide some evidence for the involvement of a number of specific genes (e.g. serotonin 5HT2a receptor gene and the dopamine D3 receptor gene) and as yet unidentified factors localised to specific chromosomal regions including 2q, 6p, 6q, 8p, 13q and 22q. These data provide suggestive, but no conclusive evidence for causative genes. Our work is aimed at identifying these genes. In collaboration with national and international colleagues, we are studying both ethnically diverse (heterogeneous) and genetically isolated (homogeneous) populations, to account for two different possibilities:

- The same, frequently occurring causative genes occur in all populations.
- Rare genes may exist in one or more genetically homogeneous populations.

Michael Denton and Jane Olsson: Human genetics project

The aim of this project over the next three years is to establish a world class, human genetics initiative involving close collaboration between the Institute for Molecular Bioscience and the Pakistan genetics community. This will involve the collaboration of a network of clinicians and researchers in Pakistan who will ascertain and collect large inbred pedigrees with human genetic diseases, suitable for gene mapping studies. In Australia, the genotyping and mutation detection studies will be undertaken and a number of Pakistani students will be trained at the IMB .

We predict that Pakistan is one of the best populations for large scale gene-mapping studies, because of its very high birth rate and high proportion of consanguineous marriages. Pakistan has one of the fastest growing populations in the world, increasing by about one million people every 12 weeks. The large average sib-ship size coupled with a high frequency of marriages between close relatives within large extended clans greatly facilitates the mapping of many disease genes.

In a pilot study conducted at the IMB during 2000, we ascertained pedigrees with various genetic disorders suitable for gene mapping studies. These disorders included diabetes, schizophrenia, mental retardation, epilepsy, depression, bipolar disorder, blindness, deafness, various skin disorders, cranio-facial and skeletal abnormalities.

We currently have a project underway to map schizophrenia genes. Several of these families have 20 or more affected individuals, representing some of the largest schizophrenia families identified to date. The analysis of such families may complement other approaches – such as sib pair studies in heterogeneous population. Indeed if large families with multiple affected individuals are useful in the search for the genetic determinants of complex disorders, then Pakistan is clearly an ideal source.

Michael R. James: Genetic epidemiology

Professor James' research interests are in the fields of genomics and genetics of complex diseases in humans and model organisms, and applying gene therapy and functional genomics to treat these diseases. In addition he has an interest in large-capacity vectors for gene therapy and functional genomics. His work involves the complex disease projects in the Genetic Epidemiology Unit, and the SNP genotyping facility at QIMR, which will become a new node of the Australian Genome Research Facility.

The genetic epidemiology of traits affecting common diseases has major impacts on the health of Australian communities including alcohol and nicotine dependence, anxiety and depression, asthma, cardiovascular risk factors, endometriosis, fertility and melanoma. In addition to establishing a laboratory for molecular genetics within the Genetic Epidemiology group at QIMR, Professor James is responsible for implementing the SNP typing program in collaboration with the Australian Genome Research Facility.

In 1994 he constructed the first whole-chromosome Radiation Hybrid (RH) map. This was the first large-scale integrated physical and genetic map complete with respect to a chromosome, and the first to systematically map ESTs. The map of chromosome 11 coincided with an urgent need to exploit huge gene and EST databases and in 1995 led to the formation of a world consortium to undertake a similar project for the whole rat genome. This Gene Map of 16,000 genes and ESTs pioneered the Positional Candidate approach to disease genes discovery and lead to a landmark high resolution comparative map (mouse/rat/human) based on fully integrated RH maps for the rat.

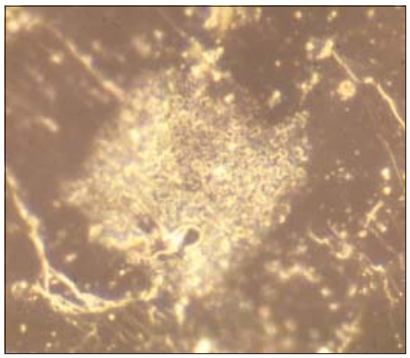
Professor James's interests also include using large genomic DNA for gene therapy and functional genomics. The delivery of genomic DNA enables genes to be transferred as complete loci and include regulatory sequences, introns and native promoter elements, increasing the likelihood of sustained physiological levels of expression in an appropriate tissue-specific and developmentally programmed manner.

Thomas H. Loy: Molecular archaeology

Molecular archaeology is a relatively recent expansion of archaeological science into the analysis of ancient proteins and DNA as applied to both plant and animal artefact, use residues and skeletal remains. The aim of our research is to provide an extra dimension to the traditional approaches used to reconstruct past cultures. Our areas of interest lie in the preservation of biomolecules, species identification, population genetics, identification and evolution of diseases in the past, and primate/ human evolution.

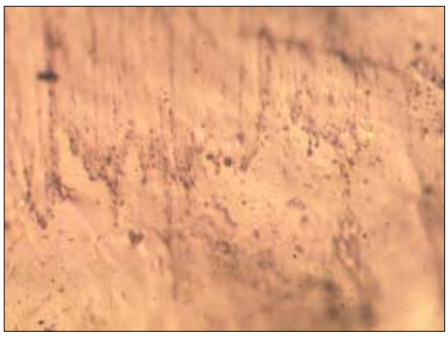
Past research emphasis lay in understanding the processes involved in the preservation of biomolecules, and from that knowledge devising efficient, relatively non-destructive, methods for extraction, purification and amplification of ancient DNA. At present the oldest confirmed blood residues on stone artifacts are about 2 million years old, from the Sterkfontein Cave site in South Africa. We have optimised our methods to permit PCR amplification from as little as 300 micrograms of bone powder and 50 microliters of aqueous extract from stone tool surfaces. Species identification using the 28S rRNA gene, and sexing of human skeletal remains is now routine. Evolutionary studies of both human and animals, especially extinct megafauna and primates, using genomic DNA and human endogenous retroviruses are ongoing.

In the past year our emphasis shifted to the detection and analysis of human diseases in the past. Two studies were undertaken using mummified tissue from Hungary and Israel, and bone samples from the Musuem of London. Many diseases leave traces of their presence as alterations of bone including pitting, remodelling, and resorbtion. Unfortunately many different and unrelated diseases can leave similar effects. The general state of health of ancient communities can tell us about living conditions and differential mortality rates as cultures developed from hunters to farmers, and later to city dwellers. We focussed on *Yersinia pestis*, the causative agent of black plague because the terminal stages of the disease result in large numbers of the bacteria being preserved in bone. We targeted the YP1 and 2 regions of the *pla* gene in *Y pestis* and were successful using bone dating to the 1347-1350 AD epidemic in London. In another study *Mycobacterium tuberculosis* was targeted specifically to investigate any change through time of of the insertion sequence IS6110, and the S12 gene, using bone and mummified tissue spanning the last 5000 years. Sequence variation in the past, compared with modern *M. tuberculosis*, shows that IS6110 sequence has changed while the S12 gene sequence has not changed over time. We are now looking to rapidly screen for bacterial and retroviral diseases in all skeletal remains that come through the lab.



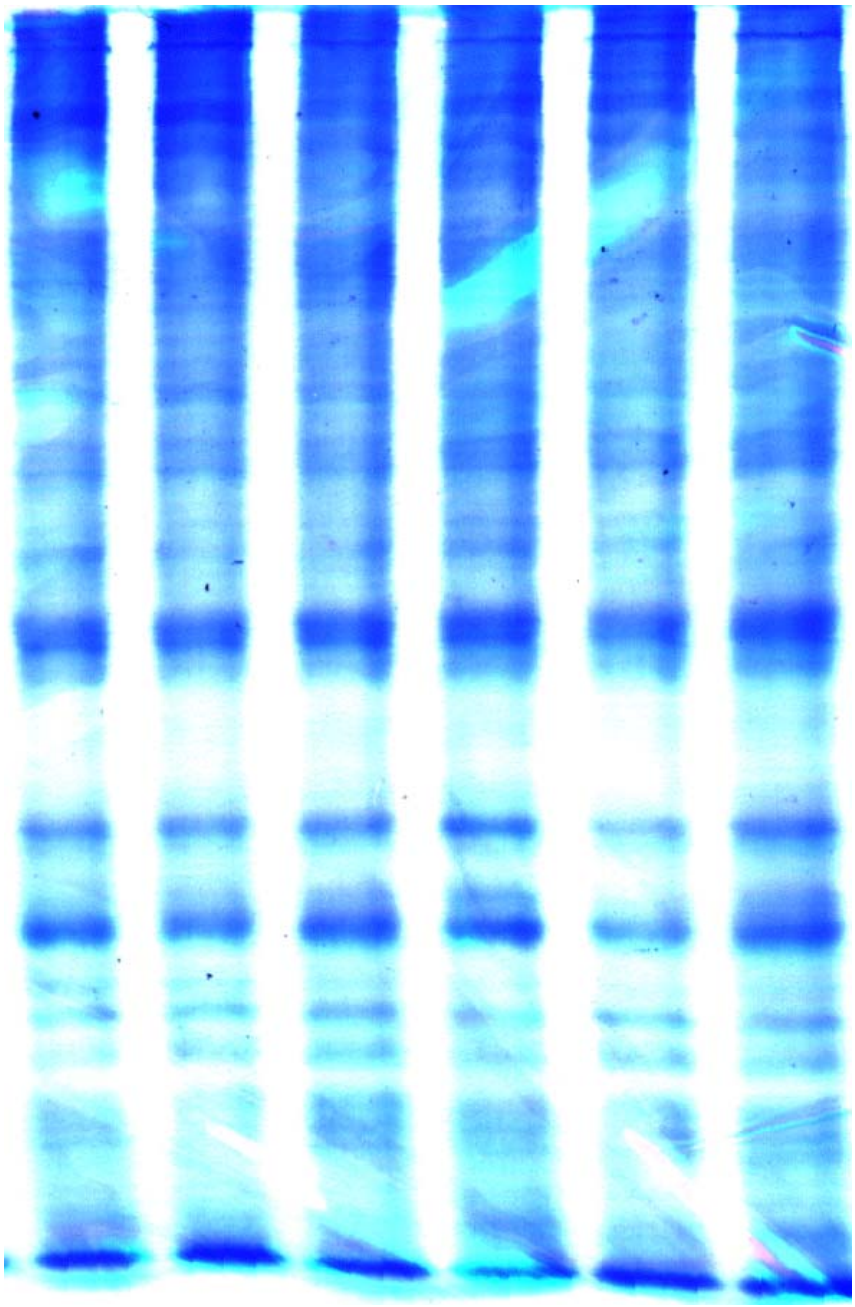
One of the most dense clusters of red blood cells ever recorded. Generally only a few isolated red cells manage to survive the drastic chemical changes that occur as blood dries. Sterkfontein Cave, member 5, ca. 2 million years old.

Finally, we are working on a project that will ultimately repair damaged ancient DNA. A major milestone was reached with the development of a method to damage plasmid DNA in a way that mimics the damage pattern of ancient DNA extracted from 60-100 thousand year old bone and tissue. Our goal is to repair oxidative and other damage to permit PCR amplification of up to 1 kb fragments. This project has important implications for retrospective forensic DNA cases.



Dragging of wet blood across the surface of a stone artifact indicates how the tool was held and in what orientation it was used during butchery. Wet blood smears indicate that fresh meat was being butchered, and not scavenged from a previous predator kill. Sterkfontein Cave, member 5, ca. 2 million years old.

Joint Ventures



Australian Genome Research Facility

The Australian Genome Research Facility, established by the Federal Government as a Major National Research Facility in 1997 has now been in operation for four full financial years.

At the four year point, the AGRF consists of two fully functioning laboratories at The University of Queensland in Brisbane and at the Walter Eliza Hall Institute in Melbourne, with expert staff and dedicated equipment that provide large scale DNA sequencing, genotyping and microarray production to research groups and industrial organisations throughout Australia as well as in the international arena.

In the 2000/2001 financial year, the AGRF conducted over 200,000 DNA sequencing analyses (generating over 100 Mb of raw DNA sequence information) from a wide variety of organisms including bacteria, plants, animals and humans.

AGRF also carried out over 1.3 million genotyping analyses for gene mapping, primarily in humans, but also in other animal and plant species.

The AGRF has been fortunate to secure a new round of funding from the MNRF Program, $14 million over the next five years. This funding will be used to upgrade its equipment base and to expand its services into SNP genotyping, in conjunction with the Queensland Institute of Medical Research, and into agricultural genomics, in conjunction with the Waite Institute and the South Australian Agricultural Research Institute (SARDI) in Adelaide.

With these resources and new partnerships, we hope also to continue and expand our policy of supporting the development of key projects of scientific and practical importance, and to place Australia at the forefront of genomic discovery internationally.

What is now needed is a framework for providing the substantive resources to enable Australian research organisations to take advantage of the infrastructure provided through AGRF and to tackle significant genomics projects of international importance.

ARC Special Research Centre for Functional and Applied Genomics

The ARC Special Research Centre for Functional and Applied Genomics (SRC) was established in 2000. The aim of the SRC is to provide and develop, limiting technologies that can expedite the identification, characterisation and utilisation of genomic information.

In the first year of operation, most of the key appointments of professional officers were completed and management procedures were established to ensure that the core technology units operate efficiently.

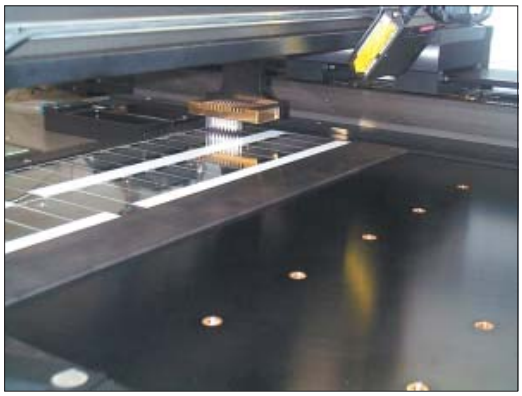
The core units are:

1 Computational Biology;
2 Microarrays;
3 Transgenic Animal Service Queensland (TASQ); Protein Expression Facility;
4 Molecular Interactions Unit;
5 Structural Biology Unit;
6 Proteomics and Mass Spectroscopy Unit; and
7 Medicinal Chemistry Unit.

To ensure optimal use of the infrastructure and expertise developed within the SRC, each of the Units offers services and materials to external clients on a full-cost-recovery basis. In 2001, such services have been used by university, research institute and industry clients from Australia and overseas.

Most of the research in the IMB utilises the infrastructure of the SRC, and scientific highlights are reported separately in this report.

A major highlight in development of infrastructure was the commissioning of the high capacity arrayer for production of cDNA microarrays, and production of quality microarrays from mouse cDNAs.



In late 2001, the Microarray Facility purchased the first set of human 70mer oligonucleotides from Compugen to meet the massive demand for quality human cDNA microarrays.

The facility also produces custom arrays for a range of customers working on everything from pineapples to cattle.

TASQ expanded the scope of its activities from the production of transgenic mice to include genotyping of progeny, embryo freezing and rederivation and other services essential to mouse-based research.

Major advances in protein structure and function analysis arise from doubling of X-ray crystallography capacity and establishment of high-throughput crystallisation infrastructure, expanded capacity for studies of molecular interactions using the new BiaCore3000 instrument, and commissioning of protein-chip technology in the form of the Ciphergen SELDI-TOF instrument.

Cooperative Research Centre for Chronic Inflammatory Diseases

The CRC for Chronic Inflammatory Diseases was awarded in 2001 with a $2.3M per annum grant from the Federal Government. It commenced operations in September under the direction of Prof. John Hamilton (CEO).

One of the three major nodes is at the IMB based in the laboratory of Professor David Hume.

Other nodes are the University of Melbourne (Prof. Hamilton, Assoc. Prof. Gary Anderson & Dr Glen Scholz) and Monash University (Prof. Paul Hertzog).

The major pharmaceutical company, Astra-Zeneca (AZ), is the industry partner.

The CRC activities are focussed on two diseases that together contribute to a massive community burden, rheumatoid arthritis and chronic obstructive pulmonary disease (COPD).

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

These cells of the innate immune system are essential for the initiation of inflammatory disease processes, and their products contribute directly to the tissue destruction that causes loss of function and chronic pain.

The Queensland node makes up approximately 40% of the CRC activity.

Cooperative Research Centre for Chronic Inflammatory Diseases

The focus is therapeutic target gene identification and validation.

In essence, we seek to expand our knowledge of the ways that macrophage function is regulated.

We want to identify genes that are regulated in macrophages in inflammatory disease processes, and determine which of those genes is absolutely required for disease progression.

We seek to develop ways of screening for potential therapies that interfere with the function of that gene target.

Professor Hume is also Director of Education in the CRC.

The CRC offers graduate students a unique environment in which to appreciate the industry approaches to research and development.

The partnership with AZ provides an opportunity to gain experience within a major drug company.

Cooperative Research Centre for the Discovery of Genes for Common Human Diseases

The IMB is a core participant in the Cooperative Research Centre for Discovery of Genes for Common Human Diseases (Gene CRC).

The IMB's Professor Brandon Wainwright is Deputy Director of the Gene CRC and Chair of the Gene CRC's Scientific Advisory Group.

Established in 1997, the Gene CRC has developed an exciting and highly competitive research portfolio that is complemented by an extensive education and ethics program, and brings together Australia's leading genetics research groups.

The IMB is joined by QIMR, Walter and Eliza Hall Institute of Medical Research, Murdoch Childrens Research Institute, and, as an associate member, The Menzies Centre for Population Health Research in Hobart. Cerylid Biosciences in Melbourne, is the administrative centre and commercial partner of the Gene CRC.

A major objective of the Gene CRC is to identify and study genes that are important in determining susceptibility to common human diseases.

The basal cell carcinoma research conducted at the IMB by Professor Brandon Wainwright and Dr Carol Wicking contributes to the Gene CRC's impressive project portfolio.

The Gene CRC is committed to empowering and engaging the Australian community for an informed debate on the applications of human genetic technology.

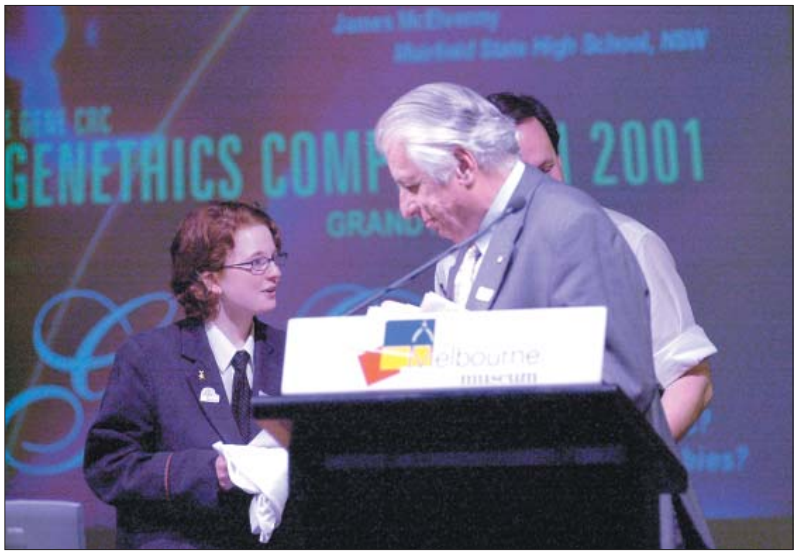
To this end, an education and ethics program, geneEDUCATION, has been developed.

This program seeks to provide knowledge and skills related to human genetic research to a wide range of people in the community, including primary and secondary students and their teachers, health professionals, financiers and the general public.

Angela Wallace, based in the IMB's Marketing and Communications Unit, is jointly appointed with the IMB and the Gene CRC to assist with the planning and implementation of the education and ethics program.

Highlights of geneEDUCATION in 2001 include:

- genETHICS Competition for secondary students
- Undergraduate Research Opportunity Program (UROP)
- Gene CRC web site - www.genecrc.org.




THE COOPERATIVE RESEARCH CENTRE FOR DISCOVERY OF GENES FOR COMMON HUMAN DISEASES
GLOSSARY
THE RESEARCH LAB
THE LEARNING CENTRE
THE GENE CRC
GENETHICS
KIDS ONLY
HOT ISSUES
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ABOUT THIS WEBSITE
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GENE CRC RESEARCH
CANCER
METABOLIC DISORDERS
AUTOIMMUNE DISORDERS
WOMEN'S HEALTH
PUBLIC HEALTH
TOOLS FOR GENE DISCOVERY
THE RESEARCH LAB
Our health is determined by many things. The food we eat, our environment both at work and home, as well as our genes. Over 6000 disorders that are caused by mutations in a single gene have been identified, leading to enhanced clinical knowledge, and often better treatment, for those affected. However, as the molecular genetics revolution proceeds there is increasing evidence for an interaction between a number of genes and the environment as a major contributory factor in more complex human diseases such as diabetes, multiple sclerosis and certain cancers. Such diseases will affect many more individuals in our community, potentially every Australian or member of their family at least some time in their lifetime, and currently place an enormous burden on our health care system.
Discovery of genes associated with common human diseases will enhance the clinical and biological understanding of these disorders and facilitate identification of those most at risk. For some diseases there may be preventative measures in lifestyle that could be adopted or screening methods to ensure early detection, leading to better treatment and prognosis in many cases. Gene identification may also identify targets for drug discovery or genes and their encoded proteins useful as therapeutics themselves.
The Gene CRC's Research Activities
THE LEARNING CENTRE
UNDERSTANDING GENETICS
FACT PAGES
RESOURCES & ACTIVITIES
GENE CRC NEWS
COMING EVENTS
UNDERSTANDING GENETICS
What exactly IS genetics?
between you and other humans.
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KIDS ONLY
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GENE GAMES
THINGS TO DO NEXT
WHAT THE WORDS MEAN
LINKS
Kids Only
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and try some fun gene games!
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Collaborations

Vital to the world-leading research at the IMB are collaborations with other institutions, both internationally and nationally, that enable mutually beneficial synergies and exchanges and further develop the IMB's scientific standing. These collaborations are with many globally recognised research institutions with over 130 international projects and a further 140 nationally. In 2001, our partners included:

Albion Fisheries, Mauritius.

Analytica Therapeutics Inc, SanFrancisco, USA.

Australian National University, Canberra.

Austrian Academy of Science, Austria.

AVRAM, Reunion Is, France.

Baylor College of Medicine, USA.

Brain Science Institute, Riken, Japan.

Bringham Young University, Salt Lake City, USA.

Cambridge University, UK.

Case Western Reserve University, Ohio, USA.

Childrens Medical Research Institute, Sydney, AUST.

CNRS, Lyon, France.

Colorado State University, USA.

Cornell University, New York, USA.

CSIRO, AUST.

Cytopia, Melbourne, AUST.

Dalhousie University, Canada.

Deakin University, Melbourne, AUST.

Duke University , USA.

Duke University Medical Centre, USA.

Edison Institute, Ohio, USA.

Emory University, USA.

Eppley Cancer Institute, Nebraska, USA.

ETH, Switzerland USA.

European Molecular Biology Laboratory, Heidelberg, Germany.

Flinders University Medical Centre, Adelaide, AUST.

Fox Chase Cancer Center, Philadelphia, USA.

Garvan Institute of Medical Research, Sydney, AUST.

Glaxo Wellcome, USA.

Glaxo Wellcome, Stevenage, UK.

Griffith University; Brisbane, AUST.

Hagedorn Institute, Denmark.

Harvard Medical School, Boston, USA.

Heinrich-Heine University, Dusseldorf, Germany.

Hong Kong University, Hong Kong.

Hopital de Beaumont, Lausanne, Switzerland.

Howard Florey Institute, Melbourne, AUST.

Illinois Natural History Survey.

IMP, Vienna.

Institut de Génétique et Biologie Moléculaire et Cellulaire, France.

James Cook University, Townsville, AUST.

John Curtin School of Medical Research, Canberra, AUST.

Kolling Institute of Medical Research, Sydney, AUST.

LaTrobe University, Melbourne, AUST.

Ludwig Institute for Cancer Research, Melbourne, AUST.

Massachusetts General Hospital, USA.

McArdle Institute for Cancer Research, Madison, Wisconsin USA.

Medical Research Council, Mammalian Genetics Unit, Harwell, U K.

Merck Laboratories, Philadelphia, USA.

Mimetopes, Melbourne, AUST.

Monash University.Melbourne, AUST.

MRC National Institute for Medical Research, U K.

National Cancer Institute, Frederick, USA.

National Institute of Chemistry.Ljubljana, Slovenia.

National Institutes of Health, Bethesda, USA.

Natural History Museum, London.

NeuroGadgets Inc, Canada.

NHGRI NIH.Bethesda, USA.

Northwestern University Medical School, Chicago, USA.

NovoNordisk , Copenhagen, Denmark.

Osaka Biosciences Institute, Japan.

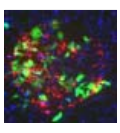
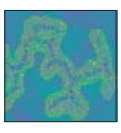
Osaka University, Japan.

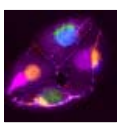
Oxford University, U K.

Peter MacCallum Cancer Institute, Melbourne, AUST.

Pharmaquest Ltd, Brisbane, AUST.

Picower Medical Research Institute, Manhassat, USA

Princess Alexandra Hospital, Brisbane, AUST.
Queensland Clinical Genetics Service, Brisbane, AUST.
Queensland Institute of Medical Research, Brisbane, AUST.
Queensland Museum, Brisbane, AUST.
Queensland University of Technology, Brisbane, AUST.
RMIT University, Melbourne, AUST.
Samuel Lunenfeld Research Institute, Canada.
San Diego Zoological Society, USA.
Scripp's University , San Diego, USA.
Sheffield University, UK.
Sir Albert Sakzewski Virus Research Centre, Brisbane, AUST.
St Vincent's Institute of Medical Research, Melbourne, AUST.
Sydney University, Sydney, AUST.
Terrace Eye Centre, Brisbane, AUST.
The New Children's Hospital, Sydney, AUST.
Tokyo Medical and Dental University, Japan.
Tokyo University, Japan.
Trieste, Italy.
University College, London, U, K.
University Hospital Nijmegen, The Netherlands.
University of Adelaide, AUST.
University of Arizona, Tucson, USA.
University of Caen, France.
University of Calgary, Canada.
University of California, San Diego, USA.
University of Copenhagen, Denmark.
University of Edinburgh, UK.
University of Geneva, Switzerland.
University of Glasgow, UK.
University of Helsinki, Finland.
University of Jyvaskala, Finland.
University of Kalmar, Sweden.
University of Kansas, Lawrence, USA.
University of Kuwait.
University of Manchester, UK.
University of Melbourne, Melbourne, AUST.
University of Michigan, Ann Arbor, USA.
University of Montreal, Canada.
University of Munich, Germany.
University of New South Wales, Sydney, AUST.
University of Newcastle, Newcastle, AUST.
University of Oregon, USA.
University of Ottawa, Canada.
University of Oulu, Finland.
University of Pittsburgh, Pennsylvania, USA.
University of Queensland, Brisbane, AUST.
University of Queensland Medical School, Brisbane, AUST.
University of Southern Queensland, Toowoomba, AUST.
University of Technology, Sydney, AUST.
University of Texas, Austin, USA.
University of the Witwatersrand, Johannesburg, South Africa.
University of Tullane, New Orleans, USA.
University of Utah, USA.
University of Utrecht, The Netherlands.
University of Wales, College of Medicine, Cardiff, UK.
University of Western Australia, Perth, AUST.
University of Wisconsin, USA.
University of York, UK.
VA Hospital Boston, USA.
Vanderbilt University, Nashville, USA.
Victorian Infectious Diseases Reference Lab , Melboourne, AUST.
Walter and Eliza Hall Institute, Melbourne.
Washington University, St Louis, USA.
Washington University School of Medicine, USA.
Wistar Institute, Philadelphia, USA.
X-ceptor Therapeutics Inc., San Diego, USA.

IMBcom Pty Ltd

In 2001, IMBcom continued to initiate regular meetings with research groups within the IMB to identify projects that have the potential to lead to spin-offs, alliances or licensing opportunities with industry partners.

One outcome of this initiative was the establishment of a small internal development grant scheme for selected projects. The aim of the development grants was to fund proof of principle studies managed in partnership with IMBcom. The three seed development grants supported in 2001 were: Crim1 - Melissa Little; Sox18 – Peter Koopman and George Muscat; and CCK insecticidal proteins- David Craik. The projects were successful in nurturing relationships and stimulating applied outcomes from projects that were at too early a stage to attract pre-seed funds such as UniSeed and BioStart.

Four new spin-out companies were also established this year:

Protagonist Pty Ltd (formerly Cytokine Mimetics)

Protagonist was established to apply a novel generic technology for the development of molecules that inhibit or mimic protein/protein interactions such as those involving cytokines. The technology enables the sculpting of protein functions onto new frameworks that have improved bioavailability characteristics when compared to the native protein. This process has the potential to revolutionise the treatment of many important diseases. First round venture capital of $3m has been invested by Start-Up Australia and Dr Mark Smythe has taken up appointment (50% time) as interim CEO. Other positions (primarily scientific) have been advertised. An application for a Biotechnology Innovation Fund grant was successful in attracting the maximum award of $250,000.

Nanomics Biosystems Pty Ltd

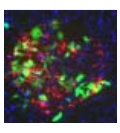
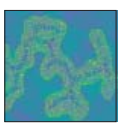
Nanomics Biosystems has a variety of high throughput screening colloidal technologies with potential applications in genomics, proteomics and combinatorial drug discovery. The core of the technology lies in the ability to cheaply produce, bar-code and individually address extremely large (> 10^{10}) compound libraries. The initial Board and Scientific Advisory Board were appointed, and Dr Dan Syrdal was seconded from Heller Ehrmann, USA as interim CEO (50% time). A number of potential applications are now being explored in collaboration with IMB scientists.

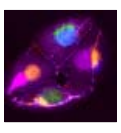
Mimetica Pty Ltd

Mimetica exploits an early stage technology opportunity involving methods for the creation of novel molecules with significant potential as new drugs. The technology uses natural peptides and known related compounds as models for the design of the new biologically active molecules, and is potentially a highly efficient method for drug candidate generation. The recently incorporated company is in advanced negotiations with three venture capital companies to secure up to $1million in funds. Mimetica Pty Ltd was successful in attracting an initial investment of $250,000 under the State Government BioStart program and an application for BIF Grant funding was submitted in the last round of 2001.

Kalthera Pty Ltd

The cyclic cystine knot (CCK) technology stems from the discovery and exploitation of a unique class of plant derived peptides with a remarkable diversity of potential applications. These include identification of natural therapeutic peptides, the generation of insect resistant plants, the creation of stable bioavailable frameworks to carry drug epitopes and the use of plants as hosts for the economical manufacture of protein drugs. Kalthera was awarded a Biotechnology Innovation Fund grant of $250,000 and as a result incorporated in October 2001. Matching funding for this grant has currently been underwritten by IMB, but other potential sources of pre-seed funding are being investigated.

Following is a summary of the activities of three previously established spin-out companies:

Xenome Ltd

Xenome harnessing the great variety of Australian venomous species by evaluating their venoms as potential therapeutics. Xenome Ltd was formed to exploit IMB's competitive edge in the isolation and exploitation of toxins from marine cone snails and other venomous species. Second round venture capital of $4.5m was raised from Biotech Capital ($3.5m) and Medica Holdings ($1.0m). Other highlights of 2001 included the award of a $1.6m AusIndustry START grant, the appointment of Prof. Tony Evans as CEO, and the identification of a new class of analgesic agents acting on the noradrenaline transport system.

Australian Genome Diagnostics (AGD)

AGD has ceased trading, resulting in a net loss to IMBcom of $150,000 ($100,000 initial investment, $50,000 loan). A final report on the wind-up of the company is to be provided by the IMB and UniQuest representatives on the Board of the company.

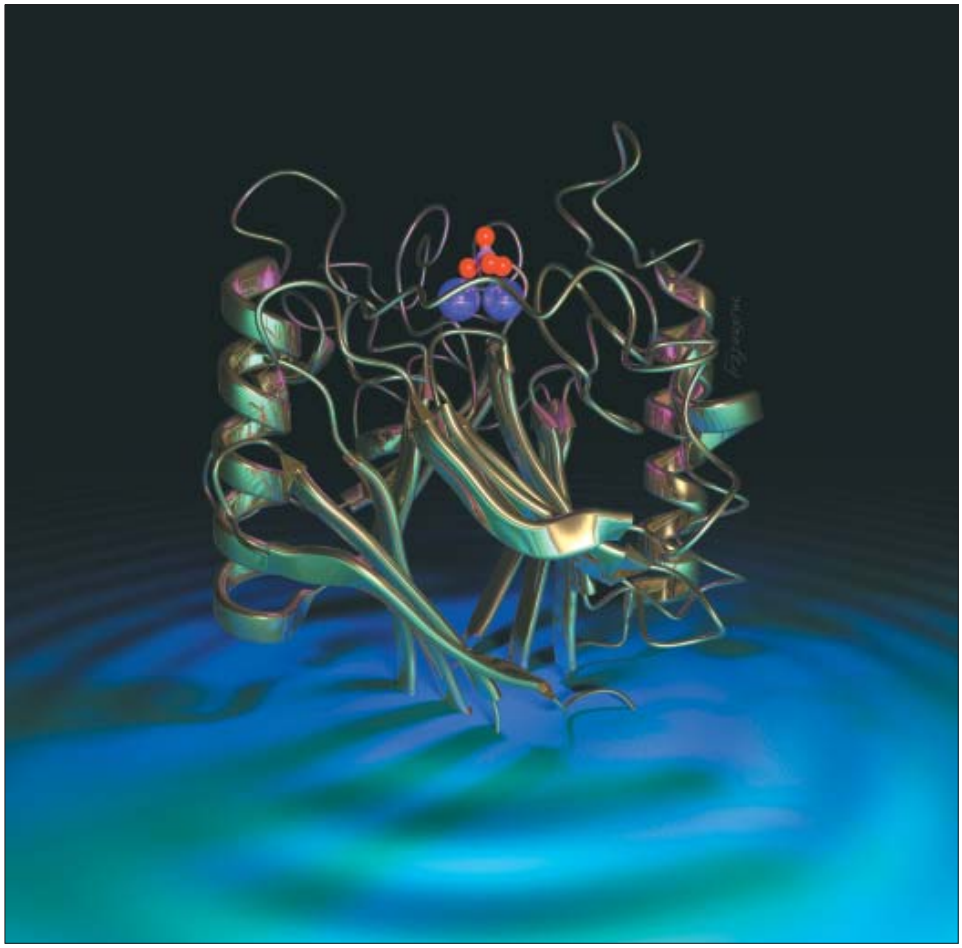
Promics Pty Ltd

Promics creates small molecules that reproduce or mimic secondary structural characteristics of proteins to make therapeutic compounds. The company rejected a scrip-for-scrip takeover offer from a US biotechnology company. Current shareholders Rothschild Bioscience and Start-Up Australia have agreed in principle to provide an additional $4 million in second round venture capital to fund clinical trials and pipeline expansion.

While the focus this year has been on establishing spin-out companies, IMBcom plans to focus attention on establishing industry alliances in 2002. Several of the big pharmaceutical companies have approached IMBcom with a view to identifying suitable projects, largely driven by the IMB's commitment to high quality research across the spectrum from gene to drug, and the subsequent opportunity to partner with IMB to feed their drug development pipelines.

A Memorandum of Understanding has been signed between Itochu Inc. and the University of Qld (IMB). The future focus of the relationship will be on the bioinformatics area in which IMB has a growing capability.

Developing Excellence







Office of Public Policy and Ethics

The Office of Public Policy and Ethics (OPPE), a new collaborative initiative between the IMB and UQ's Faculty of Social and Behavioural Sciences, was established in September 2001 with the appointment of Professor Wayne Hall as Director.

Prof. Wayne Hall AM, Director, Office of Public Policy and Ethics

The mission of OPPE is to undertake research and analysis on ethical and public policy issues raised by biotechnology and to use the knowledge gained to enhance public discussion of, and participation in, decisions about these developments. Our commitment to this agenda is reflected in the following goals:

- To develop a framework for ethical and public policy analysis.
- To identify known and potential risks and benefits of biotechnologies.
- To contribute effectively to the public debate in this area.
- To develop methods for informed and meaningful public participation in decision and policy-making.

In pursuing our goals we have undertaken research on ethical issues in risk management and are currently engaged in analyses of the policy implications of cancer and behaviour genetics.

The ultimate aim of our work is to contribute to the formulation of public policy that will minimise the risks and maximise the benefits of biotechnology.

Highlights from 2001 included the appointments of Professor Wayne Hall as Director of the OPPE and of Lucy Carter as a part time Research Assistant in September; an analysis of the ethical issues in risk management for World Health Organization and the United Kingdom Department of Health Consultation on Risks to Health, London, 23-24 October, 2001; and an estimation of the contribution that illicit drug use makes to the Global Burden of Disease for the World Health Organization.

In the coming year, OPPE will be expanded to employ two full time Senior Research Assistants, a Librarian and a part time Research Assistant, making up a multi-disciplinary group that includes a biological scientist, a philosopher, a psychologist, a sociologist, and a librarian.

In 2002, OPPE is planning to:

- Development of a Strategic Plan and the identification of research priorities.
- Analysis of the potential roles of biotechnology in reducing the disease burden of cigarette smoking.
- Analysis of the ethical issues raised in trialling and using cocaine vaccines to treat and prevent cocaine dependence for the World Health Organization.
- Analysis of the ethical aspects of human and animal neuroscience research on addiction for the World Health Organization.
- Analysis of the ethical issues and policy implications of cancer genetics.

OPPE Mission

To undertake ethical and public policy analyses of the known and potential risks and benefits of biotechnology, to contribute effectively to public debate and encourage informed public participation in decision and policy-making.

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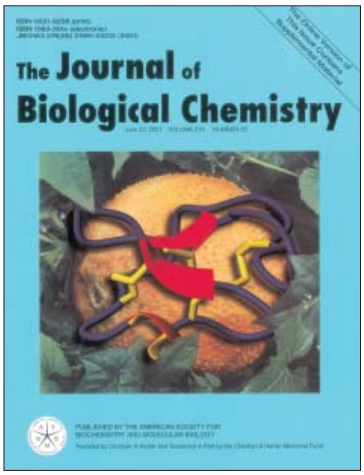

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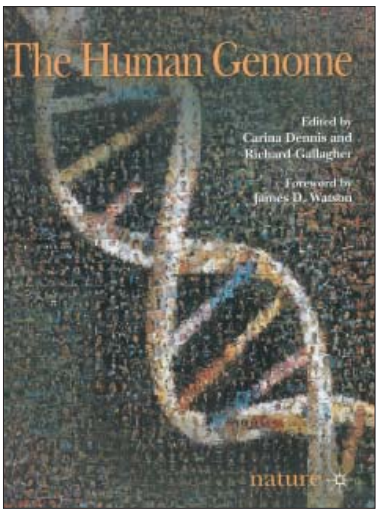


IMB Seminars

Dr Michael Ladomery
MRC Human Genetics Unit, Edinburgh, UK
The tumour suppressor gene WT1 encodes a multifunctional transcription factor involved in pre-mRNA processing.

Professor Fujio Murakami
Neuroscience Lab, Division of Biophysical Engineering, Graduate School of Engineering Science, Osaka University, Japan
Role of the floor plate in migration of precerebellar neurons.

Dr John Quackenbush
The Institute for Genomic Research, Maryland, USA
Analysis of Global Patterns of Gene Expression

Dr Ruth Arkell
MRC Mammalian Genetics Unit, Harwell, UK
ENU mutagenesis; screening for developmental phenotypes.

Professor Heinz Bonish
Institute of Pharmacology and Toxicology
University of Bonn, Germany
Discovery of 5-HT3A splice variants that influence receptor function

Mr Julian Cribb
CSIRO National Awareness Program
Mutant food or brave new world?

Dr Ricky Johnstone
Cancer Immunology Division, The Peter MacCallum Cancer Institute, Melbourne
Regulation of caspase-activation by the multidrug resistance protein, P-glycoprotein

Dr Brad Marsh
High Resolution Structure Laboratory, University of Colorado, Boulder, USA
3-D structural studies of the pancreatic beta cell by high resolution EM tomography.

Professor Rolf Prager
School of Chemistry, Physics and Earth Sciences
Flinders University, Adelaide
The application of new methods for the synthesis of oxazoles and thiazoles to natural product and peptide mimetic synthesis

Professor Chris Marshall, FRS
Insitutue of Cancer Research, UK
Interactions between small GTPase signaling pathways in cell transformation.

Dr Ian Smith
Baker Medical Research Institute, Melbourne
Beta-Amino Acid Based Inhibitors of Metalloendopeptidases: Novel Molecular Templates for Cardiovascular Drug Design

Professor Gene Myers
Informatics Research, Celera Genomics, USA
Whole Genome Assembly: Tactical and Strategic Implications

Dr Paul Gooley
Department of Biochemistry and Molecular Biology, University of Melbourne
The solution structure of a diadenosine pyrophosphatase

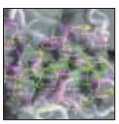
Dr Carina Dennis
Senior Editor, Nature, Washington DC, USA
Publish or Perish: Perspectives of a Nature Editor

Dr Ian Taylor
Institute for Molecular Bioscience, The University of Queensland
The New Building - History, Design and Features

Dr Keith Moffat
Biochemistry and Molecular Biology, University of Chicago, USA
Ultra-fast Time-Resolved Macromolecular Crystallography

Dr Robert Charlebois
Department of Biology, University of Ottawa, Canada; Founder, NeuroGadgets Inc., Canada
Reconstructing bacterial genomes




Professor Duncan Watts
Department of Sociology, and Center for Nonlinear Earth Systems
Columbia University, USA
Complex Networks

Dr KumKum Khanna
Signal Transduction Lab Oncology Unit, Queensland Institute of Medical Research
ATM, a central controller of cellular response to DNA damage

Dr Rhonda Perriman
Institute for Molecular Bioscience, The University of Queensland
Dissecting dynamic RNA-Protein interactions during pre-mRNA splicing.

Professor Martin Pera
Monash Institute of Reproduction and Development Centre For Early Human Development, Monash Medical Centre, Melbourne
Biology of human pluripotent stem cells

Professor Gary Hime
Department of Antomy and Cell Biology, University of Melbourne
Analysing oncogenes in Drosophila - functional studies of Cbl and Patched.

Professor Warren Ewens
Genomics and Bioinformatics program, University of Pennsylvania, USA
Statistics in bioinformatics: BLAST and expression arrays

Dr Jeff Gorman
CSIRO Health Sciences and Nutrition, Parkville, Melbourne
A perspective on the Future of Proteomics

Professor Kay Davies
Human Anatomy and Genetics, University of Oxford, UK
Flies, worms and mice in the analysis of gene function

Dr Alan Munn
Yeast Cell Biology Group, Institute of Molecular Agrobiology, Singapore
Yeast Homologs of Human WASP and WIP Have Multiple Roles in Endocytosis, Cell Division, and Organisation of the Cortical Actin Cytoskeleton

Dr Sally Dunwoodie
Children's Medical Research Institute, Sydney
Identification of novel genes required for normal embryonic development.

Ms Donmienne Leung
Institute for Molecular Bioscience, The University of Queensland
Studies on Serine and Cysteine Proteases

Dr Joel Mackay
Department of Biochemistry, University of Sydney
A finger in each pie: multifunctional zinc finger domains in the control of gene expression

Professor Phil Bourne
Supercomputer Centre, University of California, San Diego, USA
Data Driven Biology Beyond the Human Genome

Professor Angel Lopez
Cytokine Receptor laboratory, Hanson Centre for Cancer Research, Adelaide
A novel signalling pathway utilized by cytokine receptors

Dr Craig Hutton
Department of Chemistry, University of Sydney
Design and Synthesis of Inhibitors of Enzymes in the Lysine Biosynthetic Pathway

Dr Dagmar Wilhelm
Research Centre, Karlsruhe, Institute of Toxicology and Genetics, Germany
Molecular and cellular roles of the Wilms' tumour suppressor WT1 in gonad development

Dr Edith Gardiner
Bone and Mineral Research Program, Garvan Institute of Medical Research, Sydney
Elevated Osteoblastic Vitamin D Receptor in Mice — Beneficial Effects on Bone Formation and Resorption

Professor W van Gunsteren
Laboratory of Physical Chemistry, Swiss Federal Institute of Technology, Switzerland
The Key to Solving the Protein Folding Problem Lies in an Accurate Description of the Denatured State

Dr Pam Silver
Dana Farber Cancer Institute, Harvard University, USA
Genome-wide mapping of nuclear organization

Dr Adam Godzik
Bioinformatics and Systems Biology, The Burnham Institute, USA
From Fold Recognition to Function Prediction

Professor Ian Dawes
University of New South Wales
Regulation 1-carbon metabolism in yeast; agent genomic approach

Associate Professor Robert Capon
School of Chemistry, University of Melbourne
Molecular Bioprospecting: Is natural! Is good!

Dr Andrew Perkins
Department of Physiology. Monash University, Melbourne
Kruppel-like factors: three fingers in many pies

Professor Paul Carey
Department of Biochemistry, Cleveland Center for Structural Biology, USA
Raman Crystallography

Dr Mark Rizzacasa
School of Chemistry, University of Melbourne
Total Synthesis of Biologically Active Natural Products

Professor Gottfried Otting
Karolinska Institute, Sweden
Dipolar couplings, cross correlation and paramagnetism: a modern NMR toolbox.

Dr Bruce Stillman
Director, Cold Spring Harbour Laboratory, USA
Inheritance of chromosomes in eukaryotes

Dr Ben Hankamer
Wolfson Laboratories (Centre for Structural Biology) Biochemistry Department, Imperial College of Science, Technology and Medicine, London, UK
Structure determination of photosynthetic and other macromolecular assemblies using single particle analysis, electron and X-ray crystallography.

Dr Vic Arcus
School of Structural Biology, University of Auckland, New Zealand
Structural genomics and bacterial virulence: conservation and complexity in superantigen genes, architecture and activity.

Dr Brian Gabrielli
Department of Pathology, The University of Queensland School of Medicine
Specific killing of tumour cells by drugs targeting cell cycle checkpoints.

Professor Art Krieg
Department of Internal Medicine and Department of Veterans Affairs Medical Center, University of Iowa and Coley Pharmaceutical Group, USA
Actions of Immunostimulatory DNA





Developing Excellence

Professor Phillip Robinson
Childrens Medical Research Institute, Sydney
Protein kinase regulation of synaptic vesicle endocytosis

Associate Professor Tracy Brown
Acting CEO and Executive Director of Operations Meditech Research Ltd; Department of Biochemistry and Molecular Biology, Monash University, Melbourne
The clinical development of hyaluronic acid chemosensitising transport technology (hyacttm) in the treatment of cancer

Jeff Dawson
Director of Applications Development and Support, Cray Inc, USA
Bioinformatics and Supercomputer Technology - gene scanning and comparative genomics using Cray vector computer systems to provide extreme performance

The IMB is committed to building a culture of scientific excellence, entrepreneurship and technological enterprise.

IMB Graduate Program

The IMB's Graduate Program grew substantially throughout its second year in 2001.

The 2000 inaugural class of IMB enrolled students gave presentations to their Thesis Committees as part of the process to confirm their candidature.

New students had the opportunity to meet with Thesis Committees, obtaining valuable input into their projects at an early stage.

The Graduate Education Committee, formed in 2000, continued in its role to oversee the program and make recommendations to the IMB Executive.

The Graduate Coordinator, Ann Day, took responsibility for handling student matters and two student representatives provided ongoing dialogue between the student body and staff.

Graduate student enrolments increased during 2001 with the IMB enrolling 28 PhD students and two MPhil students. A total of 12 Honours students undertook their research projects within the IMB. Honours students enrol through the various schools of the University, enhancing the IMB's collaborative relationships with the University's faculties.

In 2001 PhDs were awarded to five students: Sharon Clark, Iain Sharpe, Gos Schepers, Ylva Strandberg and David Wilson, and a Masters was awarded to Nikolai Sokolenko.

IMB students shone brightly in 2001 with David Pennisi and Michelle Hill both recommended on the Dean's list for outstanding theses. Julie Dutton was awarded the Australian Society of Biochemistry and Molecular Biology Fellowship and an outstanding honours thesis was recognised when IMB student Julia Pagan was awarded the 2001 AMGEN Australia Prize for Molecular and Cellular Biology.

The IMB's Graduate Program ensures our students receive a broad-based career training to equip them with the skills to tackle the scientific challenges of the 21st century.

Graduate students participated in seminars and workshops on the topics of intellectual property, patenting, venture capital, and ethics, legal and social issues of genetic technologies. A couple of highlights of the program included an informal breakfast attended by Professor Wayne Hall from the IMB's Office of Public Policy and Ethics, as well as a Stem Cells Hypothetical, jointly presented by the IMB and The Gene CRC and featuring Professor Bob Williamson.

Developing Excellence

In August 2001, the IMB actively promoted the Graduate Program by taking part in the University's Postgraduate Study Information Evening. Staff and students of the IMB talked to a range of individuals interested in undertaking graduate studies across a diverse range of areas.

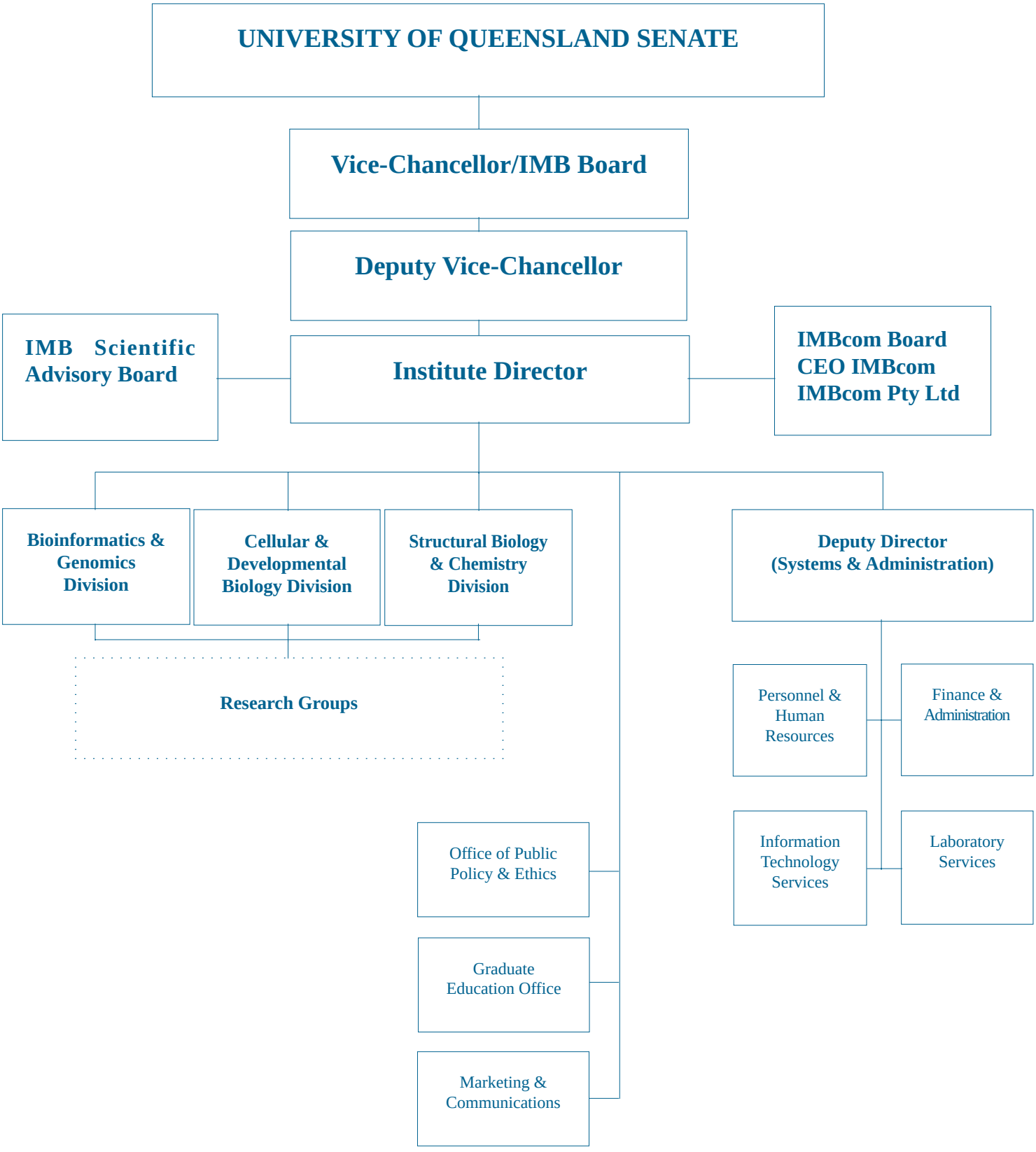
Visitors and exhibitors praised our display, commenting on the well-presented materials and enthusiasm of our staff and students alike.

SIMBA, the Students of the IMB Association, continued to effectively draw the students of the IMB together.

Throughout the year SIMBA organised a number of social events that provided opportunities for students to discuss issues pertinent to their studies and role within the IMB.

The IMB is committed to graduate education at the interface of biology, chemistry and computing.

Organisational Structure







Institute for Molecular Bioscience Board (as at 31 December 2001)

Professor John Hay	Vice-Chancellor (Chair)
Professor Paul Greenfield	Deputy Vice-Chancellor
Professor John Mattick AO	Co-Director IMB
Professor Peter Andrews	Co-Director IMB, CEO IMBcom
Professor Mick McManus	Executive Dean (rotating)
Ms Helen Lynch AM	Business Representative
Dr Russell Howard	Biotechnology Industry Representative
Professor Frank Gannon	International Scientist
Sir Sydney Schubert	Community Representative
Mr Ross Rolfe	State Government Representative
Mr Kevin Yearbury	State Government Representative

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John Mattick, Co-director, IMB
Ian Taylor, Deputy Director, IMB
Wayne Hall, Director, Office of Public Policy & Ethics

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David Fairlie
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Mark Smythe
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Toshi Yamada
Alpha Yap

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Ian Frazer
John Hancock
Michael James
Derek Kennedy
Tom Loy
Alisdair McDowall
Bryan Mowry
Matt Trau

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Nia Bryant
Ian Cassady
Roy Himes
Richard Kidd
Stephen Love
Sally Martin
Amanda Nourse
Jane Olsson
Joanne Redburn
Robert Reid
Katryn Stacey
Trung Tran

Postdoctoral research officers – Research Officer

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Tracy Arakaki
Neil Box
Jens Buchardt
Monica Bullejos
Amanda Carozzi
Peter Cassidy
Kallayanee Chawengsaksophak
Christopher Clark
Richard Clark
Sharon Clark
Elaine Costelloe
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Uwe Dressel
Tammy Ellis
Lindsay Fowles
Alison Franks
Matthew Glenn
Roland Govers
Karl Hansford
Murray Hargrave
Jonathan Harris





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Justine Hill
Shu-Hong Hu
Bixing (Ben) Huang
Lubomira Jamriska
Marion Loughnan
Andrew Lucke
Gemma Martinez
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Brendan McMorran
Pierre-Francois Mery
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Jorgen Mould
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Paavo Rahkila
Timothy Ravasi
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Horst Schirra
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Philip Sharpe
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Ylva Strandberg
Martin Stoermer
Matthew Sweet
Johan Trygg
Parimala Vajjhala
Ellen vanDam
Cynthia Whitchurch
Jon Whitehead
Dagmar Wilhelm
Lorine Wilkinsen
Megan Wilson
Fiona Wylie
Zheng Yuan

PhD Students

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Udani Abeypala
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Azita Ahadizadeh
Christopher Armishaw
Daniel Barry
Scott Beatson
Jennifer Bolton
Tom Chen
Anthony Cook
Larry Croft
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Nicholas Drinnan
Julie Dutton
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Tamarind Hamwood
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Douglas Horton
Wendy Ingram
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Gabriel Kolle
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Donmienne Leung
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Isabel Morrow

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Ryan O'Donnell
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Manuel Plan
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Ingrid Schroeder
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Dimitra Temelcos
Manuela Trabi
Budi Utama
Nicole Walsh
Shannon Walsh
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Joyce Wang
Stacey Wardrop
Christine Wells
Charlotte Widberg Flanagan
David Wilson
Takahiro Yasuda

Masters Students

Saleh Hasnawati
Darryl Irwin
Helene Johanson
Chi-Yan Lau
Maria Quimio
Claire Wade
Bo Wang

Honours Students

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Jennifer Bennetts
Perpetina Christy
Gillian Gillmore
Kelly Lammerts van Bueren
Andrew McDevitt
Nicholas Meadows
Christine Mulford
Julia Pagan
Andrew Pearson
Nadya Shale
Emma Smith
Joanna Starkey

Research Assistants

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Jennifer Berkman
Renee Beyer
Trudy Bond
Selena Boyd
Darren Brown
Vanessa Caig
Marc Campitelli
Lucy Carter
Tara Carton
Stephen Cronau
Joanne Dowd
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Charles Ferguson
Cameron Flegg
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Kylie Georgas
Simon Golding
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Ning Huang
David Ireland
Carolyn Jacobs
Kristy James
Russell Jarrott
Chris Johns
Shannon Joseph





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Darren Pickering
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Darren Smit
Nikolai Sokolenko
Darrin Taylor
Elaine Thomas
Linda Thomas
Liam Town
Brendan Tse
Juliana Venturato
Susie Verma
Daying Wen
Jacqueline Wicks
Shayama Wijedasa
Elizabeth Williams
Shaiyena Williams
Ian Wilson
Jason Wyeth
Greg Young

Scientific Support

Karl Byriel
Alun Jones
Darren Paul

Adjunct appointments

Judy Halliday
Tracie Ramsdale
Robert Raven
Sangkot Marzuki

Visiting researchers

Tian-Huey Lu
Georg Ramm
Dietmar Schomburg

Vacation and visiting scholars – Visiting Scholar

Sari Alatalo
Ute Marx
Sally Slack
Jian Sun
Jenny Ekberg
Angelica Figueroa Conde-Valvis
Emma Fornander
Daniel Gottlieb
Bert Janssen
Jenny Pettersson
Carl Wibom

Vacation and visiting scholars – Vacation Scholar

Kim Hanchard
Michael Hines
Daniel Sangermani
Oliver Tam
Fraser Wright

Vacation and visiting scholars – UROP Student

Sarah Maguire
Jessica Mar
Debby Melissen
Heidi van Paassen

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Jodie Campbell, Reception/Secretary
Barbara Clyde, Administrative Officer
Robyn Craik, Reception/Secretary
Ann Day,
Personnel Manager & Graduate Coordinator
Mileta Duggleby, Purchasing Officer
Barbara Feenstra, Reception/Secretary
Angela Gardner, Administrative Officer
Carole Key, Principal Administration Officer
Karen Korenromp, Finance Manager
Ronda Turk, Reception/Finance Assistant
Santa-Maria Trubshaw, Reception/Secretary

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Christopher Barnett, Lab Manager
Hendrick Faber, Technical Assistant
Gregory McHugh,
Technical Officer (Maintenance)
Charles Nelson, Safety Officer
David Scarce, Workshop Manager
Michael Tetley, Glassware Attendant
Dawn Walsh, Glassware Attendant

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Ondrej Hlinka, Computer Systems Officer
Luke Kirkwood, Computer Systems Officer
Maria Maddison, Computer Systems Officer
Nelson Marques, Computer Systems Officer
Lance Rathbone, Computer Systems Officer
Patrick Verhoeven, Computer Systems Officer
Ming Ju (Calvin) Wang,
Computer Systems Officer

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Russell Griggs, Communications Officer
Tania Hudspith, Marketing Officer
Angela Wallace, Education Assistant
Helen Weatherley,
Marketing & Communications Manager

IMBcom Pty Ltd

Peter Andrews, CEO IMBcom
Daniela Bellomo, Biotechnology Analyst
Ashley Bowen,
General Manager, Technology Development
Kellie Broderick, Executive Assistant
Lisa Edwards, Administration Assistant
Michael Finney,
General Manager, Commercial Development
Kim Flanagan, Administrative Assistant
Doug Horton, Commercial Intelligence Analyst
Wei-Lin (Maggie) Hsu,
Commercial Intelligence Analyst
Christine Morrison, Business Manager
Kathryn Nielsen, Manager,
Intellectual Property & Business Analysis
Peter Riddles,
General Manager, Corporate Development
Alan Scott, Finance Manager
David Wilson, Commercial Intelligence Analyst





Financial statement of operating income and expenditure
Year ended 31 December 2001

INCOME:

	Note	2000 ($AUD)	2001 ($AUD)
University of Queensland (Operating Grant)	1	2,942,718	6,664,365
University of Queensland Research Grants		200,990	100,000
State Government	2	5,500,000	2,500,000
SRC Grant (Australian Research Council)		1,631,153	1,039,320
Australian Research Council	3	1,131,271	1,668,000
Clive and Vera Ramaciotti Foundation		43,545	9,545
CRC for Discovery of Genes for Common Human Diseases		220,958	232,415
Diabetes Australia Research Trust		33,409	35,791
Department of Industry Science and Technology		166,400	0
Human Frontiers Science Program		127,242	0
Glaxo Welcome Australia		670,000	62,000
Government Employees Medical Research Fund		45,000	0
Juvenile Diabetes Foundation International		299,626	267,704
Mayne Bequest Foundation		60,000	0
The Merck Genome Research Institute		261,559	0
National Health and Medical Research Council	3	2,938,586	5,359,112
National Heart Foundation		45,000	0
Post Graduate Scholarships		28,209	15,882
Queensland Cancer Fund		230,072	116,447
Sylvia and Charles Viertel Charitable Foundation		165,000	165,000
Wellcome Trust		28,011	23,829
Commercial Income		1,371,664	2,589,861
Miscellaneous Income		415,591	272,136
TOTAL INCOME:		**$18,556,004**	**$21,121,405**
Funds brought forward from previous year	***4***	***$1,009,031***	***$3,843,597***
TOTAL FUNDS AVAILABLE		**$19,565,034**	**$24,965,002**

EXPENDITURE:

Salaries-Research		6,549,841	7,809,255
-Administration		1,090,220	1,117,375
-Infrastructure		541,043	813,527
Research Services		2,635,745	6,034,723
Education Programs	5	317,726	378,436
Administration	6	937,703	550,574
Infrastructure	7	357,436	928,651
Capital Equipment	8	2,307,116	3,132,769
IMBcom		984,608	605,214
TOTAL EXPENDITURE:		**$15,721,437**	**$21,370,523**
Funds carried forward:	***9***	***$3,843,597***	***$3,594,479***

Explanatory notes to statement of income and expenditure

1/ In-kind Contributions

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

	Department	*%*
S. Barker	Parasitology	80
D. Hume	Biochemistry	20
T. Loy	Anthropology & Sociology	100
J.Mattick	Biochemistry	20
R.Parton	Micoscopy & Microanalysis	10
J.Rothnagel	Biochemistry	80
B.Wainwright	Biochemistry	20
M.Waters	Physiology & Pharmacology	100
A.Yap	Physiology & Pharmacology	80
B.Kobe	Biochemistry	80

2/ State Government Funding received in advance for 2001

	1,750,000

3/ Fellowship/Projects from Government Agencies

Australian Research Council	
Projects	1,316,608
Fellowships	351,392
	1,668,000
National Health and Medical Research Council	
Projects	4,450,336
Fellowships	908,776
	5,359,112

4/ Funds brought Forward from 2000

University of Queensland Operating Grant	71,883
University of Queensland Research Grants	66,234
Post Graduate Scholarships	4,937
State Government	1,961,398
SRC Grant	513,119
Fellowships (as approved by funding bodies)	15,685
Project Grants (as approved by funding bodies)	1,210,339
	3,843,597

5/ Education Programs

Postgraduate scholarships	332,299
Postgraduate recruitment & training	30,180
Public Policy & Ethics	15,958
Total Education Services	**378,436**

6/ Administration

Annual Report	29,426
Marketing	18,446
Personnel Recruitment and Training	70,715
Visiting Scientists/Seminars	22,207
Fees	252,311
Entertaining	25,730
Equip Lease	22,249
Photocoping	13,436
Postage and Freight	12,023
Printing and Stationery	63,260
Telephone	48,686
Travel Expenses	16,887
Sundries	14,465
Cost Recovery	-59,268
Total Administration	**550,574**

7/ Infrastructure

Building Maintenance	71,373
Rental - Demountables/Storage	29,722
Renovations	234,696
Laundry	1,931
Minor Equipment & Furniture	35,246
Equipment Maintenance	211,253
Animals	83,890
Computer Services	119,420
Glass washing and replacement	17,617
Reticulated gases, RO water & dry ice	58,511
Sundries	27,349
Stores	37,642
Total Infrastructure	**928,651**

8/ Capital Equipment

Scientific Equipment	2,606,495
Minor Equipment	526,275
Total Capital Equipment	**3,132,769**

9/ Funds carried forward to 2002

University of Queensland Operating Grant	1,619,317
University of Queensland Research Grants	-232
Post Graduate Scholarships	3,544
State Government	-150,411
SRC Grant	164,880
Fellowships (as approved by funding bodies)	77,703
Project Grants (as approved by funding bodies)	1,879,678
	3,594,479

How can we help you?

The IMB is committed to building partnerships and collaborations with industry, government and other research organisations, contributing to world knowledge in terms of human and animal biology as well as health benefits for the global community, and ethics of the new genetics. In particular, the IMB is developing:

- **partnerships** with hospitals and medical research institutes to provide a better understanding of the genetic and biochemical basis of disease, and to develop and trial clinical candidates emerging from its research programs.
- **strategic alliances** with national and international pharmaceuticals to build technology platforms and develop novel pharmaceuticals based on the Institute's research programs.
- **collaborations** with mathematicians and computational scientists to develop new programs in bioinformatics and biological information theory which will have an impact on future design of computers and information systems.
- **joint ventures** with the CSIRO and Queensland Department of Primary Industries to transfer IMB's technologies and utilise its facilities for the development of products for plant and livestock industries.
- **exchange programs** with national and international educational institutions to build a diversity of skills across cultures and disciplines, and to enhance the IMB's ability to contribute to the developing world.

To explore how the IMB can build its relationship with your organisation or research group, please call the IMB today or alternatively, please complete and return this page.

☐ Please arrange for a representative of the Institute for Molecular Bioscience to call me to discuss potential collaborations.

☐ Please send me more information about supporting the work of the Institute.

☐ Please send me the Institute's Scientific Annual Report and newsletter.

Name: .....

Address: .....

..... ***Postcode:*** .....

Ph: ..... ***Fax:*** .....

Email address: .....

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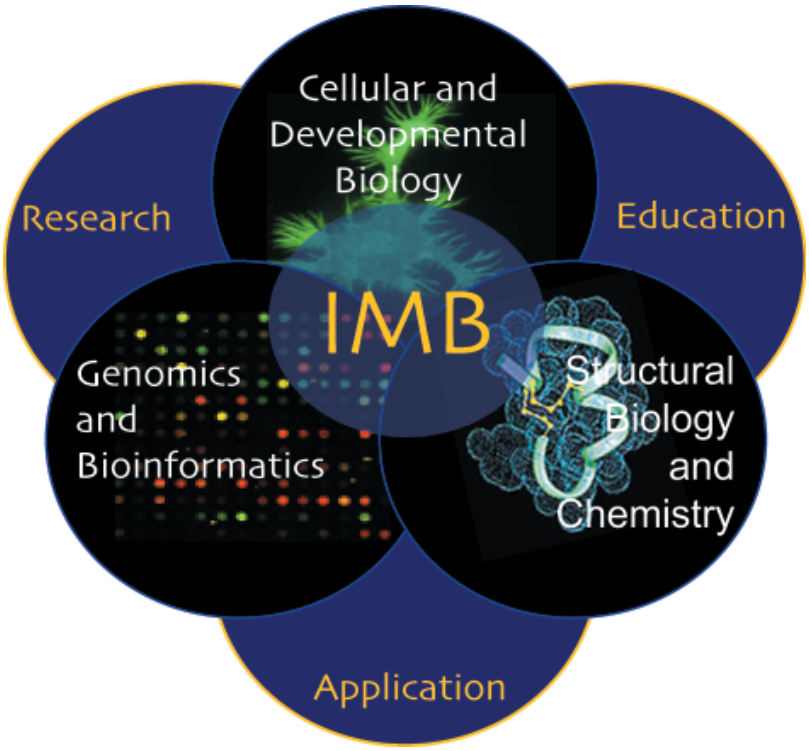

This report was designed, edited and produced by
David Fairlie, Teresa Buckley and the IMB Marketing Team

Institute for Molecular Bioscience
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