THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

IMB Institute for Molecular Bioscience

ANNUAL REPORT 2003

Recommended further reading in conjunction with this Annual Report

- IMBcom Annual Report 2003
- SRC for Functional and Applied Genomics Annual Report 2003
- ARC for Bioinformatics Annual Report 2003

The IMB acknowledges and thanks our supporters and partners

The University Of Queensland
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National Health and Medical Research Council

ARC
AUSTRALIAN RESEARCH COUNCIL

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

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

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

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

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

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

Cooperative Research Centre for
Chronic Inflammatory Diseases

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1.

Professor John Hay AC

CHAIR'S REPORT

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

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

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

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

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

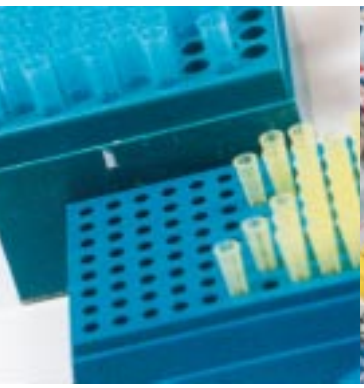
The IMB is part of a strategic cluster of research excellence at UQ - the Australian Institute for Bioengineering and Nanotechnology (AIBN) and the Queensland Brain Institute (QBI) currently under development are modelled on the successful IMB.

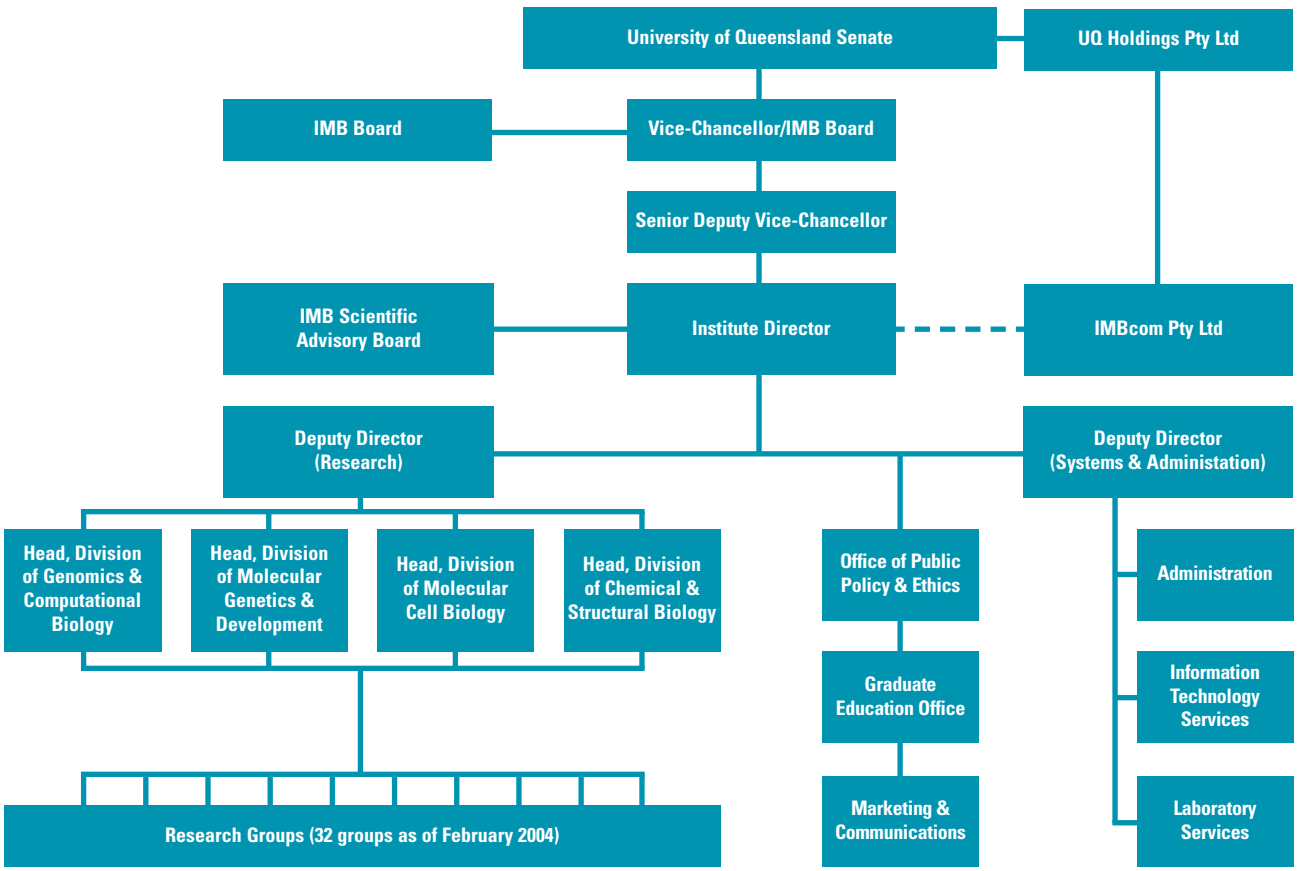
As Chair of the IMB Board, I would like to express my sincere thanks to the members of the IMB Board and Scientific Advisory Board for the contribution of their time, skills and energy to manage and develop the Institute.

Professor John Hay AC
Vice-Chancellor
The University of Queensland

2.

Organisational Chart





3.

Professor John Mattick AO

DIRECTOR'S REPORT

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

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

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

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

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

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

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

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

DIRECTOR'S REPORT CONTINUED

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

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

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

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

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

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

Professor John Mattick AO
Director
Institute for Molecular Bioscience

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

4.

IMB Advisory Board

Professor John Hay AC (Chair)

(Pictured 1)

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

Professor John Mattick AO (Director)

(Pictured 2)

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

Mr Paul Fennelly

(Pictured 3)

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

The Department's activities involve:

- Major Projects & Infrastructure
- Investment Attraction
- Public Private Partnerships
- Industry Development
- Innovation
- Small Business

From January 2000 to January 2002, Mr Fennelly was the State Director of Australian Industry Group, Victoria's largest business organisation, representing approximately 6,000 companies. Mr Fennelly was also the Queensland Director of MTIA / Australian Industry Group from 1993 - 1999. Mr Fennelly holds degrees in Law and Arts, as well as a Graduate Diploma in Industrial Law.

Members of the IMB Advisory Board: *Professor John Hay AC, Professor John Mattick AO, Mr Paul Fennelly, Mr Scott Flavell, Professor Frank Gannon, Professor Paul Greenfield, Dr Russell Howard, Dr Peter Isdale, Ms Helen Lynch AM, Professor Mick McManus, Mr Ross Rolfe, Sir Sydney Schubert.*

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

Mr Scott Flavell

(Pictured 4)

Scott Flavell has been the Director-General of the Department of Innovation and Information Economy, Sport and Recreation Queensland since 3 June 2002. Prior to his current position, Scott was the Executive Director of the Office of Energy. He has worked as an economist and policy advisor in senior positions in the Commonwealth and Queensland Governments for the past 18 years, including Queensland Treasury, the Department of the Premier and Cabinet, the Department of the Prime Minister and Cabinet and the Department of Finance.

Professor Frank Gannon

(Pictured 5)

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

Professor Paul Greenfield

(Pictured 6)

Professor Greenfield is Senior Deputy Vice-Chancellor of the University of Queensland. After graduating Bachelor of Engineering, first-class honours in chemical engineering, from the University of New South Wales (UNSW), Professor Greenfield worked in the private sector before completing a PhD at UNSW. He worked at CSIRO before winning a three-year fellowship to the U.S. In 1975, he joined the University of Queensland as a lecturer in chemical engineering and a decade later became Head of Department and then Pro-Vice-Chancellor (Physical Sciences and Engineering) before being appointed an inaugural Executive Dean in 1997. Currently, he chairs the Scientific Advisory Committee overseeing the $5.2 million Moreton Bay and Brisbane River Wastewater Management Study (since 1994); the Waste Technical Working Group, Basel Convention (since 1995); and the Advisory Board of I.P. Australia (since 1999). He is also a Director of several University companies including UniQuest Pty Ltd. In 1995, he won the Chemeca Medal, awarded jointly by the Institution of Chemical Engineers and the Institute of Engineers Australia for outstanding contribution to the profession.

Dr Russell Howard

(Pictured 7)

Dr. Howard is Maxygen's Chief Executive Officer and one of the company's co-founders (founded in 1997). Originally trained in biochemistry and chemistry, Dr. Howard has spent over 20 years studying infectious diseases, primarily malaria. Before joining Maxygen, Dr. Howard served as the President and Scientific Director of Affymax Research Institute, an institute employing combinatorial chemistry and high throughput target screening to discover drug leads. Prior to joining Affymax, Dr. Howard held various research positions at DNAX Research Institute and the National Institutes of Health. Dr.Howard received his Ph.D. in biochemistry from Melbourne University, Australia. In addition to numerous patents, Dr. Howard has over 140 publications in peer-reviewed journals. Today, Maxygen is focused primarily on development of protein pharmaceutical drugs, with other therapeutics programs in vaccines. Maxygen spun-out its chemicals manufacturing division, Codexis, in 2002 and retains its wholly-owned Agbiotech subsidiary, Verdia.

Dr Peter Isdale

(Pictured 8)

Peter Isdale was appointed Chief Executive Officer of IMBcom Pty Ltd in March 2003. He spent 15 years as a marine scientist before trading his wetsuit for a business suit at the Australian Institute of Marine Science (AIMS), the country's marine national science agency, where he had been a Principal Research Scientist who is the author or co-author of more than 30 papers in his special field of research. As the Business Director and Executive at AIMS, Dr Isdale directed the strategic development of AIMS' business and commercial interests, including licensing and company spinouts, and managed the Institute's legal and intellectual property affairs. Dr Isdale has had 17 years of directorship on company boards, and a record of achievement in the operation

and governance of both private, public and ASX-listed companies in Australia, Asia and the Pacific Rim. He is a Member of the Australian Institute of Company Directors, and currently holds the positions of non-executive director, Great Barrier Reef Research Foundation, non-executive chairman of The Wetlands and Grasslands Foundation, Senior Fellow, Chaiyong Limthongkul Foundation, Bangkok, Thailand and Adjunct Professor, Department of Land Development and Environmental Planning, School of Architecture, Texas A&M University.

Ms Helen Lynch AM

(Pictured 9)

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

Professor Mick McManus

(Pictured 10)

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

Mr Ross Rolfe

(Pictured 11)

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

Sir Sydney Schubert

(Pictured 12)

Sydney Schubert has had a career spanning 40 years with the Queensland Government, including Co-ordinator General and Director-General between 1976 and 1988. He was Executive Chair of Daikyo Group of Companies, Australia and New Zealand, from 1988 to 2000. Currently he is Chair of the CRC for Great Barrier Reef World Heritage Area, CRC for Tropical Rainforest Ecology and Management and CRC for Torres Strait. He is also Director of the Australian Tropical Forest Institute and Australian Canopy Crane.

5.

IMB Year Highlights

(Left) IMB's Jenny Martin and the new X-Ray Crystallography instrument.
(Right) New appointments Jeff Gorman and Rob Capon.

The highlights for 2003 were varied from outstanding research achievements, relocation to our new home in the Queensland Bioscience Precinct and visits from internationally acclaimed researchers.

FACILITIES

Opening of the Queensland Bioscience Precinct

The opening of the Queensland Bioscience Precinct (QBP) and subsequent relocation of the IMB into its new home was a watershed for the emergence of Queensland as a regional and international centre for advanced bioscience research.

Opened by the Federal Minister for Education, Science and Training Dr Brendan Nelson and Queensland Premier Peter Beattie on 21 May 2003, the QBP brings together for the first time under one roof all aspects of the IMB.

The Precinct offers IMB research and support staff a work environment the equal, if not better, than any other research facility in the nation.

UQ's equipment sharpening the cutting edge

The ability of IMB and UQ researchers to solve extremely difficult molecular problems has taken a giant leap forward with the installation of Australia's most powerful X-ray crystallography instrument.

This new weapon in the research arsenal of IMB and UQ will help in the fight against many human diseases such as cancer, diabetes and Alzheimer's to name a few.

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

New building allows new appointments

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

Professor Jeff Gorman (Molecular and Cellular Proteomics) and Professor Rob Capon (Centre for Biodiversity) were attracted by the leading edge facilities and collaborative opportunities available at IMB and the QBP.

Prior to joining IMB, Jeff Gorman was a senior principal research scientist with CSIRO/The Biomolecular Research Institute in Victoria. He is on the editorial boards of several leading journals in the field of protein and proteomic research.

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

RESEARCH

Anti-obesity gene flexes its muscle

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

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

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

The nature of venom reviewed in Nature

Cancer signal localised

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

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

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

Medication has helped reduce Australian suicide rate

Access to antidepressant medication had a significant impact on suicide deaths in Australia a major national study found.

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

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

Assigning function to the transcritome

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

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

Inflammatory argument

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

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

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

Venom switches function

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

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

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

AWARDS

Centenary Honour

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

National honour for Queensland researcher

Australia's peak scientific body the Australian Academy of Science awarded IMB's Melissa Little the prestigious Gottschalk Medal for medical sciences.

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

New mining technology to help identify genes

IMB researcher Rohan Teasdale won a $75,000 UQ Foundation Research Excellence Award to continue his important work using 'database mining' to extract valuable information about how cells work.

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

IMB researcher tops world list

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

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

Researcher rewarded with Federation Fellowship

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

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

GRANTS

US supports IMB research

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

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

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

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

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

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

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

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

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

New research centre in bioinformatics

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

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

CONFERENCES

ISMB Conference

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

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

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

IMB Symposium

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

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

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

COMMERCIALISATION

CEO boosts Queensland's commercialisation

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

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

Commercialisation boost for Queensland research

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

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

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

imbcom pty ltd
the commercialisation company for the institute for molecular bioscience

NANOMICS Biosystems

Below: IMBcom CEO Peter Isdale

6.

IMB Research

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

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

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

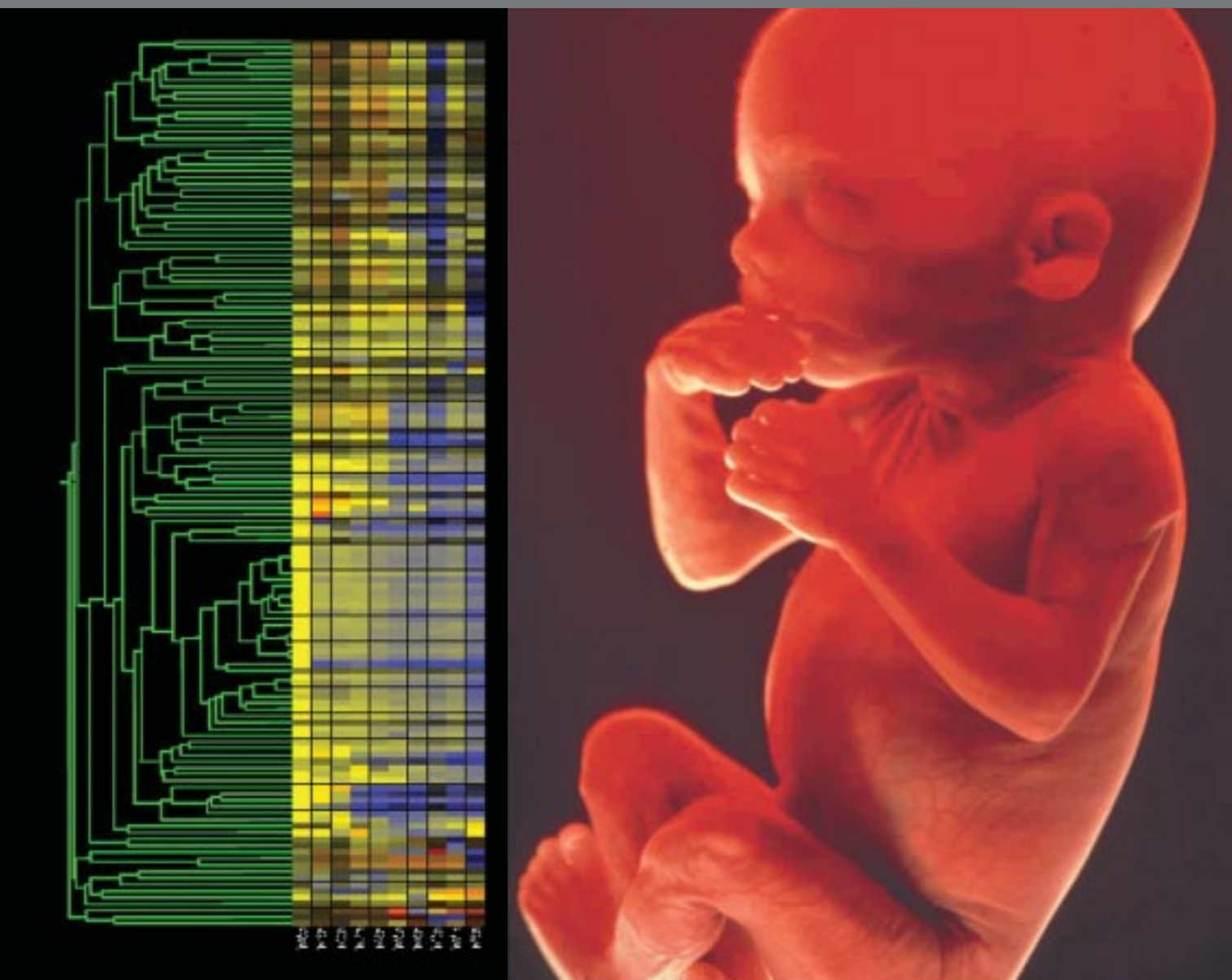
We also wish to understand what aspects of the process go awry in various disease processes, including cancer and other complex diseases that are the major health burden of our population.

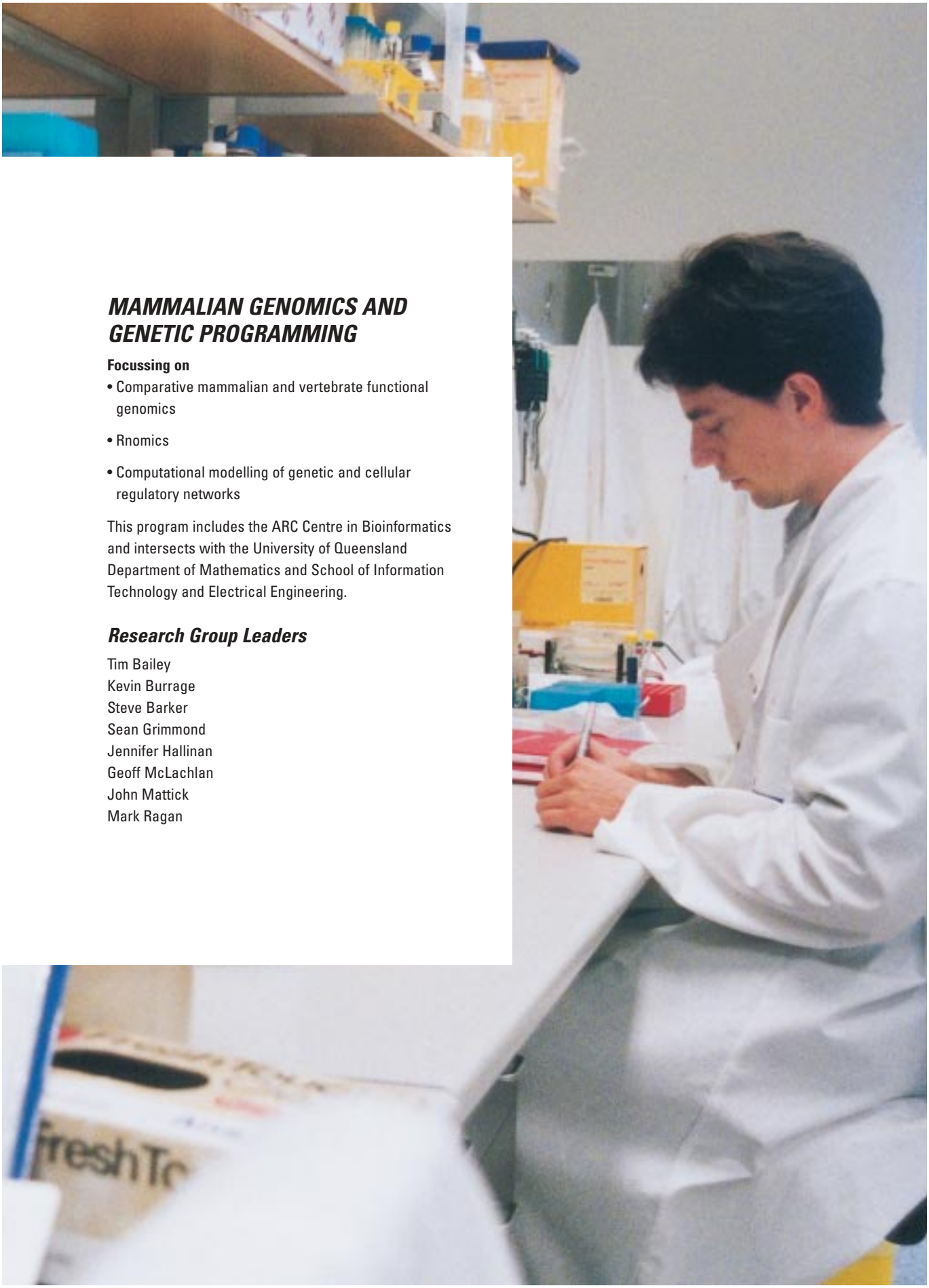
Finally, arising from these insights, we also wish to develop pharmaceutical and cellular therapies, technologies and diagnostics to prevent or repair such diseases, and to pursue other opportunities for the practical applications of our understanding of mammalian genetic programming and molecular architectures,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

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

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

"If you're going to be a biologist and alive at any point in time in human history, you'd choose to be alive right now."
Professor Brandon Wainwright, Deputy Director Research.





MAMMALIAN GENOMICS AND GENETIC PROGRAMMING

Focussing on

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

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

Research Group Leaders

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

Tim Bailey

COMPUTATIONAL BIOLOGY, BIOINFORMATICS, STATISTICAL MODELING

Research overview

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

Collaborators

Kevin Burrage Department of Mathematics, UQ and IMB

Mark Ragan, IMB

Rohan Teasdale, IMB

Sean Grimmond, IMB

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

Staff and Students

Undergraduate research scholars
Deanne Hummelstad
Bryce Shepherd

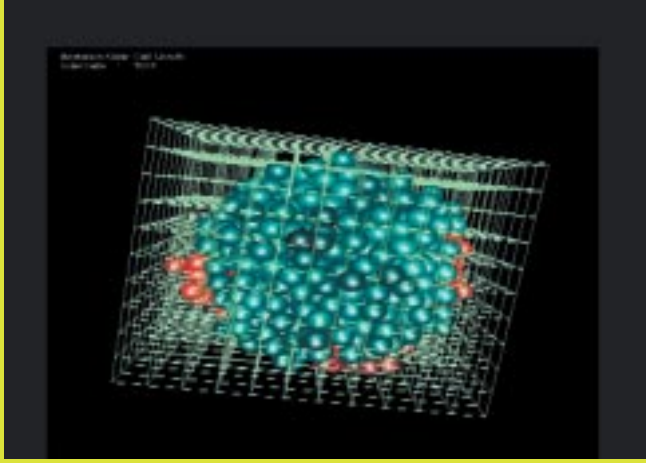
Grants

ARC *Centre in Genome/Phenome Bioinformatics*

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

Publications

Bailey, T.L., Noble, W. (2003) Searching for statistically significant regulatory modules. *Bioinformatics,* 19:1116-1125.



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

Kevin Burrage

BIOINFORMATICS

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

Project

Stochastic models and simulations for chemically reacting systems

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

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

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

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

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

Collaborators

Professor Perry Bartlett, Queensland Brain Institute, UQ

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

Grants 2004

ARC *Centre for Genome/Phenome Bioinformatics*

ARC *Discovery 2004 - 2006*

Publications

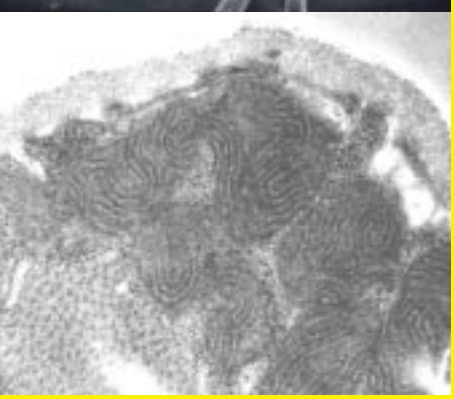
5 papers have been written in the above areas

Staff and Students

Tianhai Tian
Francis Clark
Nick Hamilton
David Woolford

Steve Barker

ARTHROPOD EVOLUTIONARY GENETICS



Research Overview

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

Projects

Mitochondrial genomics
Mitochondria have their own genomes, and in most groups of animals the order of genes is remarkably similar.

However, we discovered two extraordinary exceptions: a group of hard ticks, and lice and their kin. The arrangement of the 37 genes in the mitochondrial genomes of these animals has changed so many times it is difficult to reconstruct the evolutionary path of these mitochondrial genomes.

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

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

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

Evolutionary relationships of lice
Human head lice are a severe social problem in developed countries yet body lice, which are associated with diseases like Typhus, are not.

The two are closely related and may even be the same species. We are studying whether the head and body lice of humans are interbreeding and therefore conspecific.

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

Collaborators

Dr Michael Whiting, Bringham Young University, Utah, USA

Professor Masahito Fukunaga, Fukuyama University, Hiroshima, Japan

Associate Professor Rick Speare, James Cook University, Townsville Australia

2003 Grants

Uniseed Pty Ltd Seed funding for Hatchtech Pty Ltd

Biotechnology Innovation Fund to Hachtech Pty Ltd *A novel strategy for controlling lice of humans*

ARC Linkage Grant *Resistance to pediculicides in head lice, Pediculus humanus capitis*

ARC Grant *Origins of parasitism in the Psocodea insecta*

Fisheries Research & Development Corporation (FRDC) *Control of Perkinsus disease in abalone*

(Left) This is Pediculus humanus, the head louse of humans; (Right) A cattle tick from Zimbabwe, Amblyomma hebraeum

(0pposite page above) A wildlife tick from Australia, Haemaphysalis bremneri; (0pposite page below) The cristae of the mitochondria of a louse

Staff and Students

Postdocs	**PhD students**	**Honour students**
Renfu Shao	Natalie Leo	Cassie Jansen
Anna Murrell	Cath Covacin	Conor McMeniman
Steven Cameron		Carl Davis (with CSIRO Livestock Industries, QBP)

Publications

Murrell, A., Klompen, J.S.H., Barker, S.C. (2003) Synonymy of *Boophilus Curtice,* 1891 and *Rhipicephalus Koch,* 1844; *Boophilus* is a derived group within *Rhipicephalus. Systematic Parasitology* 56:169-172.

Hunter, J. and Barker, S.C. (2003) Susceptibility of head lice *(Pediculus humanus capitis)* to pediculicides in Australia. *Parasite Research* 90:476-478.

Barker, S.C., Whiting, M., Johnson, K. Murrell, A. (2003) Phylogeny of the lice (Insecta, Phthiraptera) inferred from small subunit rRNA. *Zoologica Scripta* 32:407-414.

Shao, R., Murrell, A., Dowton, M. Barker, S.C. (2003) Rates of gene rearrangement and nucleotide substitution are correlated in the mitochondrial genomes of insects. *Molecular Biology and Evolution* 20:1612-1619.

Murrell, A., Dobson, S., Yang, X., Lacey, E. Barker, S.C. (2003) A survey of bacterial diversity in ticks, lice and fleas from Australia. *Parasitology Research* 89:326-334.

Robinson, D., Leo, N., Prociv, P., Barker, S.C. (2003) Are head lice, *Pediculus humanus var. capitis,* potential vectors of *Rickettia prowazekii? Parasitology Research* 90:209-211.

Shao, R., Barker, S.C. (2003) The Highly Rearranged Mitochondrial Genome of the Plague Thrips, *Thrips imaginis* (Insecta: Thysanoptera): Convergence of Two Novel Gene Boundaries and an Extraordinary Arrangement of rRNA Genes. *Molecular Biology and Evolution* 20:362-370.

Barker, S.C. (2003) The Australian paralysis tick, *Ixodes holocyclus,* may be the missing link in the transmission of Hendra virus from bats to horses to humans. *Medical Hypotheses* 60:481-483.

Murrell, A., Campbell, N.J.H., Barker, S.C. (2003) The value of idiosyncratic markers and conserved tRNA sequences from the mitochondrial genomes of hard ticks (Acari: Ixodida: Ixodidae) for phylogenetic inference. *Systematic Biology* 52:296-310.

Sean Grimmond

EXPRESSION GENOMICS

Research Overview

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

Undertaking this sort of research requires an integrated pipeline that uses

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

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

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

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

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

Projects:

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

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

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

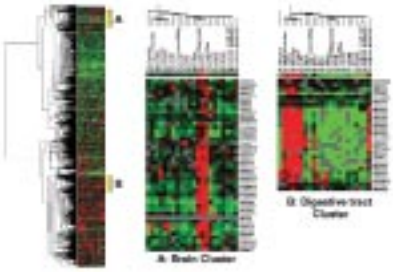
Collaborations

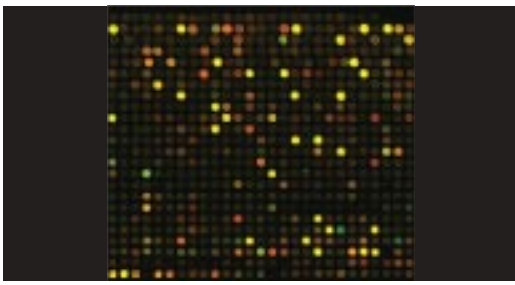
NIDDK NIH Stem Cell Genome Anatomy Project:
- Melissa Little, IMB

IMB-RIKEN Sub-Cellular Localisation Project:
- Rohan Teasdale, IMB
- Harukazu Suzuki at Genome Sciences RIKEN, Japan
- David Hume, IMB

Grants awarded

ARC Centre for Genome/Phenome Bioinformatics





Staff and Students

Research officers
Tina Maguire
Donna Mahony
Nic Waddel
Brooke Taylor

Research assistant
Milena Gongora

Bioinformatician
Darrin Taylor

PhD student
Alistair Forrest

Honours student
Rowena Cecil

Publications and papers

Ashton, K., Holmgren, K., Lankford, A.R., Matherne, G.P., Grimmond, S., Headrick, J. (2003) Effects of A1 adenosine receptor overexpression on normoxic and post-ischemic gene expression. *Cardiovasc. Res.* 57:715-26.

Ravasi, T., Huber, T., Zavolan, M., Forrest, A., Gaasterland, T., Grimmond, S., RIKEN GER Group Members, Hume, D.A. (2003) Systematic characterization of the zinc finger containing proteins in the mouse transcriptome. *Genome Research* 13:1430-42.

Forrest, A., Ravasi, T., Hume, D., Taylor, D., Huber, T., RIKEN GER Group Members, Grimmond, S.M. (2003) Protein Phosphoregulators: Protein Kinases and protein phosphatases of the mouse. *Genome Research* 13:1443-54.

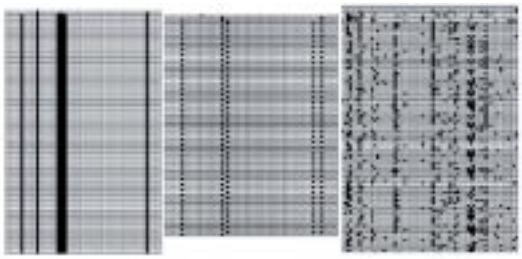
Kanapin, A., Gough, J., Grimmond, S.M. Davis, M., RIKEN GER Group Members, Teasdale, R.D. (2003) The mammalian proteome. *Genome Research* 13:335-44.

Gustincich, S., Arakawa, Y., Batalov, S., Beisel, K.W., Bono, H., Carninci, P., Fletcher, C.F., Grimmond, S.M., Hirokawa, N., Jarvis, E.D., Jegla, T., Kawasaka, Y., Miki, H., Raviola, E., Teasdale, R.D., Waki, K., Zimmer, A., Kawai, J., Hayashizaki, Y., Okazaki, Y. (2003) Analysis of the mouse transcriptome for genes involved in the function of the nervous system. *Genome Research* 13:1395-401.

Forrest, A., Taylor, D., RIKEN GER Group Members, Grimmond, S. (2003) Cell cycle regulators of the mouse. Genome Research 13:1366-75.

Grimmond, S., Miranda, K., Yuan, Z., Davis, M., Hume, D., Yagi, K., Tominaga, N., Bono, H., Hayshizaki, Y., Okazaki, Y., RIKEN GER and GSL Members, Teasdale R.D. (2003) The mammalian secretome: Functional classification of the proteins secreted into the extra-cellular environment. *Genome Research* 13:1350-9.

de Sousa Nunes, R., Rana, A., Kettleborough, R., Brickman, J., Clements, M., Rodriguez, T.A., Forrest, A., Bullock, S., Martinez Barbera, J.P., Grimmond, S.M., Avner, P., Smith, J.C., Dunwoodie, S.L., Beddington, R.S.P. (2003) Characterizing Embryonic Gene Expression Using a Non-Redundant Sequence-Based Selection Method. *Genome Research* 13:2609-20 (Journal cover)



Jennifer Hallinan

COMPLEX SYSTEMS NETWORKS

Research overview

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

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

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

Projects

Development and analysis of computational models of networks

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

Network models based on biological data

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

Grants awarded

UQ Early Career Researcher Grant *The structure and dynamics of the p53 genetic regulatory network.*

ARC Australian Centre for Genome-Phenome Bioinformatics.

Collaborators

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

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

Staff and Students

PhD student
Ben Skellett

Publications and papers

Hallinan, J. (2003). Self-organization leads to hierarchical modularity in an internet community. In Palade, V., Howlett, R. J. & Jain, L. (eds.) Proceedings of the 7th International Conference on Knowledge-Based Intelligent Information and Engineering Systems. *Lecture Notes in Artificial Intelligence* 2773 914 - 917.

Hallinan, J. (2003). Gene duplication and hierarchical modularity in intracellular interaction networks. *BioSystems.*

Wiles, J., Hallinan, J. (2003). Evolutionary computation and cognitive science. In Fogel, D. B. & Robinson, C. J. (eds.) *Computational Intelligence: The Experts Speak.* San Diego: IEEE Press: 179 - 189.

Speaking engagements

IEEE Congress on Evolutionary Computation,

The First Australian Conference on Artificial Life

7th International Conference on Knowledge-Based Intelligent Information and Engineering Systems.

Department of Pathology, University of New South Wales.

Geoff McLachlan

DATA MINING AND COMPUTATIONAL STATISTICS

Research overview

My research in statistics is in the related fields of classification, cluster and discriminant analyses, image analysis, machine learning, neural networks, and pattern recognition, and in the field of statistical inference. The focus in the latter field has been on the theory and applications of finite mixture models and on estimation via the EM algorithm.

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

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

Grants (2003)

Australian Research Council *Unsupervised Learning of Mixture Models in Data Mining Applications*

Australian Research Council *Classification of Microarray Gene-Expression Data*

National Health & Medical Research *Council Hierarchical finite mixture modelling of health outcomes: a risk-adjusted random effects approach*

Innovation Access Program *Development of market driven computational biology infrastructure for advanced education and training*

Collaborators

Dr Christophe Ambroise, University of Compiegne, France

Dr Kim Anh-Do, MD Anderson Cancer Center, University of Texas, USA

Professor Christine McLaren, University of California, Irvine, USA

Dr Kelvin Yau, University of Hong Kong

Professor Kaye Basford, School of Land and Food, UQ.

Dr Andy Lee, School of Public Health, Curtin University of Technology, Perth, Western Australia

Staff and Students

Research officers
Richard Bean
Liat Jones
Abdollah Khodkar

PhD students
Soong Chang
Justin Zhu
Katrina Monico

Prizes/keynote addresses

November-December, 2003. Invited lecturer at the winter school jointly sponsored by the universities in the French-speaking part of Switzerland, Villars-Sur-Ollon, Switzerland. Lectures on *Finite Mixture Models* and *The EM Algortihm.*

November, 2003. The fourth international conference for the Critical Assessment of Microarray Data Analysis (CAMDA 2003), Durham, North Carolina. *Use of microarray data via model-based classification in the study and prediction of survival from lung cancer* (presentation of finalist paper in the *CAMDA 2003 Challenge*).

September-October, 2003. Workshop of the Institute for Mathematics and its Applications on *Statistical Methods for Gene Expression: Microarrays and Proteomics,* University of Minnesota. *Classification of Microarray Gene-Expression Data.*

September, 2003. Opening address at the 5th Congresso Nazionale of the Italian Region of the International Biometric Society, Marina di Massa. *Some Applications of Mixture Models.*

August, 2003. 54th Meeting of the International Statistical Institute, Berlin. Organizer of invited paper session on *Mixtures and Applications.*

July, 2003. Royal Statistical Society Workshop on *The Statistical Analysis of Gene Expression Data,* Wye College Conference Centre, Kent, England. *Classification of Tissue Samples on the Basis of Microarray Gene-Expression Data.*

Publications (2003)

Kim, S.-G., Ng, S.K., McLachlan, G.J., and Wang, D. (2003). Segmentation of brain MR images with bias-field correction. In *Proceedings of WDIC2003, APRS Workshop on Digital Image Computing*, B.C. Lovell and A. Maeder (Eds.). Brisbane: Australian Pattern Recognition Society, pp. 3-8.

Mar, J.C. and McLachlan, G.J. (2003). Model-based clustering in gene expression microarrays: an application to breast cancer data. *International Journal of Software Engineering and Knowledge Engineering* 13:579-592.

Mar, J.C. and McLachlan, G.J. (2003). Model-based clustering in gene expression microarrays: an application to breast cancer data. In *Conferences in Research and Practice in Information Technology* Vol. 19, Y.-P. Chen (Ed.). Sydney: The Australian Computer Society, pp. 139-144.

McLachlan, G.J., Ng, S.K., and Peel, D. (2003). On clustering by mixture models. In *Studies in Classification, Data Analysis, and Knowledge Organization: Exploratory Data Analysis in Empirical Research,* O. Opitz and M. Schwaiger (Eds.). Berlin: Springer-Verlag, pp. 141-148.

McLachlan, G.J., Peel, D., and Bean, R.W. (2003). Modelling high-dimensional data by mixtures of factor analyzers. *Computational Statistics & Data Analysis* 41:379-388.

Ng, S.K. and McLachlan, G.J. (2003). On the choice of the number of blocks with the incremental EM algorithm for the fitting of normal mixtures. *Statistics and Computing* 13:45-55.

Ng, S.K.and McLachlan, G.J. (2003). An EM-based semiparametric mixture model approach to the regression analysis of competing-risks data. *Statistics in Medicine* 22:1097-111.

Ng, S.K. and McLachlan, G.J. (2003). On some variants of the EM algorithm for the fitting of finite mixture models. *Austrian Journal of Statistics* 32:143-161.

Ng, S.K. and McLachlan, G.J. (2003). Robust estimation in Gaussian mixtures using multiresolution kd-trees. In *Proceedings of DICTA 2003, 7th Conference of Digital Image Computing: Techniques and Applications* Vol. 1, C. Sun, H. Talbot, S. Ourselin, and T. Adriaansen (Eds.). Sydney: Australian Pattern Recognition Society, pp. 145-154.

John Mattick

RNA-BASED GENE REGULATION IN EUKARYOTIC DEVELOPMENT

Research Overview

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

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

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

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

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

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

Collaborators

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

Professor Claes Wahlstedt, Karolinska Institute, Stockholm, Sweden

Professor Peter Arctander, University of Copenhagen, Denmark

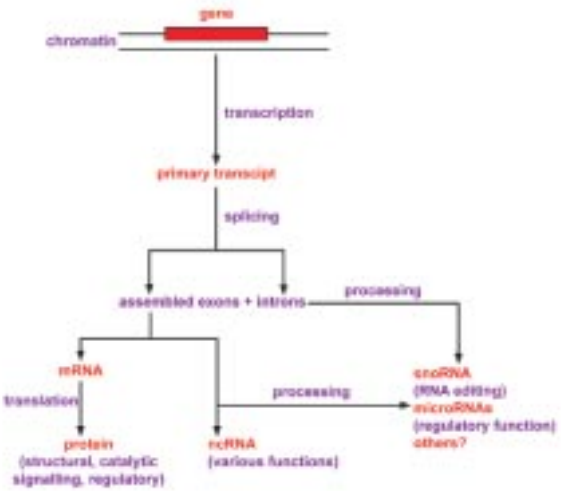
Dr John Logsdon, University of Iowa, USA

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

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

Dr Weisan Chen, Ludwig Institute for Cancer Research, Melbourne

Professor Robert Giegrich (Bielefeld University, Germany)



Staff and Students

Research officers
Dr Michael Gagen
Dr Evgenj Glazov
Dr Igor Makunin

PhD students
Khairina Tajul Arifin
Michael Pheasant
Cas Simons

Masters student
Stuart Stephen

Honours student
Michael Lai

Research assistants
Kelin Ru

Visiting scholars
Marcus Hinchcliffe
Ken Pang
HidayatTrimarsanto

Visiting researcher
Professor Peter Arctander

Publications

Mattick, J.S. (2003) Challenging the dogma: the hidden layer of non-protein-coding RNAs in complex organisms. *Bioessays* 25:930-939.

Mattick, J.S. (2003) Noncoding RNAs: a regulatory role? In *"Nature Encyclopaedia of the Human Genome"* (D. N. Cooper, ed.), Nature Publishing Group, Macmillan Publishers Ltd.

Mattick, J.S. (2003) Introns and noncoding RNAs: the hidden layer of eukaryotic complexity. *In "Noncoding RNAs: Molecular Biology and Molecular Medicine"* (J. Barciszewski and V.A. Erdmann, eds.) Landes Bioscience, Georgetown TX.

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Huang, B., Whitchurch, C.B., Mattick, J.S. (2003) Links FimX, a multidomain protein connecting environmental signals to twitching motility in *Pseudomonas aeruginosa.* J Bacteriol. 185:7068-7076.

Nouwens, A.S., Beatson, S.A., Whitchurch, C.B., Walsh, B.J., Schweizer, H.P., Mattick, J.S., Cordwell, S,J. (2003) Proteome analysis of extracellular proteins regulated by the las and rhl quorum sensing systems in *Pseudomonas aeruginosa* PAO1. *Microbiology.* 149:1311-1322.

Mattick, J.S. (2003) The human genome and the future of medicine. *Med J Aust.* 179:212-216.

Keynote and invited lectures at national and international conferences

Mattick, J.S. (2003) Programming of complex organisms: the hidden layer of noncoding RNA. Lorne Protein Conference, Lorne (plenary).

Mattick, J.S. (2003) The autopoietic programming of complex organisms: the hidden layer of noncoding RNA. Bioinformatics 2003, SocBIN – Society for Bioinformatics in the Nordic Countries, Helsinki, Finland (plenary).

Mattick, J.S. (2003) Programming of the autopoietic development of complex organisms: the hidden layer of noncoding RNA. 11th International Conference on Intelligent Systems for Molecular Biology (ISMB'2003), Brisbane (plenary).

Mattick, J.S. (2003) Genetic programming of complex organisms: the hidden layer of noncoding RNA. International Congress of Genetics (ICG'2003), Melbourne (invited).

Mattick, J.S. (2003) Genetic programming of complex organisms: the hidden layer of noncoding RNA. IXth International Congress on Inborn Errors of Metabolism (ICIEM'2003), Brisbane (plenary).

Mattick, J.S. (2003) Genomic programming of complex organisms: the hidden layer of noncoding RNA. Okinawa International Symposium: New Horizons in Molecular Sciences and Systems - An Integrated Approach, Nara, Japan (invited).

Mattick, J.S. (2003) The hidden layer of efference RNA-mediated regulatory networks: a digital feed-forward system underpinning the evolution and development of complex organisms. 2003 Congress on Evolutionary Computation (CEC'2003), Canberra (plenary).

Invited talks at other institutions

Mattick, J.S. (2003) The hidden layer of eukaryotic complexity: introns and noncoding RNAs in eukaryotic evolution and development. European Molecular Biology Laboratory (EMBL), Heidelberg, Germany.

Mattick, J.S. (2003) The autopoietic programming of complex organisms: the hidden layer of noncoding RNA. Karolinska Institute, Stockholm, Sweden.

Mattick, J.S. (2003) The autopoietic programming of complex organisms: the hidden layer of noncoding RNA. National Cancer Institute, NIH, Bethesda, USA.

Mattick, J.S. (2003) The genomic programming of complex organisms. RIKEN Genome Sciences Center, Yokohama, Japan.

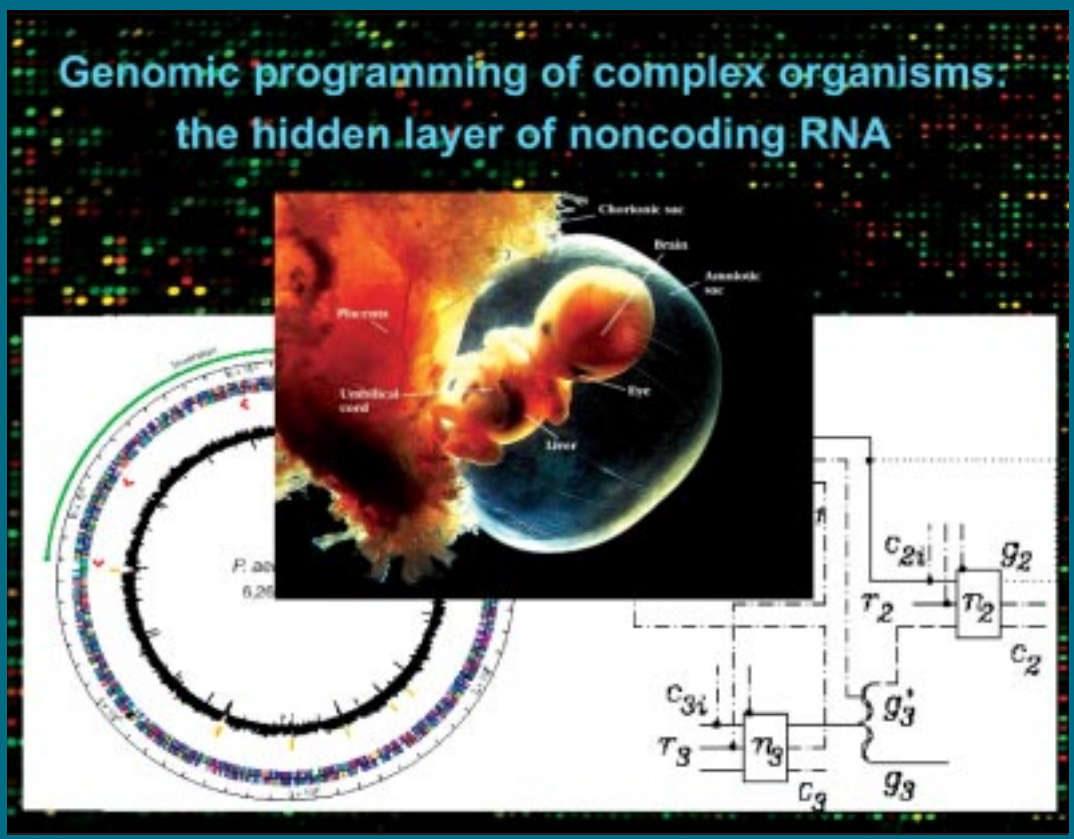
Mattick, J.S. (2003) Genomic programming of complex organisms: the hidden layer of noncoding RNA. Affymetrix Inc., Santa Clara CA, USA.

Mattick, J.S. (2003) Genomic programming of complex organisms: the hidden layer of noncoding RNA. California Institute of Technology, Pasadena CA, USA.

Awards

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

Australian Government Centenary Medal, for services to biotechnology



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

Mark Ragan

COMPARATIVE AND COMPUTATIONAL GENOMICS

Research overview

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

Projects

Automated inference of vertical and lateral gene transmission in prokaryotic genomes

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

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

Component and related projects

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

ARC Centre in Bioinformatics

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

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

Grants Awarded

ARC Centre in Bioinformatics

ARC *Computational infrastructure for high-throughput genome bioinformatics.*

Australian Partnership for Advanced Computing
Comparison of protein families among completely sequenced genomes.

Collaborators

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

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

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

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

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

Samuel Thoraval, Université Montpellier, France

Catherine Letondal, Institut Pasteur, Paris, France

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

Phoebe Chen, Deakin University, Melbourne

Staff and Students

Research officers
Robert Beiko
Nicholas Hamilton
Josef Pánek

PhD students
Cheong Xin Chan
Alex Garcia
Michael Höhl

Research assistant
Timothy Harlow

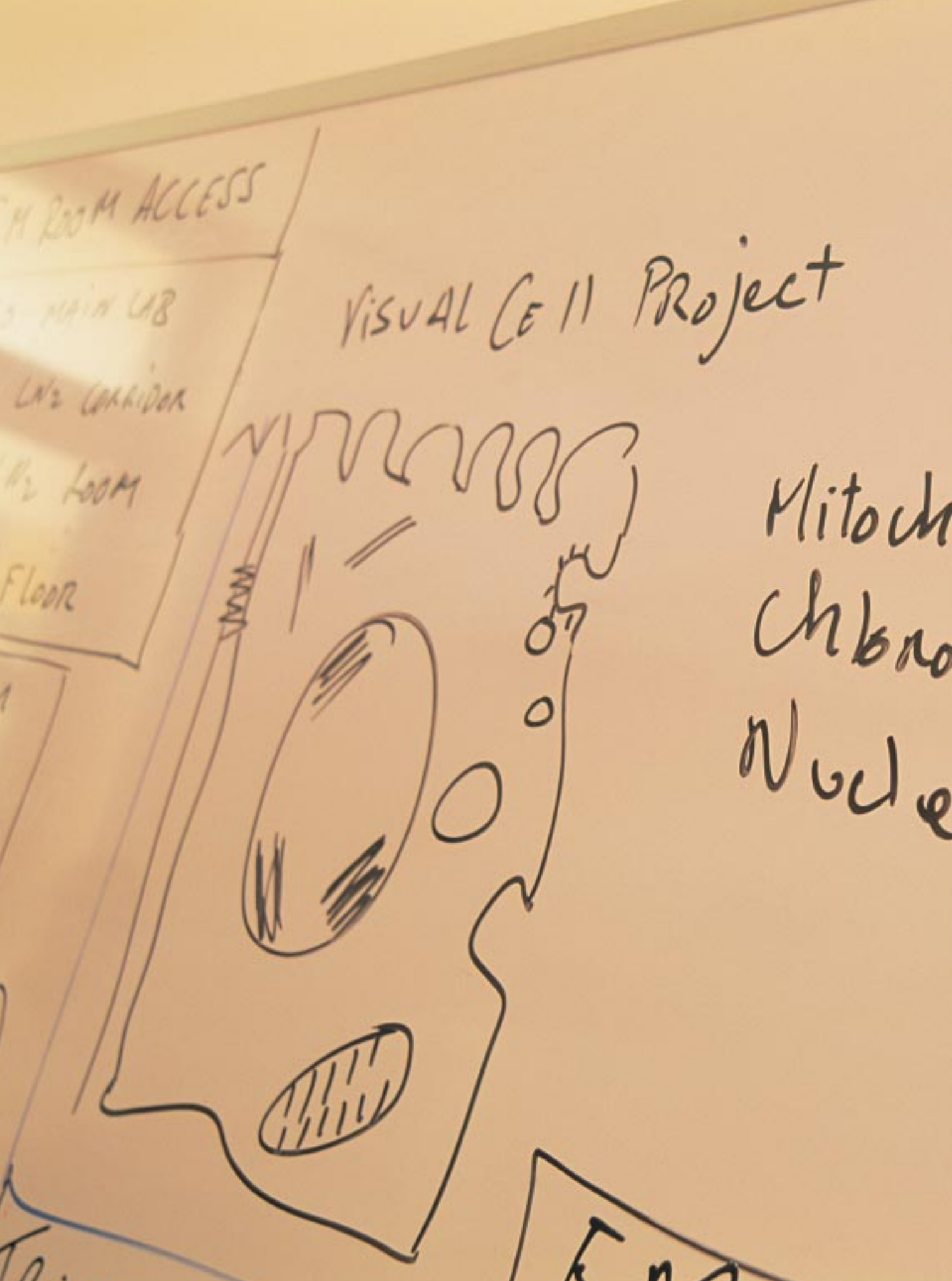
Database administrator/developer
John Opitz

Postgraduate trainee
Adrian Miranda

Volunteer
Chikako Ragan

International intern
Samuel Thoraval

Administrative assistants
Edith Hii
Lanna Wong


ACCESS
LAB
CORRIDOR
ROOM
FLOOR
VISUAL CELL PROJECT
Mitoch
Chro
Nucl

Publications and Papers

Ragan, M.A., Murphy, C.A., Rand, T.G. (2003). Are Ichthyosporea animals or fungi? Bayesian phylogenetic analysis of elongation factor 1α of *Ichthyophonus irregularis. Molecular Phylogenetics and Evolution.* 29:550-62.

Charlebois, R.L., Beiko, R.G., Ragan, M.A. (2003) Microbial phylogenomics: Branching out. *Nature* 421:217.

Pekkarinen, M., Lom, J., Murphy, C.A., Ragan, M.A., Dykova, I. (2003) Phylogenetic position and ultrastructure of two *Dermocystidium* species (Ichthyosporea) from the common perch *(Perca fluviatilis). Acta Protozoologica* 42:287-307.

Ragan, M.A. (2003) Bioinformatics: a glimpse of the future. *BioSilico* 1:119-120.

Published Abstracts

Höhl, M., Rigoutsos, I., Ragan M.A. Freeing phylogenies from alignments (2003). Program, 11th *International Conference on Intelligent Systems* in Molecular Biology, p. 117.

Garcia, A., J. Cleary, M.A. Ragan & J.-P.P. Chen. SEMA, a semantic literature annotator (2003). Program, 11th *International Conference on Intelligent Systems in Molecular Biology,* p. 66. **[Co-awardee, best Australian student poster.]**

Garcia, A., L.J. Garcia, M.A. Ragan & Y.-P.P. Chen. GPIPE, a pipeline module for JEMBOSS (2003). *Program, 11th International Conference on Intelligent Systems in Molecular Biology,* p. 83.

Beiko, R.G., R.L. Charlebois & M.A. Ragan. Genome phylogenies based on the mean normalized BLAST score (2003). *Program, 11th International Conference on Intelligent Systems in Molecular Biology,* p. 117.

Harlow, T.J., J.P. Gogarten & M.A. Ragan. A hybrid clustering approach to genome-scale recognition of protein families (2003). *Program, 11th International Conference on Intelligent Systems in Molecular Biology,* p. 115.

Conference Papers/Lectures

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

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

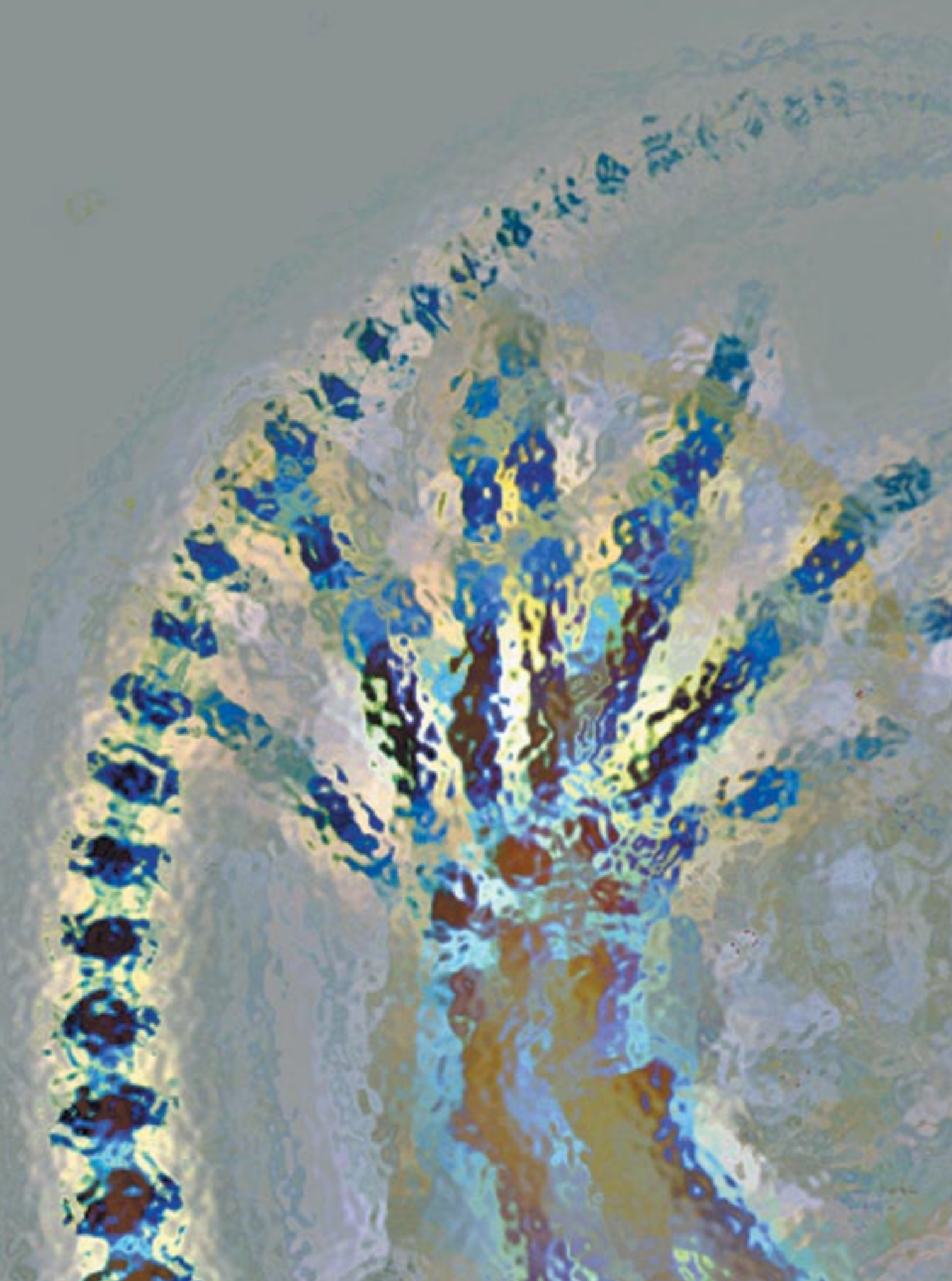
Australian Partnership in Advanced Computing APAC03, Gold Coast, October 2003 (Keynote address)

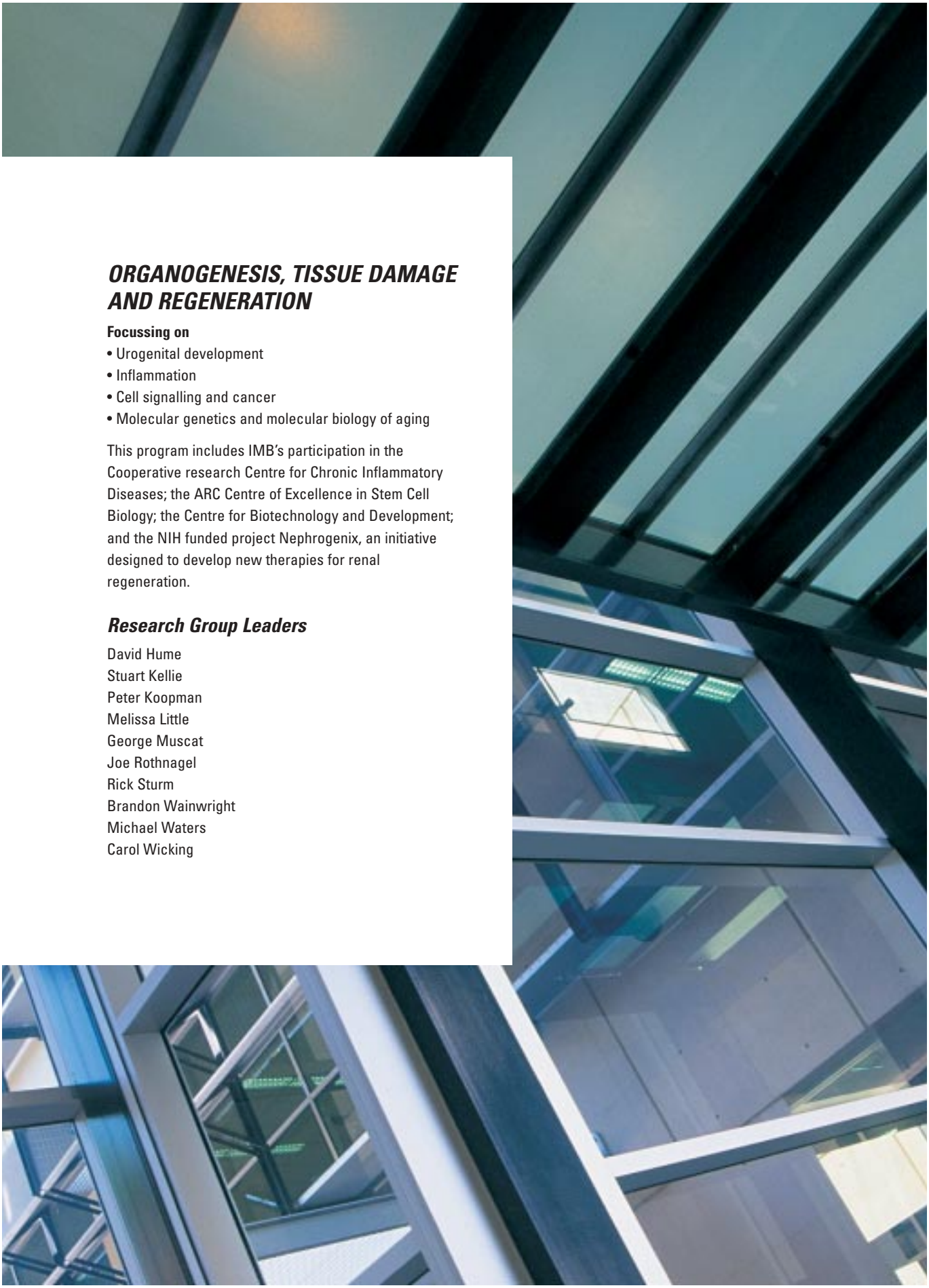
Canadian Institute for Advanced Research, Program in Evolutionary Biology, White Point Beach, Nova Scotia, September 2003

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

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

Association of Asian Societies of Bioinformatics, Yokohama, December 2003





ORGANOGENESIS, TISSUE DAMAGE AND REGENERATION

Focussing on

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

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

Research Group Leaders

David Hume
Stuart Kellie
Peter Koopman
Melissa Little
George Muscat
Joe Rothnagel
Rick Sturm
Brandon Wainwright
Michael Waters
Carol Wicking

David Hume

MACROPHAGES AND OSTEOCLASTS

Research overview

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

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

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

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

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

Projects

Functional Regulation (Matthew Sweet and Kate Stacey)

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

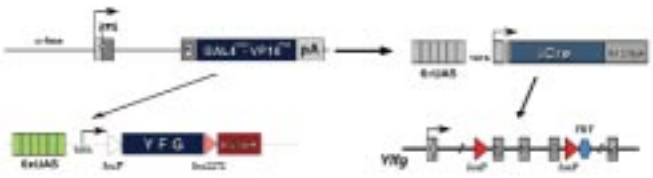
During pathogenic challenge, macrophages detect foreign products such as bacterial CpG DNA, lipopolysaccharide and bacterial lipoproteins. This activates the innate immune response and triggers the development of the acquired immune response. Bacterial CpG DNA in particular is a potent activator of a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

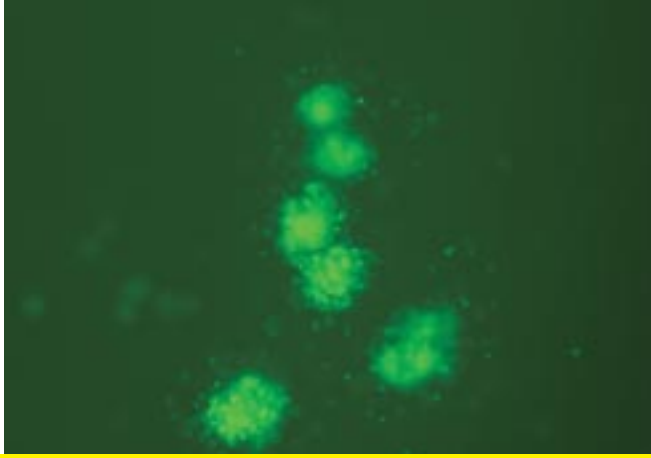
Genetic Networks underlying Macrophage Activation (Christine Wells and Tim Ravasi)

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

Gene expression in macrophages and osteoclasts (Dmitry Ovchinnikov)

The ultimate goal of my research is to establish a versatile and reliable set of modern mouse molecular genetics tools for the alteration of gene expression in macrophages and osteoclasts. These tools will allow us to overexpress genes and/or inactivate them, in





spatially and temporally controllable fashion. This will provide a novel approach to gene "replacement", allowing the simultaneous control of both gene inactivation and overexpression.

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

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

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

Grants

NHMRC Project grant *Th2-Promoting Stimulus, ES-62*

NHMRC Project grant *TLR 9 and response to foreign DNA*

NHMRC Project grant *Osteoclast-specific gene regulation*

NHMRC Project grant *COX-2 regulation of bone turnover and mechanically induced bone formation*

UQ Research Development grant *Design and prototyping of a novel dynamic mechanical bioreactor for bone tissue engineering*

ARC Discovery grant *Discovery of novel macrophage proteins*

ARC Linkage grant *Development of tyrosine kinase inhibitors*

CRC for Chronic Inflammatory Diseases (supplementary funding)

US National Institutes of Health and Australian Kidney Foundation's Bootle Bequest. *Nephrogenix Consortium*

US National Institutes of Health *Cytokine trafficking and secretion in macrophages*

Amgen Development grant

Staff and Students

Senior research fellow
Ian Cassady

Senior research officers
Roy Himes
Ian Ross
Kate Stacey
Matthew Sweet

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

Administrative officer
Julie Osborne

Lab manager
Greg Young

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

Dabatase manager (CRC)
Xiang Liu

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Myrna Constantin
Tamarind Hamwood
Katherine Irvine
Nicholas Meadows
Vera Ripoll
Tara Roberts
Kate Schroder
Brendan Tse
Nicole Walsh

Christine Wells
Andy Wu
Richa Dave

Honours students
Ming Chang

Vacation scholar
Chien-chi Lo

Publications

Bono, H., Yagi, K., Kasukawa, T., Nikaido, I., Tominaga, N., Miki, R., Mizuno, Y., Tomaru, Y., Goto, H., Nitanda, H., Shimizu, D., Makino, H., Morita, T., Fujiyama, J., Sakai, T., Shimoji, T., **Hume, D.A.,** Hayashizaki, Y., Okazaki, Y.. (2003) Systematic Expression Profiling of the Mouse Transcriptome Using RIKEN cDNA Microarrays. *Genome Res.* 13:1318-23.

Carninci, P., Waki, K., Shiraki, T., Konno, H., Shibata, K., Itoh ,M., Aizawa, K., Arakawa, T., Ishii, Y., Sasaki, D., Bono, H., Kondo, S., Sugahara, Y., Saito, R., Osato, N., Fukuda, S., Sato, K., Watahiki, A., Hirozane-Kishikawa, T., Nakamura, M., Shibata, Y., Yasunishi, A., Kikuchi, N., Yoshiki, A., Kusakabe, M., Gustincich, S., Beisel, K., Pavan, W., Aidinis, V., Nakagawara, A., Held, W.A., Iwata, H., Kono, T., Nakauchi, H., Lyons, P., **Wells, C., Hume, D.A.,** Fagiolini, M., Hensch, T.K., Brinkmeier, M., Camper, S., Hirota, J., Mombaerts, P., Muramatsu, M., Okazaki, Y., Kawai, J., Hayashizaki, Y.. (2003) Targeting a complex transcriptome: the construction of the mouse full-length cDNA encyclopedia. *Genome Res.* 13:1273-89.

Cassady, A.I., Luchin, A., Ostrowski MC, **Hume DA.** (2003) Regulation of the murine TRACP gene promoter. *J Bone Miner Res.* 18:1901-4.

Forrest, A.R, **Ravasi T**, Taylor D, Huber T, **Hume DA,** Grimmond S. (2003) Phosphoregulators: protein kinases and protein phosphatases of mouse. *Genome Res.* 13:1443-54.

Grimmond, S.M., Miranda, K.C., Yuan, Z., Davis, M.J., **Hume, D.A.,** Yagi, K., Tominaga, N.,, Bono, H., Hayashizaki,Y., Okazaki, Y., Teasdale, R.D. (2003) The mouse secretome: functional classification of the proteins secreted into the extracellular environment. *Genome Res.* 13:1350-9.

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Numata, K., Kanai, A., Saito, R., Kondo, S., Adachi, J., Wilming, L.G., **Hume, D.A.,** Hayashizaki, Y., Tomita, M. (2003) Identification of Putative Noncoding RNAs Among the RIKEN Mouse Full-Length cDNA Collection. *Genome Res.* 13:1301-6.

Okazaki, Y., **Hume, D.A.** (2003) A guide to the Mammalian genome. *Genome Res.* 13:1267-72

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Sasmono, R.T., Oceandy, D., Pollard, J.W., Tong, W., Pavli, P., Wainwright, B.J., Ostrowski, M.C., **Himes, S.R., Hume, D.A.** (2003) A macrophage colony-stimulating factor receptor-green fluorescent protein transgene is expressed throughout the mononuclear phagocyte system of the mouse. *Blood* 101:1155-63

Stacey, K.J., Young, G.R., Clark, F., Sester, D.P., **Roberts, T.L.,** Naik, S., **Sweet, M.J., Hume, D.A.** (2003) The molecular basis for the lack of immunostimulatory activity of vertebrate DNA. *J Immunol.* 170:3614-20.

Sweet, M.J., Hume, D.A. (2003) CSF-1 as a regulator of macrophage activation and immune responses. *Archivum Immunologiae et Therapiae Experimentalis.* 51:169-77

Tajul-Arifin, K., Teasdale, R., **Ravasi, T., Hume, D.A.,** Mattick, J.S. (2003) Identification and analysis of chromodomain-containing proteins encoded in the mouse transcriptome. *Genome Res.* 13:1416-29.

Walsh, N.C., Cahill, M., Carninci, P., Kawai, J., Okazaki, Y., Hayashizaki, Y., **Hume, D.A., Cassady, A.I.** (2003) Multiple tissue-specific promoters control expression of the murine tartrate-resistant acid phosphatase gene. *Gene* 307:111-23.

Wells, C.A., Ravasi, T., Faulkner, G.J., Carninci, P., Okazaki, Y., Hayashizaki, Y., **Sweet, M.J.,** Wainwright, B.J., Hume, D.A. (2003) Genetic control of the innate immune response. *BMC Immunol.* 4:5

Wells, C.A., Ravasi, T., Sultana, R., Yagi, K., Carninci, P., Bono, H., Faulkner, G., Okazaki, Y., Quackenbush, J., **Hume, D.A.,** Lyons, P.A. (2003) Continued discovery of transcriptional units expressed in cells of the mouse mononuclear phagocyte lineage. *Genome Res.* 13:1360-5.

Zavolan, M., Kondo, S., Schonbach, C., Adachi, J., **Hume, D.A.,** Hayashizaki, Y., Gaasterland, T. (2003) Impact of alternative initiation, splicing, and termination on the diversity of the mRNA transcripts encoded by the mouse transcriptome. *Genome Res.* 13:1290-300.

Patents

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

Key Conference Presentations

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

Hume, D.A., Sasmono, T., Ravasi, T., Wells, C.A. Himes, S.R. Transcriptional Regulation of Macrophage Differentiation. Lorne Genome Conference, Lorne, Australia

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

Stuart Kellie

MACROPHAGE SIGNALLING

Research overview

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

Projects

Generation of target validation platforms for functional analysis of macrophage genes

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

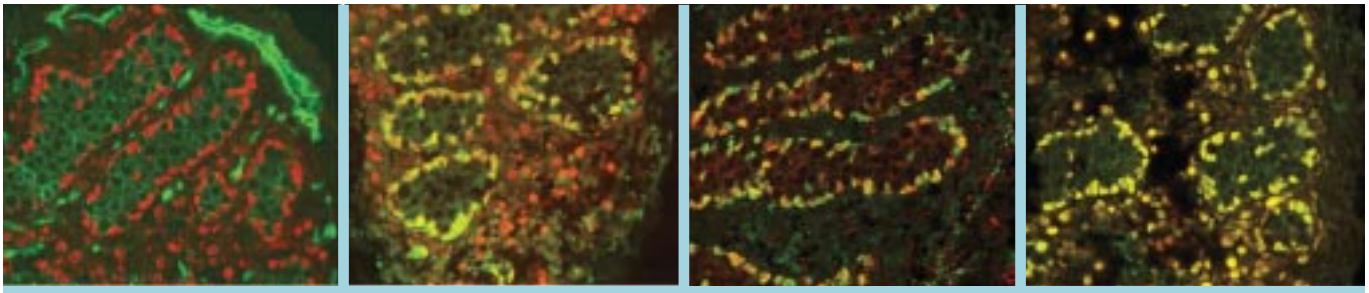
Tyrosine phosphatases in macrophage function

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

Kinases in macrophage function

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

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



E14.5 male gonad sections (12um): SFI PECAM; SFI GATA4; GATA4 Sox9; SFI Sox9

Peter Koopman

MOLECULAR GENETICS OF MAMMALIAN DEVELOPMENT

Research Overview

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

Projects

Sex Determination and Gonadal Development

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

Sox Gene Function and Evolution

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

Molecular Genetics of Vascular Development

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

Development of Male Germ Cells

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

Staff and Students

Research officers
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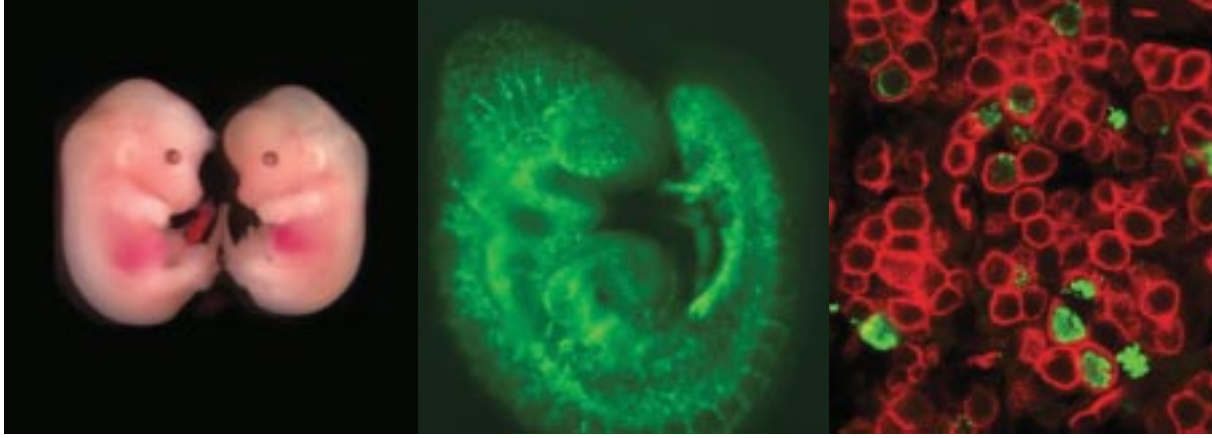

Publications

Fowles, L.F., Bennetts, J.S., Berkman, J.L., Williams, E., Koopman, P., Teasdale, R.D. and Wicking, C. (2003) Genomic screen for genes involved in mammalian craniofacial development. *Genesis* 35:73–87.

Koopman, P., Loffler, K.A. (2003) Sex determination: The fishy tale of Dmrt1. *Current Biology* 13:R177–179.

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Loffler, K.A, Zarkower, D., Koopman, P. (2003) Etiology of ovarian failure in blepharophimosis-ptosis-epicanthus inversus syndrome: FOXL2 is a conserved, early-acting gene in vertebrate ovarian development. *Endocrinology* 144:3237–3243.

Schepers, G., Wilson, M., Wilhelm, D., Koopman, P. (2003) SOX8 is expressed during testis differentiation in mice and synergizes with SF1 to activate the *Amh* promoter *in vitro. J. Biol. Chem.* 278:28101–28108.

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Takada, S and Koopman, P (2003). Origin and possible roles of the Sox8 transcription factor gene during sexual development. Cytogenetic and Genome Research 101:212–218.

Beverdam, A, Wilhelm, D and Koopman, P (2003). Molecular characterization of three gonadal cell lines. *Cytogenetic and Genome Research* 101:242–249.

Bowles, J, Teasdale, R, James, K and Koopman, P (2003). Dppa3 is a marker of pluripotency and has a human homologue that is expressed in germ cell tumours. *Cytogenetic and Genome Research* 101:261–265.

Plenary or keynote speaker

Koopman P. (2003) Regulation of endothelial phenotype by the transcription factor SOX18. Gordon Research Conference, Angiogenesis and Microcirculation, Newport, RI, USA, 11–15 August.

Koopman, P. (2003) Sex determination, Sox genes, and developmental biology in the genome era. *Opening Symposium*, Institute for Molecular Bioscience, University of Queensland, 19 May.

Koopman, P. (2003) Sox8, like Sox9, is expressed during testis differentiation in mice and synergizes with SF1 to activate the Amh promoter in vitro. Third International Symposium on Vertebrate Sex Determination, Kailua-Kona, Hawaii, 24–28 March.

Invited seminars

Koopman, P. (2003) Sex determination in mice: Sry, testes and everything in between. *European Molecular Biology Laboratory, Mouse Biology Program,* Rome, Italy, 14 July.

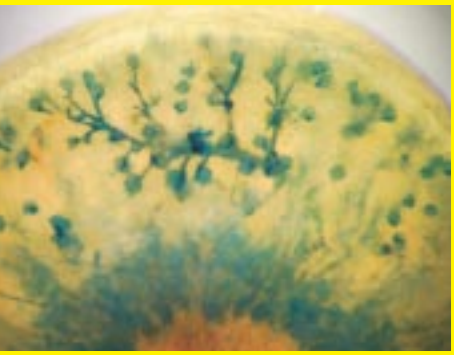
Koopman, P. (2003) Sox transcription factors and the regulation of vascular and hair follicle development in mice. European Molecular Biology Laboratory, Mouse Biology Program, Rome, Italy, 14 July.

Koopman, P. (2003) Regulation of angiogenesis in mice by SOX transcription factors. *Biomedical and Biomolecular School, Griffith University,* Brisbane, Queensland, 9 April.

Koopman, P. (2003) Piecing together the molecular genetic pathway of sex determination and gonadal development in mammals. *Monash Institute of Reproduction and Development,* Melbourne, 20 November.

Melissa Little

RENAL DISEASE



Research Overview

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

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

The kidneys therefore also play an important role in maintaining fluid balance, blood volume and electrolyte balance. On top of this, they regulate blood pressure, bone density and number of red blood cells via the production of specific growth factors.

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

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

Projects

A master gene involved in generating a kidney

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

Using comparative biochemistry to understand function

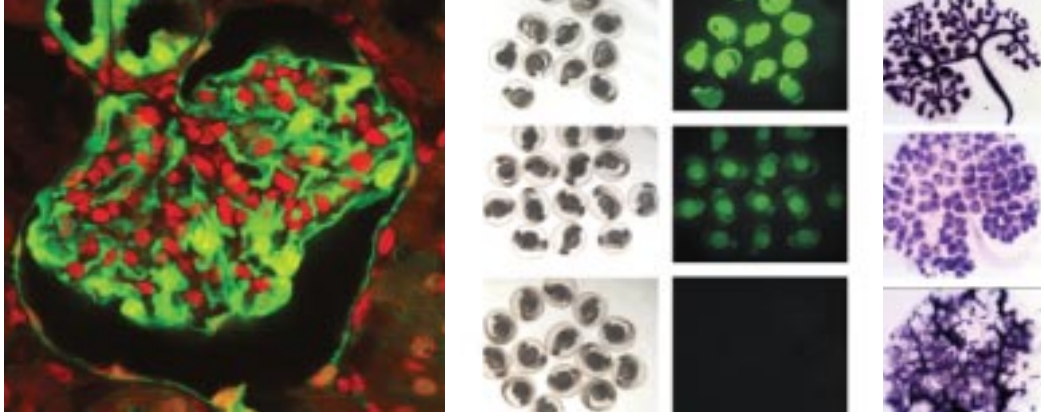
One of the genes that we have discovered plays a role in the development of the kidney is Crim1. This gene makes a protein that determines the ability of a number of other growth factors to move around as well as regulating the cells they can act on. We have shown that a loss of this gene results in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

Towards new therapies for renal disease

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

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

These two long-term questions are being tackled in this laboratory by systematically cataloguing all the secreted and cell surface proteins produced during kidney development using the genomic technique of expression profiling using glass microarray chips. Novel growth factors isolated from these screens are then assessed for their role in kidney development



using organ culture assays. They can then be assayed for their ability to direct embryonal stem cells towards as renal fate. In addition, we have established an embryonal kidney transplantation assay in which we can test the effect of novel growth factors on the development of the kidney in vivo. Novel cell surface markers are being used to isolate putative renal stem cells or purify renal progenitors from differentiating embryonal stem cells.

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

Grants awarded in 2003

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

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Publications

Vajjhala, P.R., Macmillan, E., Gonda, T., Little, M. (2003) The Wilms' tumour suppressor protein, WT1, undergoes CRM1-independent nucleocytoplasmic shuttling. *FEBS Lett.* 554:143-8.

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Kolle, G., Jansen, A., Yamada, T., Little, M. (2003) In ovo electroporation of Crim1 in the developing chick spinal cord. *Dev Dyn.* 226:107-11.

Samuel, T., Douglas-Denton, R., Hoy, W.E., Hughson, M., Little, M.H., Bertram, JF. (2003) Nephron endowment and potential therapies for nephron deficit. *Todays Life Sciences.* 15(5), 30-33

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George Muscat

NUCLEAR HORMONE RECEPTORS AND GENE REGULATION

Research overview

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

Projects

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

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

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

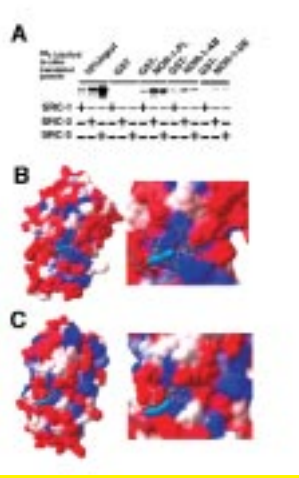
Specific projects in our laboratory include:

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

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

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

Using structure-function analysis we recently identified the first small molecule regulator of this class of orphan NRs. The NR4A subgroup is selectively activated by the purine anti-metabolite and anti-neoplastic/anti-inflammatory compound 6-Mercaptopurine. Analogues of which are used in the treatment of leukemias, autoimmune disorders and prevention of organ transplant rejection, gout and herpes virus infections.



This suggests that the signalling pathways inhibiting proliferation via inhibition of de novo purine and/or nucleic acid biosynthesis are involved in the regulation of NRA4A activity. Furthermore, we hypothesize that the NR4A subgroup mediates the genotoxic stress response, and believe this subgroup may function as sensors, which respond to genotoxicity.

The NR4A subgroup clearly represents an exciting scientific challenge, and unlocking the molecular mechanisms that mediate NR4A-dependent transcription provides the platform for the identification of novel drug targets

Grants awarded

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

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

NHMRC *Transcriptional control of blood vessel development. (With Peter Koopman)*

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

UQ Research & Development Grant *Understanding the pathophysiological role of the orphan nuclear receptor, Nurr1 in Neurological disease: pharmacogenomic identification of Nurr1 genes. (With Dr Helen Cooper)*

Collaborators

Peter Koopman, IMB

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

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Mary Wang
Tamara Allen
Jyotsna Pippal

MPhil student
Catherine Jones

The team that identified a new target in the battle of the bulge.

Publications

Dressel, U., Allen, T.L., Pippal, J.B., Rohde, P.R., Lau, P., Muscat, G.E. (2003) The Peroxisome Proliferator Activated Receptor {beta}/{delta} agonist, GW501516, regulates the expression of genes involved in lipid catabolism and energy uncoupling in skeletal muscle cells. *Mol Endocrinol.* 17:2477-2493

Figueroa, A., Cuadrado, A., Fan, J., Atasoy, U., Muscat, G.E., Munoz-Canoves, P., Gorospe, M., Munoz, A. (2003) Abstract Role of HuR in skeletal myogenesis through coordinate regulation of muscle differentiation genes. *Mol Cell Biol.* 23:4991-5004.

James, K., Hosking, B., Gardner, J., Muscat, G.E., Koopman, P. (2003) Abstract Sox18 mutations in the ragged mouse alleles ragged-like and opossum. *Genesis.* 36:1-6.

Wansa, K.D., Harris, J.M., Yan, G., Ordentlich, P., Muscat, G.E. (2003) Abstract The AF-1 domain of the orphan nuclear receptor NOR-1 mediates trans-activation, coactivator recruitment, and activation by the purine anti-metabolite 6-mercaptopurine. *J Biol Chem.* 278:24776-90.

Speaking engagements

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

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

Sept 2003. Late-breaking science session. Endocrine Society of Australia ESA-SRB 2004

Anything Else

- Member of the editorial board for *Nuclear Receptor.* A journal to be published by Biomed central limited.
- Editorial board member of Journal of Biological Chemistry. 2003-2008

Specifically, we aim to understand the role of skeletal muscle in cardiovascular disease and to elucidate the functional role of orphan receptors in metabolism.

Joe Rothnagel

MOLECULAR ANALYSIS OF CUTANEOUS SYSTEMS

Research overview

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

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

Projects

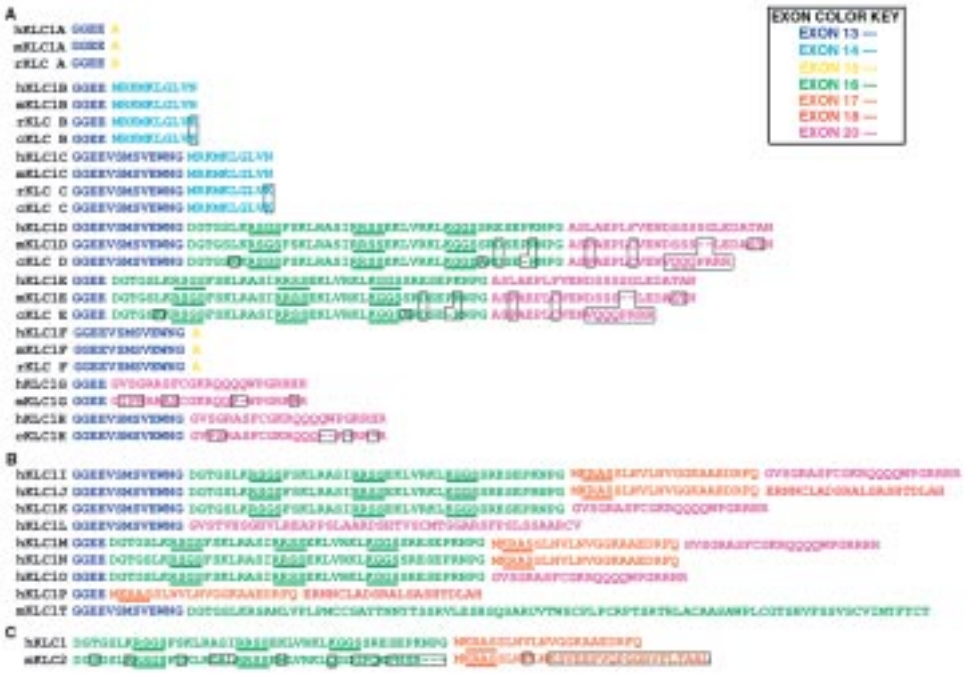
A major focus of this laboratory is currently directed towards the use of tissue specific promoters for use in expression vector constructs. We use keratin promoters as the model system because they show cell type and differentiation state specific expression. In addition, they are some of the most efficient mammalian promoters thereby ensuring high levels of expression. In parallel to the promoter studies we are also investigating the role of post-transcriptional mechanisms in regulating the final levels of gene products. This has led to the development of short cis-sequences (GeneDimmer & GeneBooster) that can be used to turn up or down gene expression.

In addition we have examined alternative splicing of key transcripts expressed by keratinocytes using both data mining and candatiate gene approaches. This has resulted in the amazing finding that the kinesin light chain gene has the potential to produce over 280,000 alternative forms from the differential splicing of exons 13 to 23. We have also analysed the alternatively-spliced exons of the Gli1 oncogene that result in 5' leader sequences with differing translational capacities. Only the transcript with the highest translational capacity was associated with basal cell carcinoma. We have also characterised the mouse and human *Frizzled-3* genes and identified several alternatively spliced variants that are predicted to interact with each other to modulate Wnt signalling.

Grants

NHMRC *Alternative splicing of GLI1 and its role in tumorigenesis*

Uniquest Pty Ltd *GeneDimmer Development grant*



Collaborators

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Timothy Rayner, Child Health Research Institute, Adelaide

Pritinder Kaur, Peter MacCallum Cancer Centre, Melbourne

Paul Bowden, University of Wales College of Medicine, Cardiff, UK

Richard Presland, University of Washington, Seattle, USA

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Lexie Friend	Jonathan Beesley	
	Amy McCart	
	Wolfgang Hofmeister	

Publications

Ellis T, Smyth I, Riley E, Bowles J, Adolphe C, Rothnagel JA, Wicking C, Wainwright BJ. (2003) Overexpression of Sonic Hedgehog suppresses embryonic hair follicle morphogenesis. *Dev Biol.* 263:203-15.

McCart AE, Mahony D, Rothnagel JA. (2003) Alternatively spliced products of the human kinesin light chain 1 (KNS2) gene. *Traffic.* 4:576-80.

Rick Sturm

MELANOCYTE BIOLOGY AND PIGMENTATION GENETICS

Research overview

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

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

Projects

MC1R polymorphism in skin cancer risk phenotypes

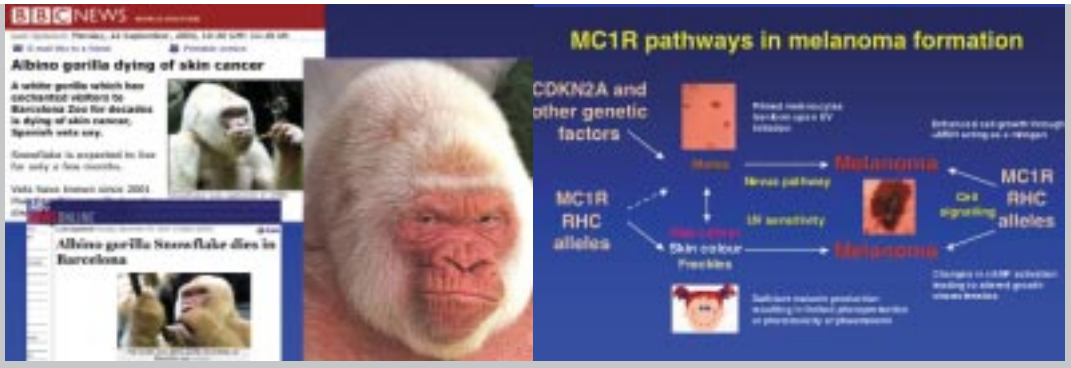
Population studies have revealed the coding region of the human melanocortin-1 receptor (MC1R) gene to be remarkably polymorphic, with over 30 allelic variants so far identified.

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

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

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

Given that pigmentary traits such as fair skin, lack of tanning ability and propensity to freckle have been identified as risk factors for both melanoma and non-melanocytic skin cancer (NMSC), it follows that MC1R variants that are associated with these pigmentary traits should also be found in association with an increased risk for these forms of skin cancer.



Several of the studies of the MC1R variants in relation to the RHC phenotype have suggested their association with the number of freckling sites or sun-induced lentigines. In most cases two MC1R variants are required to express the red hair-fair skin phenotype. In particular the R151C, R160W and D294H variants are the most commonly associated variants seen in the South East Queensland population with at least one of these alleles found in 93% of those with red hair.

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

Functional testing of MC1R variant alleles

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

Culture of human melanoblast stem cells from skin

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

Oculocutaneous albinism in a Polynesian community

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

Grants awarded

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

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

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

Collaborations

Nicholas Hayward, Queensland Institute of Medical Research.

Helen Leonard, Queensland Institute of Medical Research.

Nicholas Martin, Queensland Institute of Medical Research.

Peter Parsons, Queensland Institute of Medical Research.

Jenny Stow, IMB

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

Meenhard Herlyn, Wistar Institute, Philadelphia, USA.

Staff and Students		
Research officers Richard Newton	**Research assistants:** Darren Smit Wei Chen	**PhD students:** Brooke Gardiner Anthony Cook Luke Kirkwood Helene Johanson

Publications and papers

Leonard, J.H.,. Marks, L.H., Chen, W.,. Cook, A.L., Boyle, G.M., Smit, D.J., Brown, D.L., Stow, J.L., Parsons, P.G., Sturm, R.A. (2003) Screening of human primary melanocytes of defined melanocortin-1 receptor genotype: pigmentation marker, ultrastructural and UV-survival studies. *Pigment Cell Research,* 16:198-207

Sturm R.A., Duffy, D.L., Box, N.F., Newton, R.A.,. Shepherd, A.G, Chen, W., Marks, L.H., Leonard, J.H., Martin, N.G. (2003) Genetic Association and Cellular Function of MC1R Variant Alleles in Human Pigmentation. *Proceedings of the 5th International Melanocortin Meeting. Annals of the NY Academy of Science,* 994:348-358.

Sturm, R.A. Duffy D.L., Box N.F., Chen W., Smit D.J.,. Brown D.L, Stow J.L., Leonard J.H. Martin. N.G. (2003) The role of melanocortin-1 receptor polymorphism in skin cancer risk phenotypes. *Proceedings of XVIIIth International Pigment Cell Conference. Pigment Cell Research,* 16:266-272

Cook, A.L., Donatien, P.D., Smith, A.G., Murphy, M., Jones, M.K., Herlyn, M., Bennett, D.C.,, Leonard, J.H., Sturm, R.A. (2003) Human Melanoblasts in Culture: Expression of BRN2 and Synergistic Regulation by Fibroblast Growth Factor-2, Stem Cell Factor and Endothelin-3. *Journal of Investigative Dermatology,* 121:1150-1159.

Conferences

R.A. Sturm "Human pigmentation and melanoma: MC1R genotype, phenotype and population genetics". First Annual Melanoma Research Congress, Wyndham Franklin Plaza Hotel, Philadelphia, Pennsylvania, USA, June 16-18, 2003

R.A. Sturm. "Human pigmentation and skin cancer: MC1R genotype, phenotype and population genetics" Mutagenesis and Experimental Pathology Society of Australasia, Conference on Prevention, Repair and Regeneration of Environmental Epithelial Damage, The Veterinary Science Conference Centre, The University of Sydney, November 26-28, 2003.

Other

Associate Editor of Pigment Cell Research

Associate Editor of Melanoma Research

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

Brandon Wainwright

MOLECULAR GENETICS OF HUMAN DISEASES

Research overview

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

Projects

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

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

Key projects include:

- Structure/function of the patched tumour suppressor gene
- The cellular origin of basal cell carcinoma and common brain tumours.
- Regulation of the inflammatory response by CFTR
- Origin of the cystic fibrsosis inflammatory response
- Novel mouse modifer genes affecting lung development and inflammation

Staff and Students

Research officers
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Liam Town

Honours students
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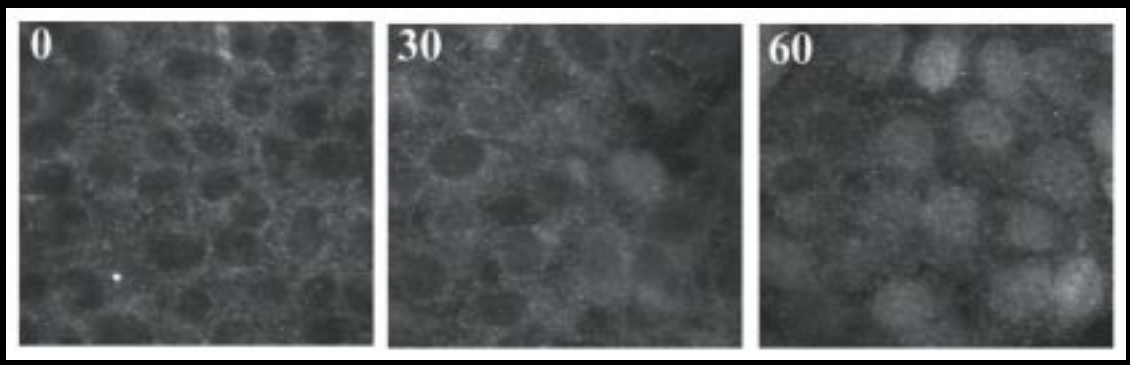


A key signalling molecule c-fos activates transcription 60 minutes after infecting epithelial cells with Pseudomonas aeruginosa

Publications

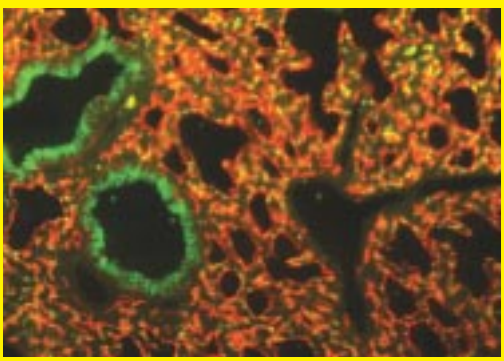
Evans, T.M., Ferguson, C., Wainwright, B.J., Parton, R.G., Wicking, C. (2003) Rab23, a negative regulator of hedgehog signaling, localizes to the plasma membrane and the endocytic pathway. *Traffic.* 4:869-84.

Ellis, T., Smyth, I., Riley, E., Bowles, J., Adolphe, C., Rothnagel, J.A., Wicking, C., Wainwright, B.J. (2003) Overexpression of Sonic Hedgehog suppresses embryonic hair follicle morphogenesis. *Dev Biol.* 263:203-15.

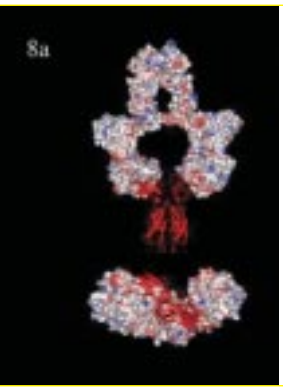
Wells, C.A., Ravasi, T., Faulkner, G.J., Carninci, P., Okazaki, Y., Hayashizaki, Y., Sweet, M., Wainwright, B.J., Hume, D.A. (2003) Genetic control of the innate immune response. *BMC Immunol.* 4:5.

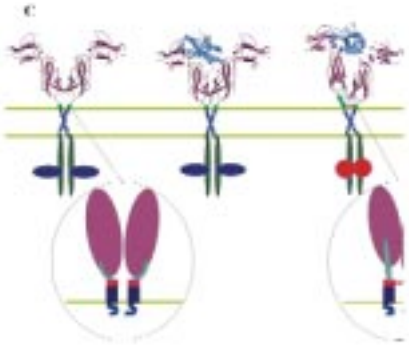
Oceandy, D., McMorran, B., Schreiber, R., Wainwright, B.J., Kunzelmann, K. (2003) GFP-tagged CFTR transgene is functional in the G551D cystic fibrosis mouse colon. *J Membr Biol.* 192:159-67.

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



The human cystic fibrosis gene (green) is active in mouse lung and corrects the cystic fibrosis defect.





(Left) Molecular modelling of GH receptor agonist monoclonal antibody docking to GH receptor; (Centre) Targeting knock-in mutations to the signalling domain of GH receptor decreases growth proportionate to severity of mutation; (Right) A new model for GH receptor activation based on relative rotation of receptor subunits.

Michael Waters

GROWTH HORMONE AND CYTOKINE SIGNALLING

Research overview

The final height of an individual is determined by the actions of growth hormone during childhood and adolescence. In the adult, growth hormone is an important metabolic agent regulating body composition and strength, opposing the actions of insulin. In old age, growth hormone status determines lifespan, at least in animal models. We study the means used by growth hormone to achieve these changes, from high resolution protein structures to genetically engineered animals.

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

Projects

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

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

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

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

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

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

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

Grants awarded

NHMRC *Proliferative role of nuclear GH and cancer.*

NHMRC *The genetic programs induced by growth hormone*

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

NHMRC *Structure – function studies on the growth hormone receptor*

Collaborators

International

Prof G Morel, CNRS Lyon, France

Prof R Ross, University of Sheffield, UK

Prof S. Swanson, Chicago, USA

Dr B Hendricks, Utrecht, Netherlands

Prof D Langosch, Munich, Germany

Prof S Frank, Alabama, USA

Prof S Gilmour, University of Auckland, New Zealand

Prof M Parker, St Vincents Medical Research Institute, Sydney

Dr K Eidne, University of Western Australia

Prof D Jans, Monash University, Melbourne

Prof Patrick Tam, Children's Medical Research Institute, Sydney

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Rebecca Pelekanos
Yu Wan
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Publications

Parsons, S.A., Banks, G.B., Rowland, J.A., Coschigano, K.T., Kopchick, J.J., Waters, M.J., Noakes, P.G. (2003) Genetic disruption of the GH receptor does not influence motoneuron survival in the developing mouse. *Int J Dev Biol* 47:41-49.

Haase, H.R., Ivanovski, S., Waters, M.J., Bartold, P.M. (2003) Growth hormone regulates osteogenic marker mRNA expression in human periodontal fibroblasts and alveolar bone-derived cells. *J Periodontal Res.* 38:366-74.

Shang, C.A., and Waters, M.J. (2003) Constitutively Active Stat5 can replace the requirement for GH in adipogenesis of F442A. *Mol Endocrinol.* 17:2494-508.

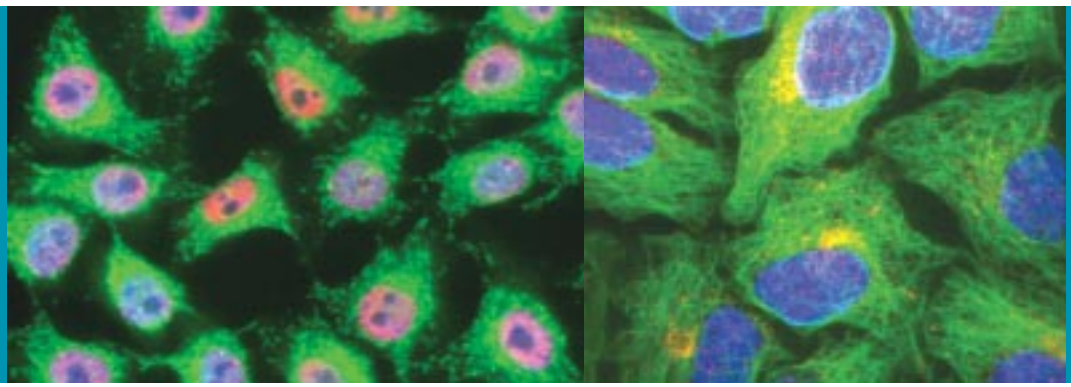
Raccurt, M., Tam, S.P., Lau, P., Mertani, H., Lambert, A., Garcia-Caballero, T., Li, H., Brown, R.J., McGuckin, M.A., Morel, G., Waters, M.J. (2003) Suppressor of cytokine signalling gene expression is elevated in breast cancer. *Brit J Cancer* 89:524-32.

Wan, Y., Zheng, Y.Z., Harris, J.M., Brown, R., Waters, M.J. (2003) Epitope map for a GH receptor agonist monoclonal antibody, MAb 263. *Molecular Endocrinology* 17:2240-50.

Conferences, invited lectures

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

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



Carol Wicking

DEVELOPMENTAL GENES AND HUMAN DISEASE

Research overview

Defects arising from abnormal embryonic development are a major cause of infant mortality and childhood disability. Many such disorders are characterised by anomalies of the limbs and craniofacial region, supporting the conservation of molecular processes governing the development of these structures. We are involved in isolation of novel genes involved in embryonic development of the limb and face, as well as more fully characterising the role of these and other known genes in embryogenesis and disease.

Projects

Regulation of the hedgehog pathway by intracellular trafficking and sterol levels

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

Microarray analysis in a mouse model of limb development

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

Identification of genes involved in craniofacial development

Defects in facial development are a common feature of human dysmorphology syndromes. Using the mouse as a model system, we have adopted a genomics approach based on subtractive hybridisation to enrich for genes expressed in pharyngeal arches, the precursors to the mammalian face. As a result we have isolated a large number of both novel and previously identified genes whose expression pattern during embryogenesis suggests a specific role in the development of a range of organ systems. Functional and cell biological characterisation of a number of these genes is currently underway.

Collaborators

Rob Parton, IMB
Brandon Wainwright, IMB
Marcelo Bento Soares, University of Iowa, USA
Pete Scambler, Institute of Child Health, London, UK
Joy Richman, University of British Columbia, Vancouver, Canada
Andrew Lidral, University of Iowa, USA
S. Peter Klinken, University of Western Australia

Staff and Students

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Kelly Lammerts van Bueren

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Edwina McGlinn
Jenny Bennetts

Summar scholar
Vicki Metzis

Publications

Fowles, L.F., Bennetts, J.S., Berkman, J.L., Williams, E., Koopman, P., Teasdale, R.D., Wicking, C. (2003) Genomic screen for genes involved in mammalian craniofacial development. *genesis* 35:73-87.

Ellis, T., Smyth, I., Riley, E., Graham, S., Elliot, K., Narang, M., Kay, G.F., Wicking, C., Wainwright, B. (2003) *A Patched1* conditional null allele in mice. *genesis* 36:158-161.

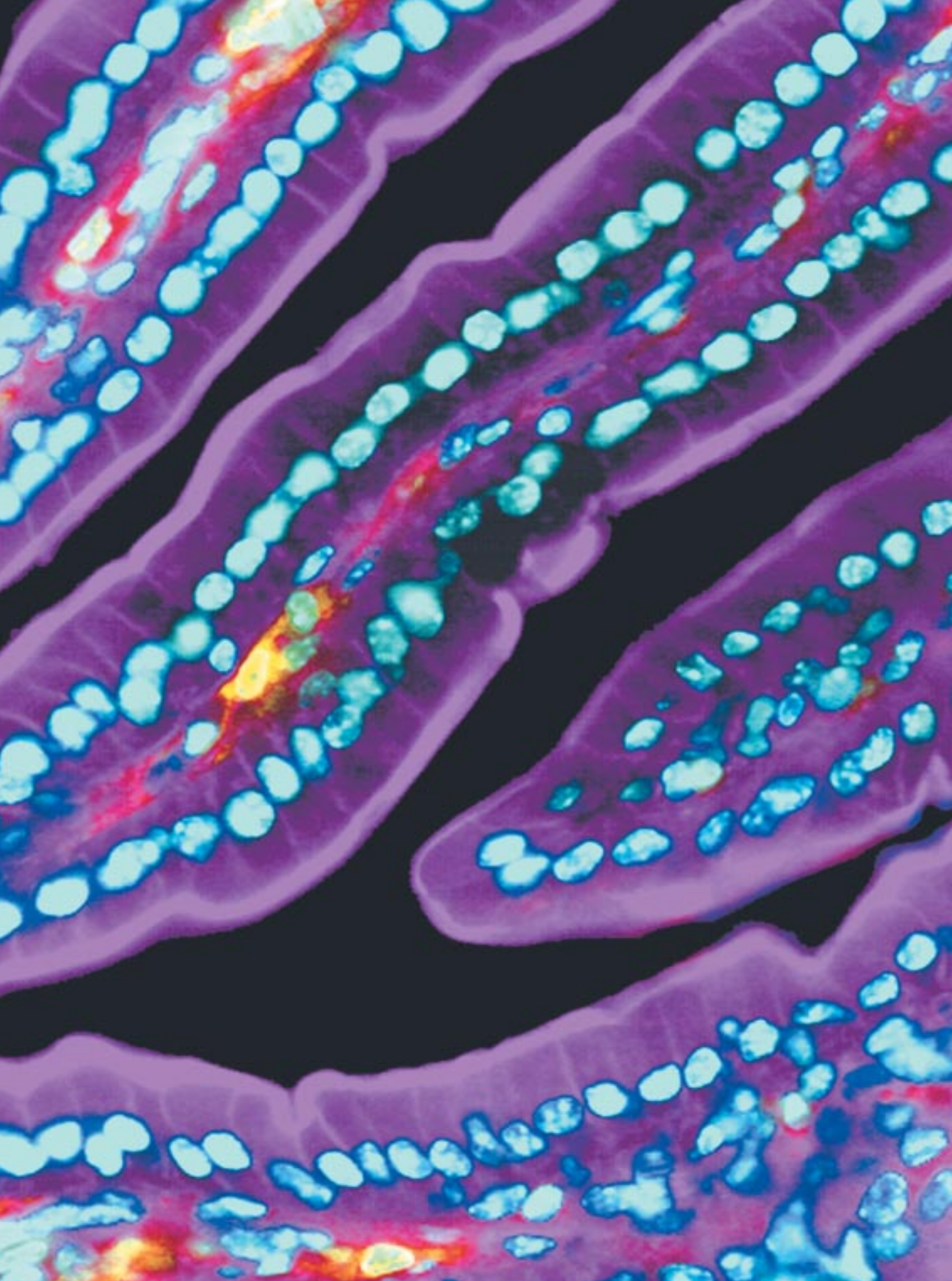
Ellis, T., Smyth, I., Riley E., Bowles, J., Adolphe, C., Rothnagel, J.A., Wicking, C., Wainwright, B.J. (2003) Overexpression of Sonic Hedgehog suppresses embryonic hair follicle morphogenesis. *Dev. Biol.* 263:203-215.

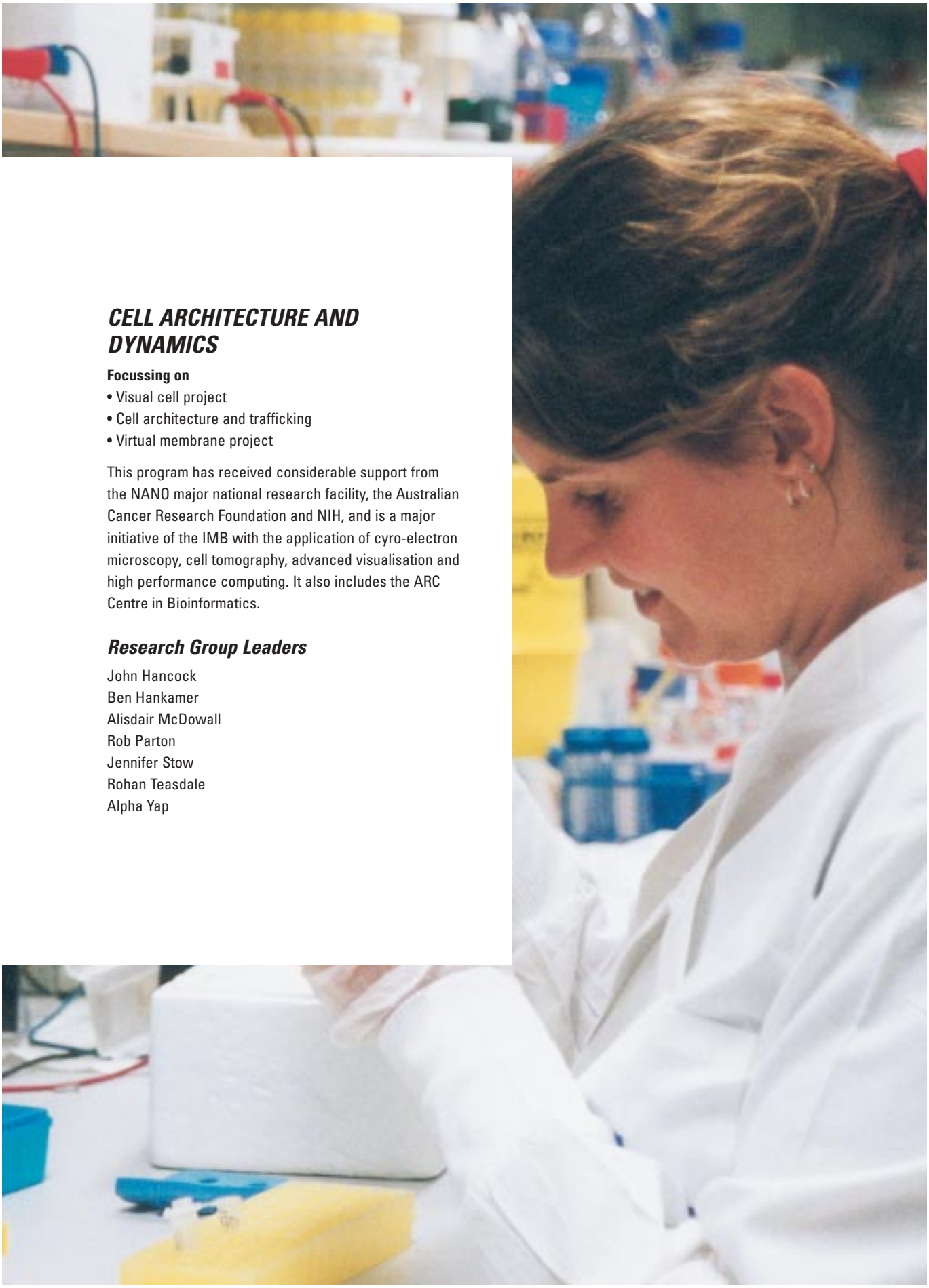
Evans, T.M., Ferguson, C., Wainwright, B.J., Parton, R.G., Wicking, C. (2003) Rab23, a negative regulator of hedgehog signaling, localizes to the plasma membrane and the endocytic pathway. *Traffic* 4:869-884.

Conferences & Seminars

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

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





CELL ARCHITECTURE AND DYNAMICS

Focussing on

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

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

Research Group Leaders

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

John Hancock

SIGNAL TRANSDUCTION

Research overview

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

Projects

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

- Molecular mapping of the proteins and lipids of plasma membrane microdomains.
- Electron microscopic visualization and quantitative characterization of surface microdomains to build up a high-resolution 2D map of the microdomains of the inner plasma membrane.
- Investigation of the dynamic regulation of microdomain localization of Ras and Ras-interacting proteins in response to physiological stimuli.
- Mechanism of Raf-1 activation, to characterize the multistep Raf-1 activation process spatially within the plane of the plasma membrane.
- Characterization of the mechanism(s) whereby K-ras is transported to the plasma membrane and how Ras proteins engage different endocytic pathways.

Collaborators

Yoav Henis and Yoel Kloog, University of Tel Aviv, Israel

Mark Philips, New York University, USA

Brian Gabrielli, Queenland Institute of Medical Research

Grants

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

Queensland Cancer Fund *Switch-like signaling in the Raf/MEK cascade*

ARC *Investigation of the mitotic function of MEK*

NHMRC *Plasma membrane structure and function*

Staff and Students

Research officers
Sandrine Roy
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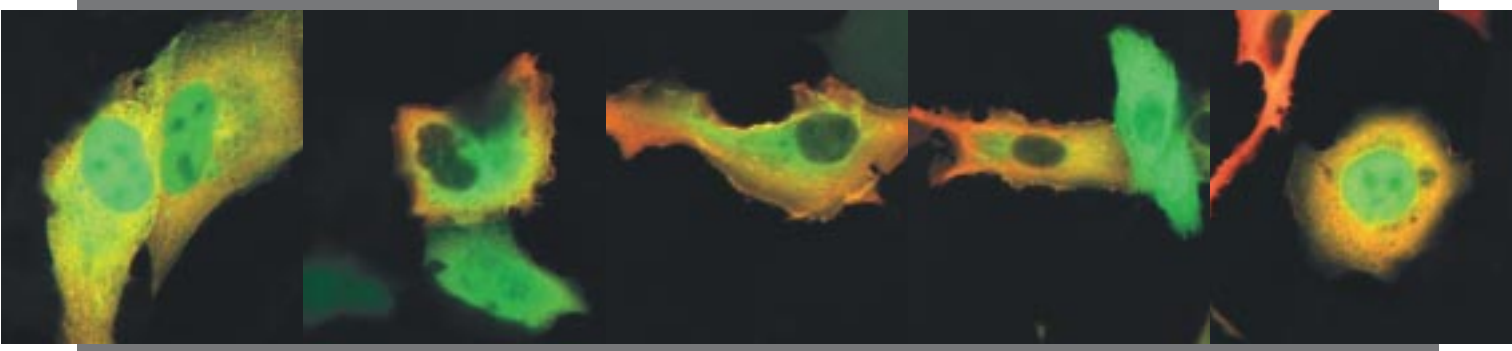
Research fellow
Kim Yap-Weber



Publications

Hansen, M, Prior, I.A., Hughes, P.E., Oertli, B., Chou, F.L., Willumsen, B.M., Hancock, J.F., Ginsberg, M.H. (2003) C-terminal sequences in R-Ras are involved in integrin regulation and in plasma membrane microdomain distribution. *Biochem Biophys Res Commun.* 311:829-38.

Harding, A., Hsu, V., Kornfeld, K., Hancock, J.F. (2003) Identification of residues and domains of Raf important for function in vivo and in vitro. *J Biol Chem.* 278:45519-27.

Hancock, J.F. (2003) Ras proteins: different signals from different locations. *Nat Rev Mol Cell Biol.* 4:373-84.

Wyse, B.D., Prior, I.A., Qian, H., Morrow, I.C., Nixon, S., Muncke, C., Kurzchalia, T.V., Thomas, W.G., Parton, R.G., Hancock, J.F. (2003) Caveolin interacts with the angiotensin II type 1 receptor during exocytic transport but not at the plasma membrane. *J Biol Chem.* 278:23738-46.

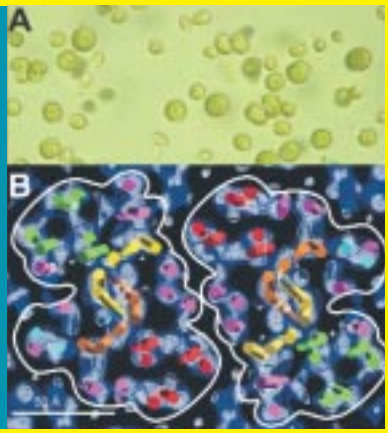
Prior, I.A., Parton, R.G., Hancock, J.F. (2003) Observing cell surface signalling domains using electron microscopy. *Sci STKE* 8:PL9.

Harding, A., Giles, N., Burgess, A., Hancock, J.F., Gabrielli, B.G. (2003) Mechanism of mitosis-specific activation of MEK1. *J Biol Chem.* 278:16747-54.

Prior, I.A., Muncke, C., Parton, R.G., Hancock, J.F. (2003) Direct visualisation of Ras proteins in spatially distinct cell surface microdomains. *J Cell Biol.* 160:165-70.

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

Ben Hankamer



MEMBRANE PROTEIN STRUCTURES

Research Overview

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

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

Projects

Structural Biology

Single Particle analysis

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

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

Electron Crystallography

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

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

Cubic Phase crystallization

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

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

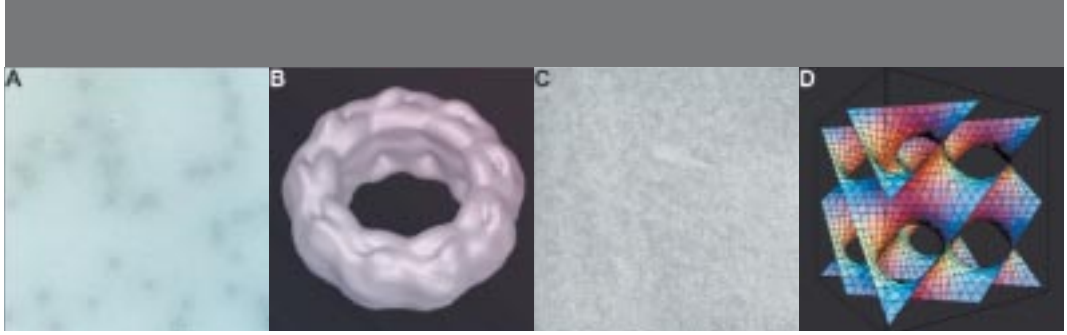
Biology and Biotechnology

Bio-Hydrogen

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

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

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



(Opposite page) A Chlamydomonas reinhardtii cells (biohydrogen), B Photosystem II structure determined by electron crystallography
(Above) A Single particle images, B 3D Reconstruction of PSPA, C 2D Crystal of photosystem II, D Cubic phase matrix

Grants

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

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

Collaborations

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

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

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

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

Associate Professor Alasdair McDowall, IMB

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

Staff and Students

Research officer	Research assistants	Honours student
Jens Rupprecht	Rosalba Rothnagel Michael Landsberg	Cameron Votan

Publications and papers

Sennoga, C., Heron, A., Seddon, J.M., Templer, R.H., Hankamer, B. (2003) Membrane-protein crystallization in cubo: temperature-dependent phase behaviour of monoolein-detergent mixtures. Acta Cryst Section D *Biological Crystallography* 59: 239-246

Conferences

Boden Artificial Photosynthesis Conference 2003

Broome Crystallography Conference 2003

Seefeld Electronmicroscopy Conference 2003

Combio 2003

Alasdair McDowall

CRYO-ELECTRON MICROSCOPY OF VITREOUS SECTIONS

Research overview

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

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

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

Projects

3D electron (cryo ET) tomography of cellular organelles

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

The ultimate vision of the Visual Cell Project

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

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

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

Collaborators

Professor Jacques Dubochet, University of Lausanne, Switzerland

Dr Mark Blackford, Australian Nuclear Science and Technology Organisation, ANSTO, , Menai, N.S.W

Dr Minoo Moghaddam and Dr Gerald Both, CSIRO Molecular Science, North Ryde, NSW 1670, Australia

2003 Grants

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

(From left) Figure 1, the detail of this cryo-section of native cellular chloroplast ultrastructure is well defined; other captions to go here

Staff and Students		
Research officer Matthais Floetenmeyer	**Laboratory technician** Eunice Grinan	

Publications

Hankamer, B., Rothnagel, R., McDowall, A., Ericksson, G., Clark, F., Banks, J., Pailthorpe, B., Sennoga, C., Heron, A., Seddon, J., Templer, R., Crout, D. (2003) Systematic approaches for membrane protein structure determination. AsCA,03/Crystal 23, 11-13 Aug. Broome, Australia.

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

Rob Parton

CELL SURFACE IN HEALTH AND DISEASE

Research overview

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

Projects

Caveolin functional studies

To address the role of caveolae and caveolins in cellular function we investigated whether caveolin mutants would act as dominant negative inhibitory mutants making use of our earlier finding that entry of the virus, SV40, occurs via caveolae. Two mutants had a specific inhibitory effect on SV40 infection.

With John Hancock we showed that one of the mutants was a highly potent inhibitor of Ras signalling and this inhibition was specific to the palmitoylated form of Ras, H-ras, with no effect on the related but non-palmitoylated isoform, K-ras. Inhibition was overcome by adding cholesterol to the cells.

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

Characterisation of Ras microdomains; novel methods and new paradigms

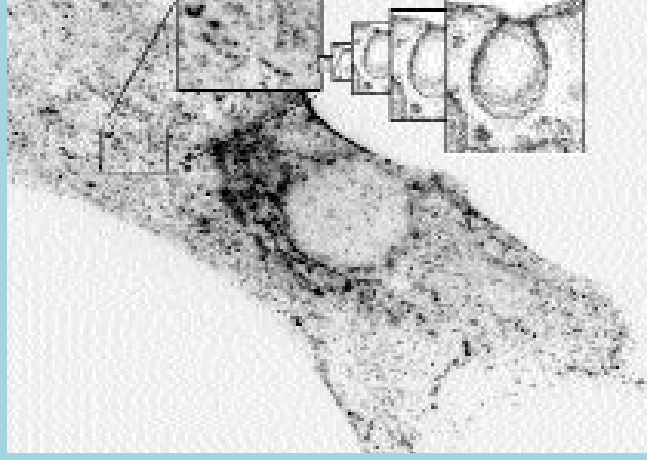
In order to characterise the domains with which H-ras and K-ras associate, we employed subcellular fractionation and developed new electron microscopic (EM) techniques. The studies generated a new concept in cell biology; dynamic lipid raft association regulated by the GTPase state of the Ras protein.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

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

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

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

This may have physiological importance as we have found that in regenerating liver, in which lipid bodies accumulate to high levels, endogenous caveolin redistributes from plasma membrane caveolae to lipid bodies. Experiments are in progress to examine whether liver regeneration is affected in caveolin-1 null mice.



Staining for caveolin-1, the major protein of caveolae, in a fibroblast. The dark staining indicates the caveolin-1 protein. The insets show caveolae by electron microscopy.

A major focus of future experiments is to understand the role of caveolin in lipid regulation and to test the hypothesis that regulated association of caveolin with lipid bodies and surface caveolae plays a role in cholesterol homeostasis. These studies have implications for many disease states including atherosclerosis and Niemann-Pick disease.

Caveolae and caveolin-3 in muscle

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

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

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

Caveolins in zebrafish

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

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

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

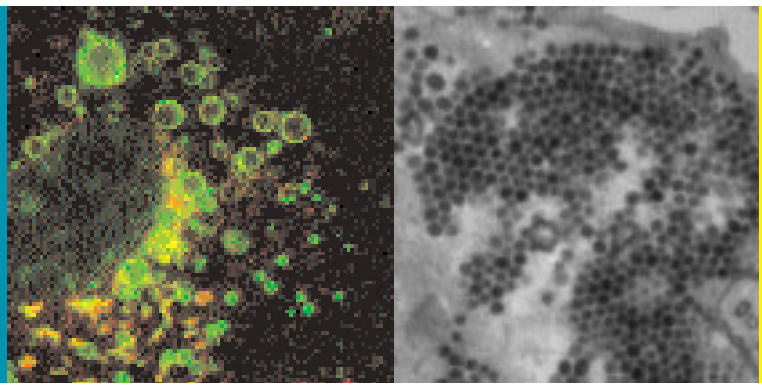
We have localised caveolin-1 and caveolin-3 and have ablated the expression of both successfully. This is providing new insights into caveolin function. For example, we have shown a role for caveolin-3 in myoblast fusion and myotube differentiation and have mimicked this by expression of a dystrophy-associated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

Caveolae Biogenesis

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

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

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



(Left) Caveolin (green staining) associated with lipid bodies; (Right) Caveolae in a human fibroblast as seen by electron microscopy. The dense staining is due to labelling of the interior of the caveolae by a marker attached to cholera toxin.

Grants awarded

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

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

Collaborators

Prof. Jean Gruenberg, University of Geneva, Switzerland

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

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

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

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

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

Prof. Monte Westerfield, University of Oregon, USA

Prof. Richard Pagano, Mayo Clinic, USA

Prof. Michel Desjardins, University of Montreal, Canada

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

Prof. Kathryn North, Institute for Neuromuscular Research, Sydney

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

Prof. John Hancock, IMB

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

Associate Professor Alpha Yap; UQ, IMB;

Dr. Carol Wicking, IMB;

Dr. Rohan Teasdale, IMB

Prof. Brian Key; School of Biomedical Sciences, UQ

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

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Publications

Parton, R.G. (2003). Caveolae--from ultrastructure to molecular mechanisms. *Nat Rev Mol Cell Biol.* 4:162-7.

Parton, R.G., Richards, A.A. (2003). Lipid rafts and caveolae as portals for endocytosis: New insights and common mechanisms. *Traffic.* 4:724-738.

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Wyse, B.D.,. Prior, I.A., Qian, H., Morrow, I.C., Nixon, S., Muncke, C., Kurzchalia, T.V., Thomas, W.G., Parton, R.G., Hancock, J.F. (2003). Caveolin interacts with the angiotensin II type 1 receptor during exocytic transport but not at the plasma membrane. *J Biol Chem.* 278:23738-46.

Conferences

Parton, R.G. (2003) Meeting of the Juan March foundation; 'Membranes, Trafficking and Signalling during Animal Development' Madrid, Spain. Invited speaker

Parton, R.G. (2003) Euresco Conference on 'Microdomains, lipid rafts and caveolae'. Tomar, Portugal. Invited speaker

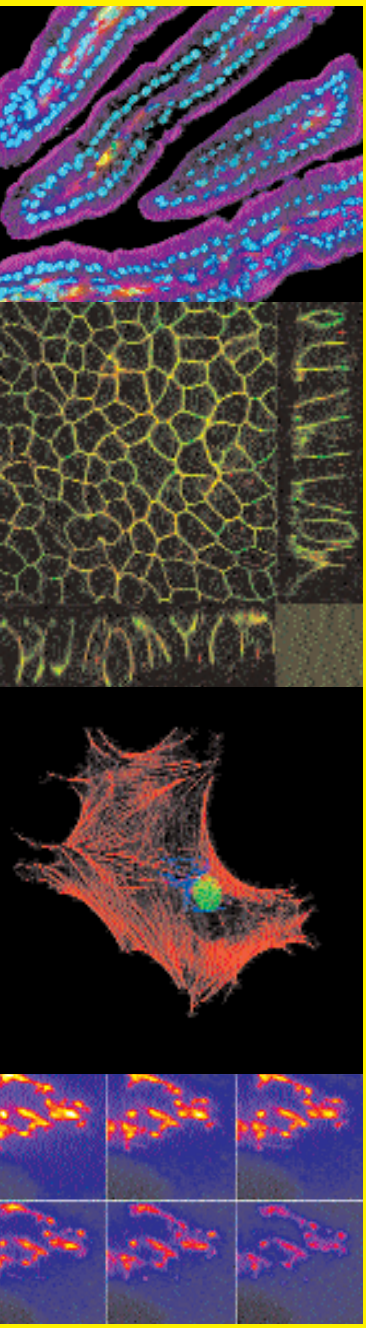
Parton, R.G. (2003) XIX International Congress of Biochemistry & Molecular Biology, Toronto, Canada. Chairman and invited speaker (postponed due to SARS outbreak)

Parton, R.G. (2003) FASEB summer research conference, 'Glucose transporter biology', Snowmass, Colorado. Invited speaker

Parton, R.G. (2003) 10th Congress of the Federation of Asian and Oceanic Biochemists and Molecular Biologists, Bangalore, India. Invited speaker

Parton, R.G. (2003) Combio Melbourne. Session chairman and member of international organising committee

Parton, R.G. (2003) The Third Hunter Cellular Biology Meeting, Pokolbin NSW. Invited Speaker



Jennifer Stow

PROTEIN TRAFFICKING IN HUMAN DISEASE

Research Overview

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

Projects

Cadherin trafficking in epithelial cells

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

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

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

Cytokine secretion in inflammatory macrophages

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

Vesicle budding on Golgi membranes

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

Grants awarded

NHMRC *Trafficking of E-cadherin in epithelial cells.*

National Institutes of Health, USA *Cytokine Trafficking and Secretion in Macrophages.*

Collaborators

Rohan Teasdale (IMB)

Rick Sturm (IMB)

Alpha Yap (IMB)

David Hume (IMB)

Peter Gunning, The Children's Hospital at Westmead, Sydney

Paul Gleeson, The University of Melbourne

David James, Garvan Institute of Medical Research, Sydney

Sharad Kumar, Hanson Centre for Cancer Research, Adelaide

Michael Caplan, Yale University School of Medicine, New Haven, Connecticut, USA

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Daniele Sangermani,

Honours student
Stephanie Wood

Publications

Miranda, K.C., Joseph, S.R., Yap, A.S., Teasdale, R.D., Stow, J.L. (2003). Contextual binding of p120ctn to E-cadherin at the basolateral plasma membrane in polarised epithelia. *J Biol Chem.* 278:43480-8.

Sturm, R.A., Duffy, D.L., Box, N.F., Chen, W., Smit, D.J., Brown, D.L., Stow, J.L., Leonard, J.H., Martin, N.G. (2003). The role of melanocortin-1 receptor polymorphism in skin cancer risk phenotypes. *Pigment Cell Res.* 16:266-72.

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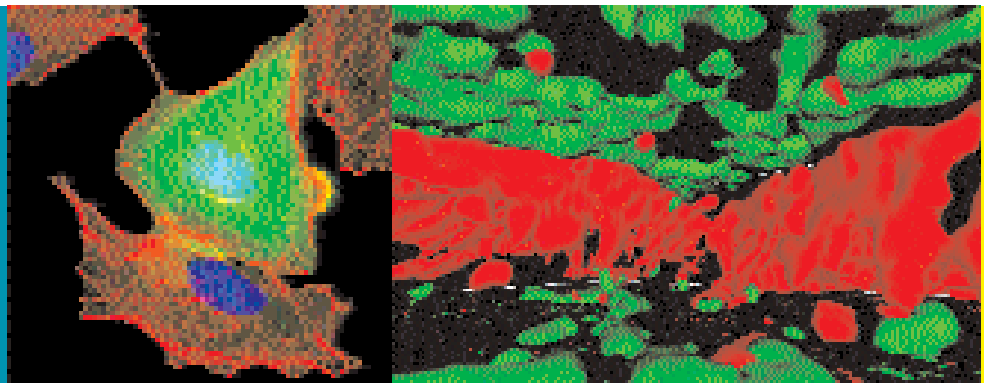

Rohan Teasdale

COMPUTATIONAL CELL BIOLOGY

Research overview

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

Possessing the combination of cellular and bioinformatic skills allows our group more intuitive insights into the application of computational biology within cellular biology.

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

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

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

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

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

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

Projects

Bioinformatic discovery of new genes, proteins and pathways

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

The Golgi Apparatus: Computational discovery and functional genomics of novel Golgi proteins

The Golgi is an organelle central to the biosynthetic pathway of eukaryotic cells. It plays a principal role in the post-translational modification of newly synthesised proteins and in the sorting, packaging and distribution of these proteins to various destinations. It is estimated that at least 1000 proteins make up the protein complement of the Golgi, of which less than 200 are currently characterised.

Efficient screens that identify novel Golgi proteins would clearly enhance our present understanding of the biological role of the Golgi. Based on a exhaustive computational interrogation of the genomes of various organisms for predictable novel Golgi resident proteins combined with the experimentally validation of their localisation we intend to define the full protein complement of the Golgi. We have successfully applied this strategy to predict greater than 300 putative Golgi residents, of which, we have already experimentally validated eight novel Golgi proteins. In addition, we will commence the development of a functional genomics approach focused on defining the function of novel Golgi resident proteins. This will include grouping the novel Golgi proteins based on computational defined features; localisation to sub regions of the Golgi, co-expression during cellular and developmental stages and mapping protein-protein interaction networks.

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

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

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

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

Intracellular Localisation signals.

How do distinct intracellular regions of the cell maintain their unique composition of proteins and lipids? For these organelles to maintain their function integrity, specific resident proteins must be retained while non-residents proteins allowed passage through them. Individual proteins must have "signals" that are responsible for their intracellular localisation. We are currently in the process of identifying such signals on several different proteins. In addition, we are identifying novel proteins that contain these localisation signals within the human genome. These novel proteins are then tested for localisation to particular organelles and then functionally characterised.

Towards renal regeneration
Stem cell-based therapy, utilising either adult or embryonic stem cells, is an unproven approach to the treatment of kidney disease. Our group is a member of a consortium formed to perform the basic research required to define the potential of renal regeneration. Our role in the consortium is to provide the expertise in cell biology and computational analysis to novel genes of interest identified throughout this research effort.

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

Grants awarded in 2003

University of Queensland Foundation Research Excellence Awards.

NHMRC Career Development Award RD Wright Biomedical Development Award

NHMRC Project Grant Sorting nexins and their role in endosomal trafficking.

ARC Discovery Project Grant Membrane proteins within the mouse transcriptome-annotation of their organisation and subcellular localisation.

Collaborations

Sean Grimmond IMB

Melissa Little IMB

Jenny Stow IMB

Mike Waters IMB

Tim Bailey IMB

Malcolm McConville, Department of Biochemistry and Molecular Biology, University of Melbourne

Paul Gleeson, Department of Biochemistry and Molecular Biology, University of Melbourn

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Melvena Teasdale
Shane Zhang

Visiting scholar
Kelly Hanson

Publications and papers -2003

Bowles, J., Teasdale, R.D., James, K., Koopman, P. (2003) Dppa3 is a marker of pluripotency and has a human homologue that is expressed in germ cell tumours. *Cytogenet Genome Res.* 101:261-5.

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van Vilet, C., Thomas, E.C., Merino-Trigo, A., Teasdale, R.D., Gleeson, P.A. (2003) Intracellular Sorting and Transport of Proteins. *Prog. Biophys. Mol. Biol.* 83:1-45.

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

Alpha Yap

CADHERIN SIGNALING AND MORPHOGENESIS

Research overview

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

1. We found that E-cadherin, the principal cadherin molecule found in epithelial tissues, functions as an adhesion-activated cell signalling receptor. In particular, upon adhesion E-cadherin activates signalling via the small GTPase, Rac, and the lipid kinase PI3-kinase.
2. An important potential target of this signalling receptor is the Arp2/3 complex, a protein machine that nucleates assembly of actin filaments. We were the first to discover that E-cadherin interacts with the Arp2/3 complex to mark sites for actin assembly within cells. We are now exploring the general hypothesis that cadherin-activated signalling controls the subcellular localization and activity of Arp2/3 to modulate cell shape changes and motility in response to productive cell-cell recognition.

Projects

Members of my group are studying

1. The molecular mechanism responsible for recruiting Arp2/3 to E-cadherin
2. The molecular regulators of Arp2/3 activity at cadherin contacts (including WASP/WAVE proteins, cortactin and ena/VASP family proteins)
3. The molecular basis of cadherin-activated Rac and PI3-kinase signalling.
4. The morphogenetic consequences of cadherin-activated cell signalling and cooperativity with the actin cytoskeleton.

Grants

NHMRC *Dora Lush Scholarship to Madhavi Maddugoda*

Collaborators

Sean Grimmond IMB

Brian Key Department of Anatomy and Devlopmental Biology, UQ

Robert Parton IMB

Jennifer Stow IMB

Alan Fanning University of North Carolina, Chapel Hill, USA

Frank Gertler Massacheusetts Institute of Technology, Boston USA

Aki Kusumi Nagoya University, Japan

Denise Montell Johns Hopkins University, Baltimore USA

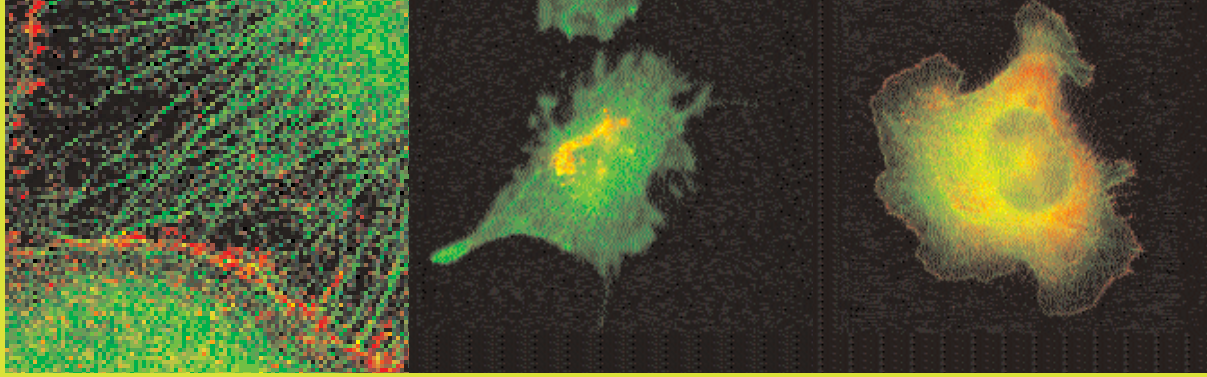
Al Reynolds Vanderbilt University, Nashville, USA

David Sacks Harvard Medical School, Boston, USA

Lila Solnica-Krezel Vanderbilt University, Nashville, USA

Taodami Takenawa Tokyo University, Japan

Scott Weed University of Colorado Health Science Center, USA



Staff and Students

Research officers
Astrid Kraemer
Jian-Hong Pang
Annette Shewan

PhD students
Radiya Ali
Marita Goodwin
Falak Helwani
Ailsa McCormack
Andrew Paterson
Jeanie Scott

Research assistants
Merali Boyle
Matthew Crampton
Madhavi Maddugoda
Teresa Munchow
Suzie Verma

Honours students
Samantha Stehbens

Undergraduate students
Amanda Hammond
Stephen White

Any prizes, keynote addresses or other honours in 2003

Publications

Peifer, M., Yap, A.S. (2003) Traffic control: p120-catenin acts as a gatekeeper to control the fate of classical cadherins in mammalian cells. *J Cell Biol.* Nov 10;163(3):437-40.

Miranda, K.C., Joseph, S.R., Yap, A.S., Teasdale, R.D., Stow, J.L. (2003) Contextual binding of p120ctn to E-cadherin at the basolateral plasma membrane in polarized epithelia. *J Biol Chem.* Oct 31;278(44): 43480-8.

Goodwin, M., Kovacs, E.M., Thoreson, M.A., Reynolds, A.B., Yap, A.S. (2003) Minimal mutation of the cytoplasmic tail inhibits the ability of E-cadherin to activate Rac but not phosphatidylinositol 3-kinase: direct evidence of a role for cadherin-activated Rac signaling in adhesion and contact formation. *J Biol Chem.* Jun 6;278(23):20533-9.

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Kraemer, A., Yap, A.S. (2003) Coupling adhesion to actin bundles in the inner ear. Novel functions for novel cadherins. *EMBO Rep.* Mar;4(3):244-5.

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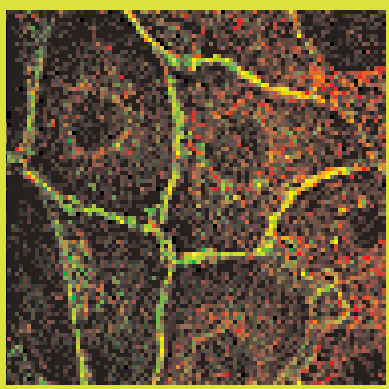
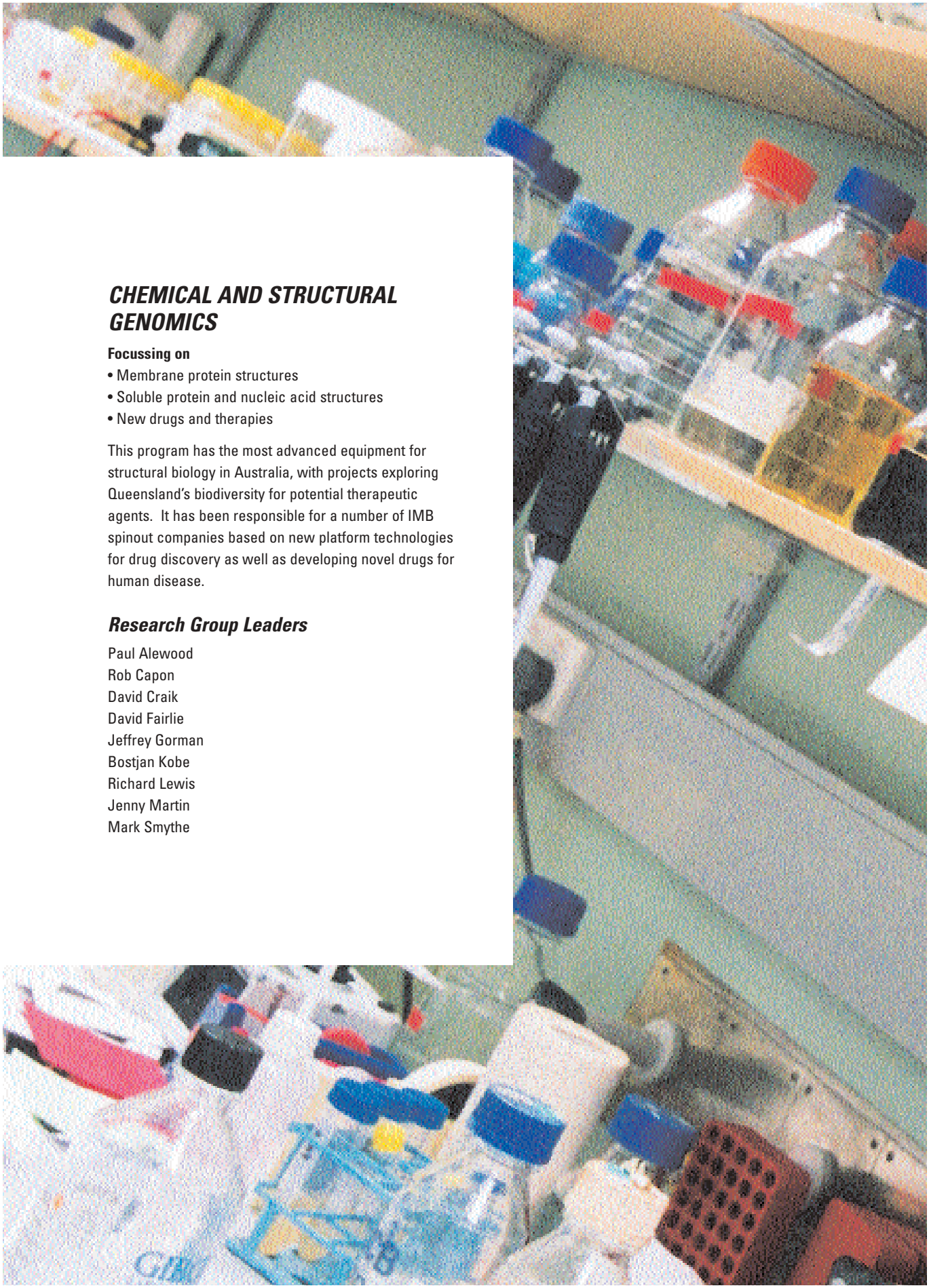




CHEMICAL AND STRUCTURAL GENOMICS

Focussing on

- Membrane protein structures
- Soluble protein and nucleic acid structures
- New drugs and therapies

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

Research Group Leaders

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

Paul Alewood

BIOACTIVE MOLECULES, CHEMICAL PROTEIN SYNTHESIS AND PROTEOMICS

Research overview

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

Projects

Toxins

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

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

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

Milk proteomics

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

New generation antibiotics

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

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

Protein chemical synthesis

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

Collaborators

Professor Steve Kent, Institute for Biophysical Dynamics, University of Chicago, USA

Prof Ian Smith, Baker Heart Research Institute, Melbourne

Professor Ed Nice, Ludwig Institute for Cancer Research, Melbourne

Professor Carolyn Geczy, School of Medical Sciences, University of New South Wales, Sydney

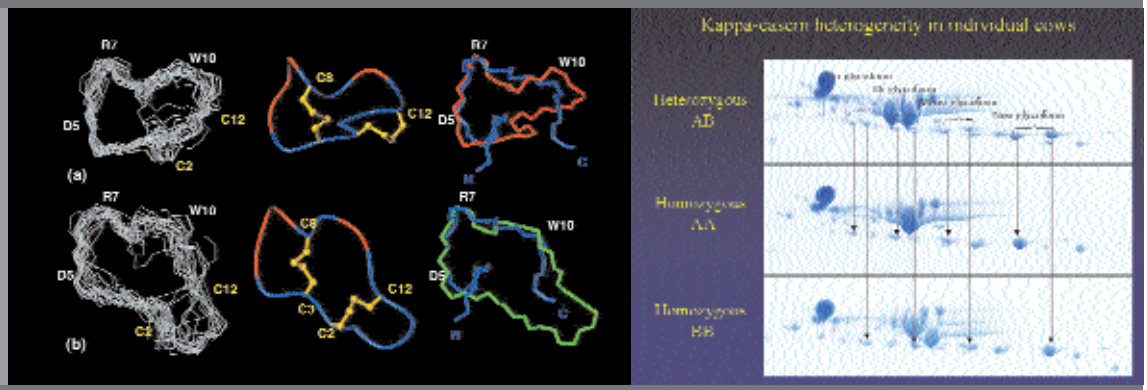
Professor Phil Kuchel, The University of Sydney

Dr Jamie Vanderberg, Garvan Institute of Medical Research, Sydney

Grants awarded in 2003

ARC Grant *Tuning the catalytic apparatus of HIV-1 Protease*

NHMRC Development Grant *Development of a new class of antibiotics*



(Left) Three dimensional NMR ribbon structures of cyclic analogues of a-conotoxin ImI overlayed with the native toxin. (Right) Two dimensional gels of milk from individual cows showing the genetic contribution of k-casein heterogeneity.

Staff and Students

Research officers
Paramjit Bansal
Peter Cassidy
John Holland
Christopher Armishaw

PhD students
Gene Hopping
Jean Jin
Lita Imperial
Ryan O'Donnell
Natalie Steen

Research assistants
Aaron Poth

Visiting scholars
Andreas Brust
Maria Wahlstrom

Vacation scholars
Stuart Fritz
Jennifer Smith

Publications

Alewood, D., Birinyi-Strachan, L.C., Pallaghy, P.K., Norton, R.S., Nicholson, G.M., Alewood, P.F. 2003 Synthesis and characterization of delta-atracotoxin-Ar1a, the lethal neurotoxin from venom of the Sydney funnel-web spider (Atrax robustus). *Biochemistry* 42:12933-40.

Torres, A.M., Bansal, P.S., Sunde, M., Clarke, C.E., Bursill, J.A., Smith, D.J., Bauskin, A., Breit, S.N., Campbell, T.J., Alewood, P.F., Kuchel, P.W., Vandenberg, J.I. (2003) Structure of the HERG K+ channel S5P extracellular linker: role of an amphipathic alpha-helix in C-type inactivation. *J Biol Chem.* 278:42136-48.

Sharpe, I.A., Palant, E., Schroeder, C.I., Kaye, D.M., Adams, D.J., Alewood, P.F., Lewis, R.J. (2003) Inhibition of the norepinephrine transporter by the venom peptide chi-MrIA. Site of action, Na+ dependence, and structure-activity relationship. *J Biol Chem.* 278:40317-23.

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Hogg, R.C., Hopping, G., Alewood, P.F., Adams, D.J., Bertrand, D. Alpha-conotoxins PnIA and [A10L]PnIA stabilize different states of the alpha7-L247T nicotinic acetylcholine receptor. (2003) *J Biol Chem.* 278:26908-14.

Torres, A.M., Bansal, P., Alewood, P.F., Bursill, J.A., Kuchel, P.W., Vandenberg, J.I. (2003) Solution structure of CnErg1 (Ergtoxin), a HERG specific scorpion toxin. *FEBS Lett.* 539:138-42.

Blanchfield, J.T., Dutton, J.L., Hogg, R.C., Gallagher, O.P., Craik, D.J., Jones, A., Adams, D.J., Lewis, R.J., Alewood, P.F., Toth, I. (2003) Synthesis, structure elucidation, in vitro biological activity, toxicity, and Caco-2 cell permeability of lipophilic analogues of alpha-conotoxin MII. *J Med Chem.* 46:1266-72.

Hodgson, W.C., Eriksson, C.O., Alewood, P.F., Fry, B.G. (2003) Comparison of the in vitro neuromuscular activity of venom from three Australian snakes (Hoplocephalus stephensi, Austrelaps superbus and Notechis scutatus): efficacy of tiger snake antivenom. *Clin Exp Pharmacol Physiol.* 30:127-32.

Nicke, A., Loughnan, M.L., Millard, E.L., Alewood, P.F., Adams, D.J., Daly, N.L., Craik, D.J., Lewis, R.J. (2003) Isolation, structure, and activity of GID, a novel alpha 4/7-conotoxin with an extended N-terminal sequence. *J Biol Chem.* 278:3137-44.

Rob Capon

CENTRE FOR MOLECULAR BIODIVERSITY

Research overview

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

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

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

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

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

Projects

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

Collaborations

Novartis Animal Health Australasia

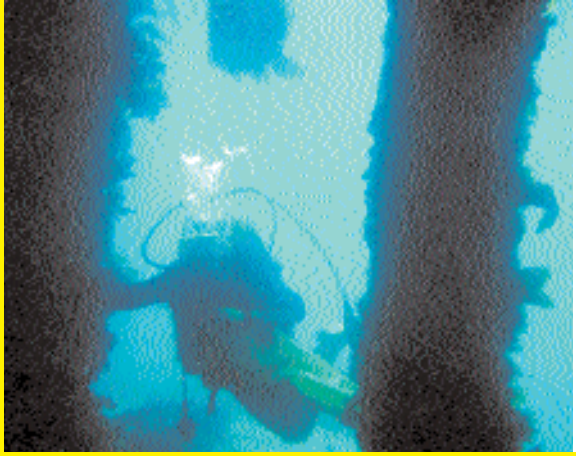
Microbial Screening Technologies

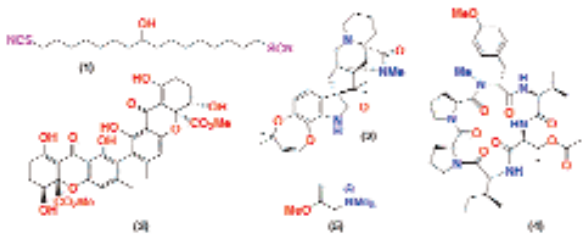
PharmaMar

University of Melbourne, School of Botany

Grants Awarded

ARC Linkage Grant *Anticancer Agents from Australian Marine Biodiversity*





Staff and Students		
Research officers Mike Stewart Nick Trotter **Visiting student** Torsten Peterle	**Research assistant** Ben Mooney	**PhD students** Ben Clark Leith Fremlin Ranjala Ratnayake Michelle McNally Ed Liu

Conferences and Invited Lectures

19th Royal Australian Chemical Institute Organic Conference (Lorne)

CSIRO: Biopharmaceuticals, Concept to Clinic (Melbourne)

Queensland Government: Ideas@Powerhouse (Brisbane)

Queensland Government: Science Meets Parliament (Brisbane)

AusBiotech: Biodiscovery (Brisbane)

Queensland Department of Primary Industries: Microbes: Biodiversity, biodiscovery & biotechnology (Caloundra)

World Federation of Culture Collections (Melbourne)

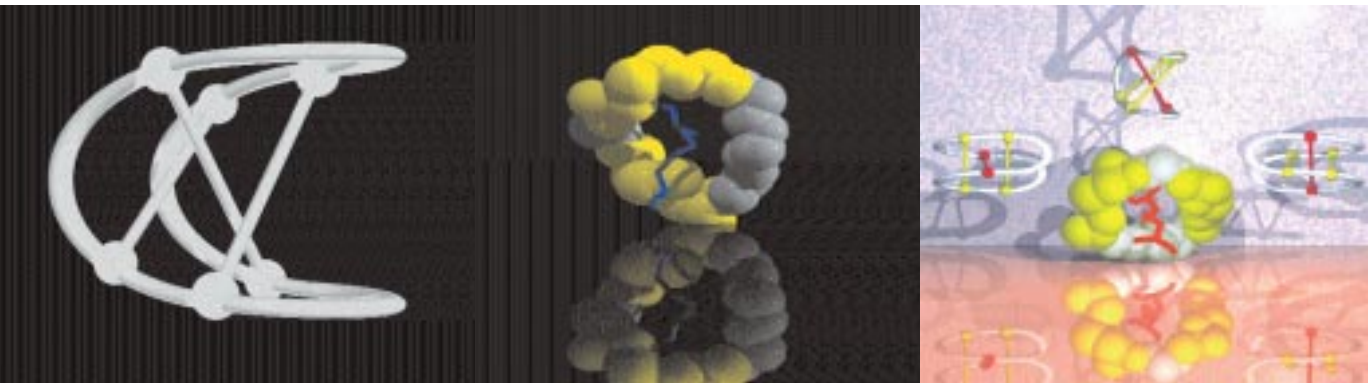
Asia Pacific Biochemical Engineering Conference (Brisbane)

Other

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

Publications (2003)

Capon, R.J., Skene, C., Stewart, M., Ford, J., O'Hair, R.A.J., Williams, L., Lacey, E., Gill, J.H., Heiland, K., Friedel, T. (2003) Aspergillicins A-E: five novel depsipeptides from the marine-derived fungus *Aspergillus carneus. Org. & Biomol. Chem.* 1:1856-1862.



(From left) Schematic representations of the cyclic cystine knot topology of the cyclotide family of proteins discovered by our group. a) Topology of the backbone and disulfide bonds; b) The unique embedded ring of the structure; c) Artistic impression of the cyclic cystine knot motif.

David Craik

NMR SPECTROSCOPY

Research overview

Our group uses NMR spectroscopy to determine the structures of proteins that are important in drug design programs and in agriculture. By elucidating the structures of biologically active proteins we are able to identify regions crucial for activity and can use this information to design new drugs. We have a particular interest in the discovery and structural characterisation of novel protein topologies.

Research Projects

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

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

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

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

Grants

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

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

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

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

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

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

NHMRC Industry Fellowship *Norelle Daly*

2003 AMRAD Postdoctoral Award Justine Hill

Highlights

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

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

Major lectures:

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

Invited public lecture at Nanyang University in Singapore.

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

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

Staff and Students

Research officers
Richard Clark
Michelle Colgrave
Norelle Daly
Justine Hill
Amanda Nourse
Johan Rosengren
Horst Schirra
Manuela Trabi

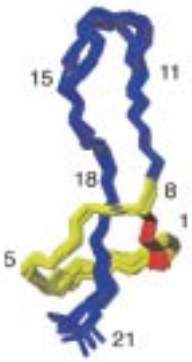
PhD students
Daniel Barry
Michael Korsinczky
Erica Lovelace
Emma Millard
Jason Mulvenna
Manuel Plan
Maria Quimo
Angela Salim
Lillian Sandø
Ivana Saska
Shane Simonsen

Honours student:
Louise Dempster

Research assistants:
Rekha Bharathi
Fiona Foley

Visiting researchers:
Bin Chen
Ulf Goransson
Marco Retzlaff
Seetharama Satyanarayanajois

Visiting scholar
Uta Kuepper



Published papers in 2003

Lay, F.T., Schirra, H.J., Scanlon, M.J., Anderson, M.A., Craik, D.J. (2003) The three-dimensional solution structure of NaD1, a new floral defensin from Nicotiana alata and its application to a homology model of the crop defense protein alfAFP. *Journal of Molecular Biology* 325:175-188.

Craik, D.J., Clark, R.J. (2003) NMR and Drug Discovery. *Burger's Medicinal Chemistry and Drug Discovery* (Ed: D J Abraham) 6th Edition, Chapter 11, Wiley.

Nicke, A.C., Loughnan, M., Millard, E.L., Alewood, P.F., Adams, D.J., Daly, N.L., Craik, D.J., Lewis, R.J. (2003) Isolation, structure and functional characterization of a-GID, a novel 4/7 a-conotoxin with an extended N-terminal sequence. *Journal of Biological Chemistry* 278:3137-3144.

Daly, N.L., Clark, R.J., Craik, D.J. (2003) Disulfide folding pathways of cystine knot proteins: tying the knot within the circular backbone of the cyclotides. *Journal of Biological Chemistry* 278:6314-6322.

Rosengren, K.J., Daly, N.L., Plan, M.R., Waine, C., Craik, D.J. (2003) Twists, knots and rings in proteins: structural definition of the cyclotide framework. *Journal of Biological Chemistry* 278:8606-8616. **[Cover feature]**

Craik, DJ., Daly, N.L., Saska, I., Trabi, M., Rosengren, K.J. (2003) Structures of naturally-occurring circular proteins from bacteria. *J Bacteriology* 185:4011-4021.

Craik, D.J., Anderson, M.A., Daly, N.L. (2003) Circular proteins tied in knots. *Today's Life Sciences* 15:28-32.

Blanchfield, J.T., Dutton, J.L., Hogg, R., Gallagher, O.P., Craik, D.J., Adams, D.J., Lewis, R.J., Alewood, P.F., Toth, I. (2003) The synthesis, structure elucidation, in vitro biological activity, toxicity and Caco-2 cell permeability of lipophilic analogues of α-conotoxin MII. *J. Med. Chem.* 46:1266-1272.

Barry, D.G., Daly, N.L., Clark, R. J., Sandø, L., Craik, D.J. (2003) Linearisation of a naturally occurring circular protein maintains structure but eliminates hemolytic activity. *Biochemistry* 42:6688-6695.

Marx, U.C, Korsinczky, M.L.J., Schirra, H.J., Jones, A., Condie, B., Otvos, L., Craik, D.J. (2003) Enzymatic cyclisation of the potent Bowman-Birk protease inhibitor SFTI-1: Solution structure of linear precursor peptide. *Journal of Biological Chemistry* 278:21782-21789. **[Cover feature]**

Janssen, B.J.C., Schirra, H.J., Lay, F.T., Anderson, M.A., Craik, D.J. (2003) The structure of PhD1, a novel plant defensin with five disulfide bonds. *Biochemistry* 42:8214-8222.

Meutermans, W.D.F., Bourne, G.T., Golding, S.W., Horton, D.A., Camitelli, M.R., Craik, D.J., Scanlon, M.J., Smythe, M.L. (2003) Difficult macrocyclisations: New strategies for synthesising cyclic tetrapeptides. *Organic Letters* 5:2711-2714.

Rosengren, K.J., Clark, R.J., Daly, N.L., Goransson, U., Jones, A., Craik, D. J. (2003) Microcin J25 has a Threaded Sidechain-to-Backbone Ring Structure and Not a Head-to-Tail Cyclized Backbone. *J. Amer. Chem. Society* 125:12464-12474.

Goransson, U., Craik, D.J. (2003) Disulfide mapping of the cyclotide kalata B1: chemical proof of the cyclic cystine knot. *J Biol Chemistry* 278:48188-48196.

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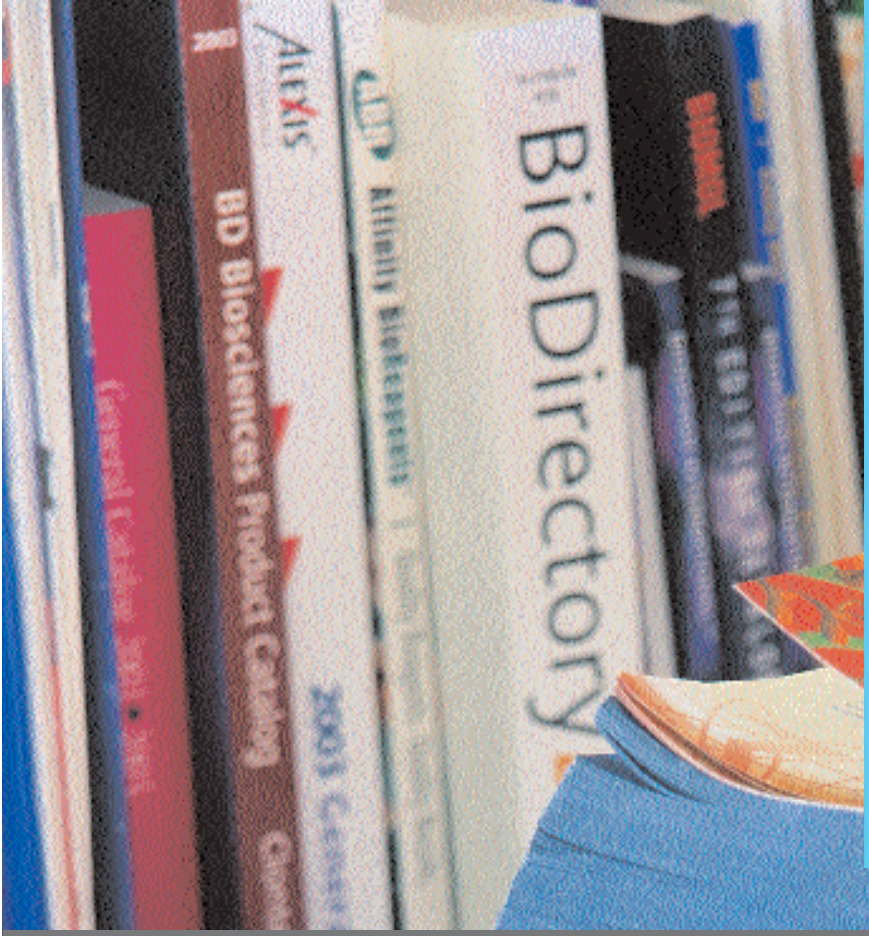
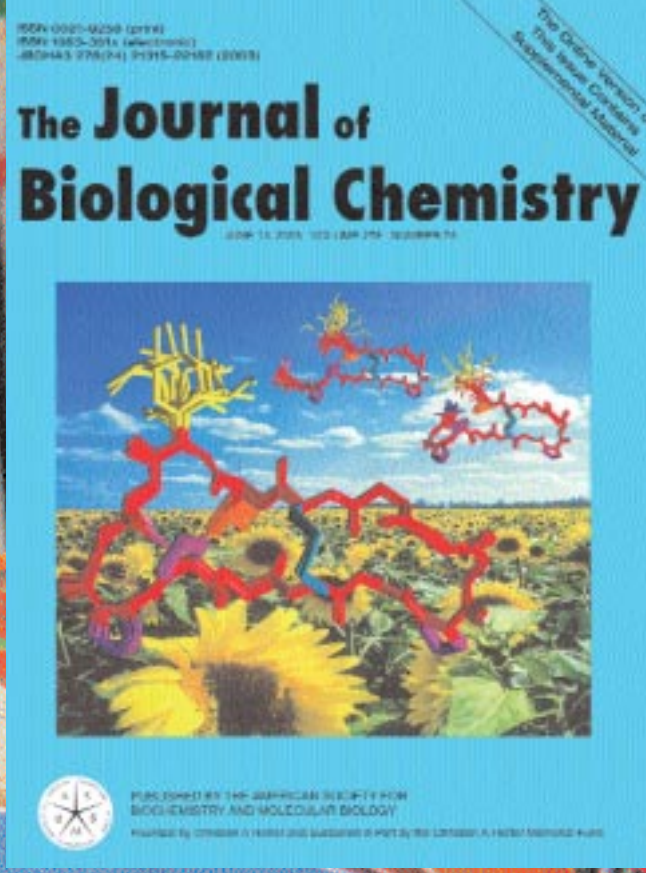
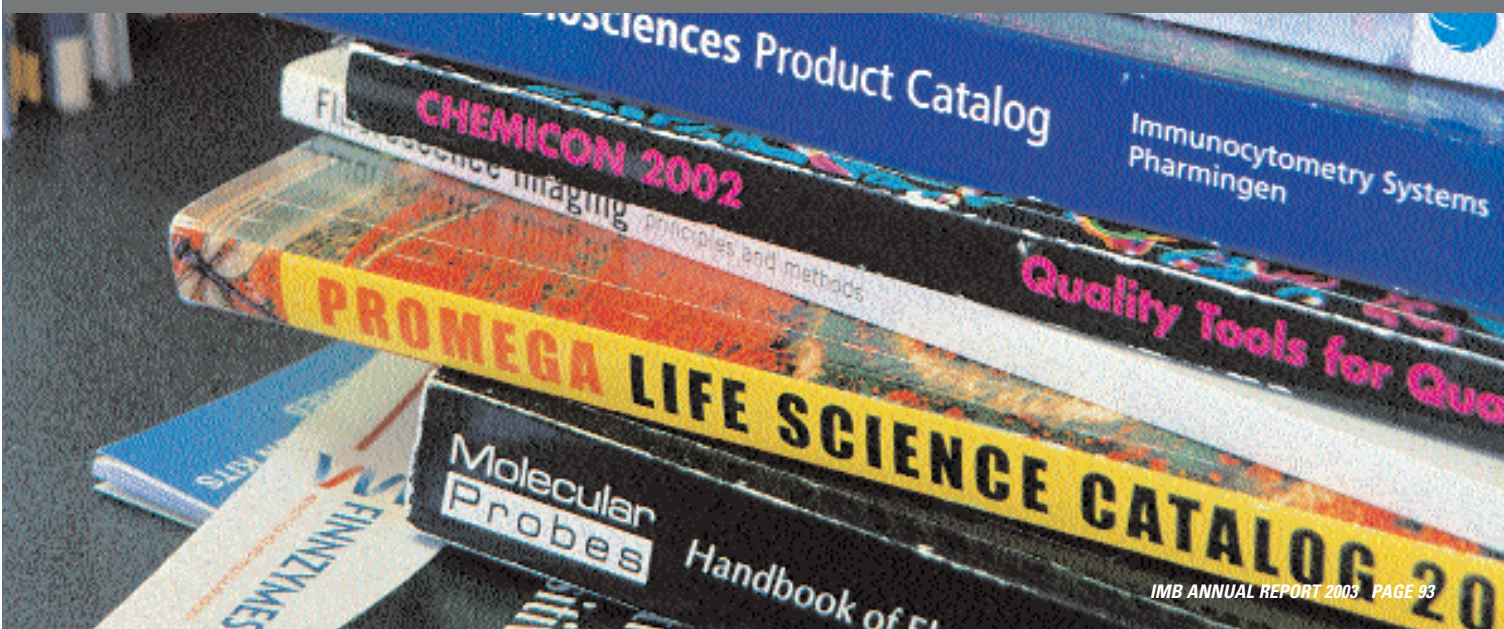




(Opposite page - from left) Solution structure of palicourein, the largest cyclotide yet discovered, along with the South American plant, Palicourea condensata, from which it is derived; Cover from the Journal of Biological Chemistry from the issue in which we described the concepts of "twist, knots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

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



David Fairlie

CHEMISTRY AND HUMAN THERAPEUTICS

Research overview

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

Research Overview

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

Project Areas

Fundamental Chemical Studies

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

Drug Design, Discovery and Development

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

Molecular Recognition

Our group uses computers to identify patterns in biomolecular recognition. We are attempting to understand the origin and reasons for such patterns, and are developing generic strategies for rationally creating small molecules that mimic or interfere with such interactions. We have recently completed computer modelling analyses of all known structures of protease-bound ligands, GPCR-binding proteins/peptides, and receptor-bound transcription factors. We have established the frequency with which such classes of receptors recognize their ligands in beta strand, turn, and helix shapes respectively. We have also created a database consisting of millions of sorted small organic molecules for use *in silico* in matching to pharmacophores or receptors during ligand- or receptor- based drug design.

Fig1a Fig1b Fig1c Fig1d

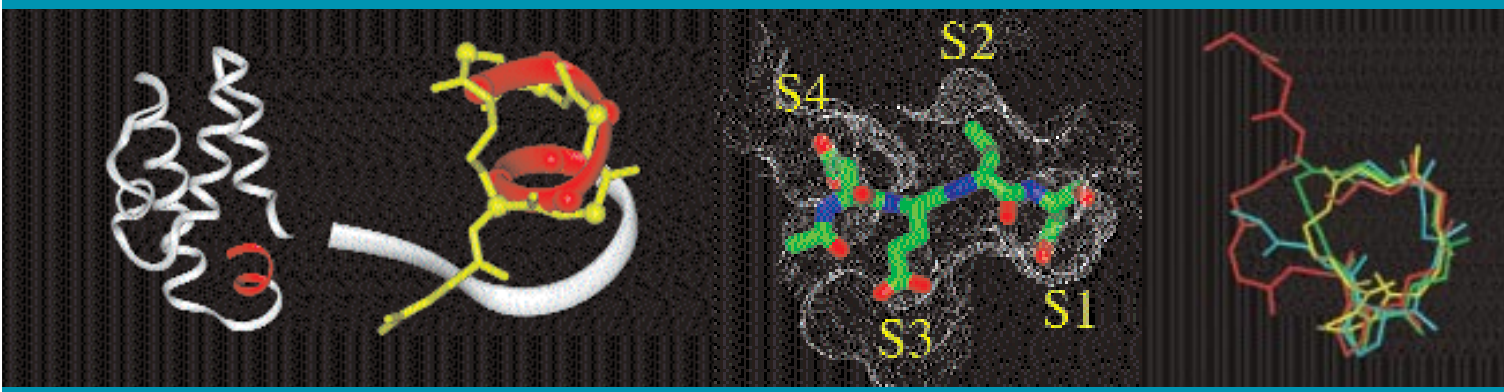


Figure 1: Cytokine structure (Fig1a) for which a loop (red) has been mimicked (Fig1b) by a small molecule (yellow); Structure of a beta strand inhibitor bound in the active site of caspase 3 (Fig1c); NMR structure for several cyclic and acrylic agonists and antagonist of a GPCR (Fig1d).

Protein Surface Mimics

We are designing and synthesizing new classes of small organic molecules that mimic bioactive secondary (strand, sheet, helix, turns, combinations) and tertiary (multi-loop, multi-helix, multi-sheet bundles) structural surfaces of proteins. Multi-helix and multi-sheet molecules also led in some cases to supramolecular nanostructures resembling those formed by amyloidogenic proteins associated with neurodegenerative diseases. We use 2D NMR spectroscopy to determine structures for selected chemical mimics which are then compared with protein structures. Successful structural mimicry has translated into functional mimicry, and we are now attempting to discover how universal our generic approaches are for mimicking bioactive protein surfaces.

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

Collaborations

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

Grants

NHMRC Project Grant *Convertase Inhibitors As A New Class Of Anti-Inflammatory Drugs*

NHMRC Project Grant *Design & Development Of Small Molecules To Regulate Protease Activated Receptor-2*

NHMRC Project Grant *Agonists and Antagonists of the Human Complement C3a Receptor*

NHMRC Project Grant *Design & Evaluation of Inhibitors of Phospholipases A2 as Anti-inflammatory Drugs*

NHMRC Development Grant *Developing Anti-Inflammatory Drugs Based on Inhibition of a Human Enzyme*

ARC Discovery Grant *Macrocyclic Peptidomimetics*

ARC Discovery Grant *Metal Clips For Folding Short Peptides Into Helices*

ARC Seed Grant *The Australian Protease Network*

2nd Hans Werthén Scholarship *Pia Kahnberg*

NHMRC CJ Martin Fellowship *Michael Kelso*

ARC Australian Professorial Fellowship *Fairlie*

Staff and Students

Senior research staff
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Yogendra Singh
Martin Stoermer

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Huy Hoang

Len Pattenden
Gavin Bryant

Masters student
Aarti Kishore

Honours students
Tessa Nall
Jacky Suen

UROP students
Sarah Smith
Paul Jauncey
Carol Burnton

Sabbatical visitor
Dr. Wendy Loughlin

Publications 2003

Glenn, M.P., Kelso, M.J., Tyndall, J.D.A., Fairlie, D.P. (2003) Conformationally Homogeneous Cyclic Tetrapeptides : Useful Three Dimensional Scaffolds. *J. Am. Chem. Soc.* 125:640-641.

Kelso, M.J., Hoang, H.N., Oliver, W.N., Sokolenko,N., March, D.R., Appleton, T.G., Fairlie, D.P. (2003) A Cyclic Metallopeptide That Induces Alpha Helicity In Short Peptide Fragments of Thermolysin. *Angew Chem. Int. Edit.* 42:421-424.

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Lucke, A.J., Tyndall, J.D.A., Singh, Y., Fairlie, D.P. (2003) Designing supramolecular structures from models of cyclic peptide scaffolds with heterocyclic constraints, *J. Molecular Graphics and Modelling* 21:341-355.

Woodruff, T.M., Arumugam, T.V., Shiels, I.A., Reid, R.C., Fairlie, D.P., Taylor, S.M. .(2003) A Potent Human C5a Receptor Antagonist Protects Against Disease Pathology in a Rat Model of Inflammatory Bowel Disease. *J. Immunol.* 171:5514-5520.

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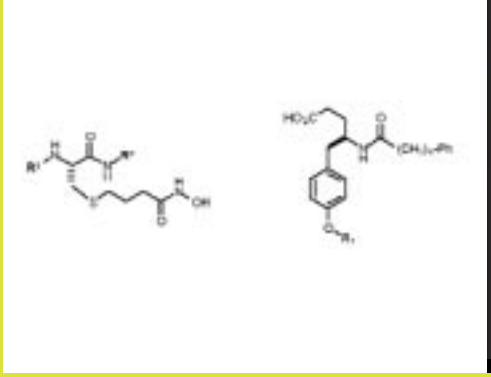
Williamson, A.L., Brindley, P.J., Abbenante, G., Datu, B.J.D., Prociv, P., Berry, C., Girdwood, K., Pritchard, D.I., Fairlie, D.P., Hotez, P.J., Zhan, B., Loukas, A. (2003) Hookworm Aspartic Protease, Na-APR-2, Cleaves Human Hemoglobin and Serum Proteins in a Host-Specific Fashion, *J. Infect. Diseases,* 187:484-494.



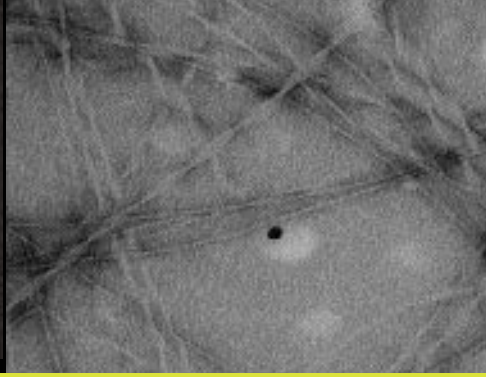


Fig2a *Fig2b* *Fig2c* *Fig2d*

Figure 2: Structures of potent and selective inhibitors of human histone deacetylases (Fig2a) and human secretory phosopholipase A2 Group IIa (Fig 2b) that are orally active and respectively exhibit anticancer and anti-inflammatory activity; NMR-derived structures of an alpha helix mimetic in water (Fig 2c). The molecule is conformationally stable to 600C, 8M Guanidine.HCl and trypsin digest; Nanofibres comprising twisted beta sheet peptides formed from template-assembled bundles of alpha helical peptides (scale 200nm) (Fig 2d).

Stoermer, M.J., Butler, D.N., Warrener, R.N., Weerasuria, K.D.V., Fairlie, D.P. (2003) Cycloadditions of Isobenzofuran to a Constrained Template Bearing Neighboring Dienophiles. *Chem. Eur.* J., 9:2068-2071.

Kelso, M.J., Fairlie, D.P. Current Approaches To Peptidomimetics in *Molecular Pathomechanisms And New Trends In Drug Research,* Chapter 44, pp. 579-598 (Eds Toth I & Keri G) Taylor & Francis London and New York 2003.

Beyer, R.L., Kelso, M.J., Hoang, H.N., Appleton, T.G., Fairlie, D.P. (2003) "Helix-Inducing Metal Clips in Short peptides" in *Biomolecular Chemistry,* Proc. First Int. Symp. Biomolecular Chemistry, December 2-5, Awaji, Japan, Chapter 3, pp. 146-149 (Ed. Y. Baba), Maruzen Co. Ltd Tokyo, 2003.

Hoang, H.N., Bryant, G.K., Kelso, M.J., Beyer, R.L., Appleton, T.G., Fairlie, D.P. (2003) Short Peptide Alpha Helices Induced by Multiple Metal Clips *J. Inorg. Biochem.* 96:146.

Cusack, R.M., Grondahl, L., Fairlie, D.P., Hanson, G.R., Gahan, L.R. (2003) Studies of the interaction of potassium(I), calcium(II), magnesium(II), and copper(II) with cyclosporin A. *J. Inorg. Biochem.* 97:191-198.

Conferences

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

"Template-Assembled Peptide Helices, Loops, Sheets and Nanofibres". Fairlie DP, Singh Y, Sharpe P, Stoermer MJ ; American Chemical Society, Organic Division, Mar 24, 2003 (New Orleans, USA).

"Proteinases and Inhibitor Design", Fairlie DP 2nd International Industry Conference on Protease Inhibitors, IBC, Sept. 3-4, 2003 (Zurich).

"Protease Ligand Conformation and Inhibitor Design", Fairlie DP 57th Harden Conference, Proteinase, Structure and Function, Royal Societies for Biochemistry and Chemistry, Sept. 9-13, 2003 (Oxford).

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

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

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

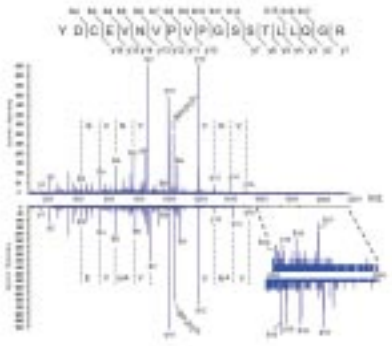
"Towards Mimics Of Protein Surfaces" Fairlie, D. P. Symposium on Biomolecular Chemistry Kyushu University, Dec 6, 2003 (Fukuoka, Japan).

Other Developments

2003-, Co-Editor of Current Medicinal Chemistry

Started International and National protease research networks (www.protease.net, www.protease.net.au) to facilitate interdisciplinary research interactions in the field of proteases, their inhibitors and receptors. The networks involve over 100 international research groups and 90 Australian research groups.

Jeffrey Gorman



MOLECULAR AND CELLULAR PROTEOMICS

Research overview

Research carried out by this new group will exploit the platform of contemporary protein chemistry and proteomics.

This platform is broadly applicable to defining the chemical features of purified proteins, interactions between proteins at the molecular and cellular levels and the dynamics of the protein repertoires of cells in response to disease states and other stimuli.

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

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

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

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

Projects

Interactions and structures of proteins in assembled virus particles.

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

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

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

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

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

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

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

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

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

In collaboration with Dr Murray Whitelaw's group from the University of Adelaide, we have demonstrated that the transcriptional potency of hypoxia-inducible factor (HIF)-transcriptional complexes is inhibited by hydroxylation of a specific asparagine residue of HIF. Oxygen activates this post-translational modification and it also serves as the substrate for the hydroxylase (Factor that Inhibits HIF, or FIH) which hydroxylates the

regulatory asparagine of HIF. This normoxic hydroxylation inhibits the recruitment of the transcriptional co-activator p300/CBP to the DNA-bound complex, thereby repressing transcription. The purpose of this regulation is to prevent transcription of genes whose products are only required to respond to low cellular oxygen levels.

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

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

Collaborators

Prof John Bateman, Murdoch Childrens Research Institute, Melbourne

Professor John Hancock, IMB

Professor Rob Parton, IMB

Professor Paul Young, Department of Microbiology, University of Queensland

Dr Murray Whitelaw, School of Molecular and Biomedical Science, University of Adelaide

Dr Peter Collins, National Institutes of Health, Bethesda, Maryland, USA

Professor Mark Peeples, Columbus Children's Research Institute and The Ohio State University, USA

Grants

ARC Linkage Infrastructure and Facilities Grant *(LIEF) Time of Flight Mass Spectrometry and Robots*

NHMRC Project *Identification and functions of posttranslational modifications in the Dioxin/Arnt transcription factor. With Murray Whitelaw*

AntiCancer Council of South Australia *Role of the Hypoxia Inducible Factor in Tumourigenesis. With Murray Whitelaw and Daniel Peet.*

Queensland Cancer Fund *Proteomics approaches to the early detection of prostate cancer. With R. Gardiner, J. Clements, T. Walsh, J. Bartley, and T. Pettitt*

Other

Member of the editorial boards of the journals *Molecular and Cellular Poteomics and Protein and Pepteide Letters*

Staff and Students

Research officers	Research assistants	PhD students
Gary Shooter	Ngari Teakle	Hong Soon Chin
Professional officer	Tristan Wallis	Keyur Dave
Alun Jones		

Publications

Lando, D., Gorman, J.J., Whitelaw, M.L., Peet, D.J. (2003) Oxygen-Dependent Regulation of Hypoxia-Inducible Factors by Prolyl and Asparaginyl Hydroxylation. *European Journal Biochemistry,* 270:781-790.

Campanale, N., Nickel, C., Daubenberger, C.A., Whelan, D.A., Gorman, J.J., Klonis N., Becker, K., Tilley, L. (2003) Identification and Characterization of Heme-Interacting Proteins in the Malaria Parasite, *Plasmodium falciparum. J. Biol. Chem.* 278:27354-27361.

Macdonald, W.A., Purcell, A.W., Mifsud, N., Ely, L.K., Williams, D.S., Gorman, J.J., Clements, C.S., Kjer-Nielsen, L., Koelle, D.M., Borrow, S.R., Tait, B.D., Holdsworth, R., Brooks, A.G., Lovrecz, G.O., Lu, L., Rossjohn, J., McCluskey, J.A. (2003) Naturally selected Dimorphism Within the HLA-B44 Supertype Alters Class I Structure, Peptide Repertoire and T Cell Recognition. *J. Exp. Med.* 198:679-691.

Bostjan Kobe

STRUCTURAL BIOLOGY OF PROTEIN – PROTEIN INTERACTIONS

Research overview

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

Projects

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

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

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

Grants awarded

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

Collaborators

David Hume, Institute for Molecular Bioscience, University of Queensland

Jenny Martin, Institute for Molecular Bioscience, University of Queensland

Thomas Huber, Department of Mathematics, University of Queensland

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

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

Jimmy Botella, Department of Botany, University of Queensland

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

David Fairlie, Institute for Molecular Bioscience, University of Queensland

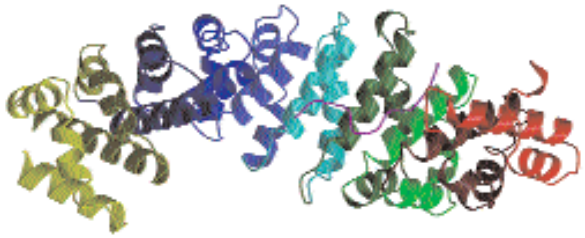
Don McManus, Queensland Institute of Medical Research, Brisbane

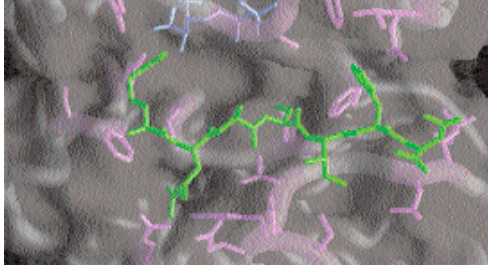
Bruce Kemp, St. Vincent's Institute of Medical Research, Melbourne

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

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

Jeff Ellis, CSIRO Plant Industry, Canberra





(From left) Crystal structure of the nuclear import receptor importin-alpha; Binding of a substrate to protein kinase A.

Peter Anderson, Flinders University of South Australia, Adelaide

Andrey Kajava, Centre de Recherches de Biochimie Macromoléculaire, CNRS, France

Roman Jerala, National Institute of Chemistry, Ljubljana, Slovenia

Matthias Koehler, Franz-Volhard-Klinik, Berlin, Germany

Murray Stewart, Medical Research Council Laboratory of Molecular Biology, Cambridge, UK.

Marcos Roberto de M. Fontes, Departamento de Física e Biofísica, Instituto de Biociências - UNESP, Botucatu, Brazil,

Barbara Valent, Department of Plant Pathology, Kansas State University, Kansas, USA

Robert F. Standaert, Department of Chemistry, University of Illinois at Chicago, USA

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Huang-Teck Lee
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PhD studenta
Robert Serek
Sundy (Ni Yen) Yang
James Clark

MPhil students
Thorsten Kampmann
Carmel Walsh

Honours students
Marek Mrozkiewicz
Sarah Chilcott
Dmitri Mouradov

Publications and papers in 2003

Brinkworth, R.I., Breinl, R.A., Kobe, B. (2003) Structural basis and prediction of substrate specificity in protein serine/threonine kinases. *Proc. Natl. Acad.* Sci. USA 100:74-79.

Wooh, J.W., Kidd, R.D., Martin, J.L., Kobe, B. (2003) Comparison of three commercial sparse matrix crystallisation screens. *Acta Cryst.* D59:769-772.

Smyth, D.R., Mrozkiewicz, M.K., McGrath, W.J., Listwan, P., Kobe, B. (2003) Crystal structures of fusion proteins with large affinity tags. *Protein Sci.* 12:1313-1322.

Fontes, M.R., Teh, T., Jans, D.A., Brinkworth, R.I., Kobe, B. (2003) Structural basis for the specificity of bipartite nuclear localisation sequence binding by importin-alpha. *J. Biol. Chem.* 278: 27981-27987.

Kobe, B. (2003) Great expectations: Structural biology amidst world politics. *Australian Biochemist* 34:24-27.

Fontes, M.R., Teh, T., Toth, G., John, A., Pavo, I., Jans, D.A., Kobe, B. (2003) The role of flanking sequences and phosphorylation in the recognition of SV40 large T-antigen nuclear localisation sequence by importin-alpha. *Biochem. J.* 375:339-349.

Kobe, B. (2003) Protein regulation, protein-protein interactions and structural genomics. *Acta Chim. Slov.* 50:547-562.

Conferences

Kobe, B., Breinl, R.A., Brinkworth R.I. (2003) Identification of substrates of protein kinases. – 28th Annual Conference on Protein Structure and Function, Lorne, Victoria, Australia, 9-13 February.

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Kobe, B., Breinl, R.A., Brinkworth, R.I. (2003) Using structural information in functional genomics: Identification of substrates of protein kinases. – AsCA'03/Crystal-23, Broome, Western Australia, 10-13 August.

Fontes, M.R., Teh, T., Toth, G., John, A., Pavo, I., Jans, D.A., Kobe, B. (2003) The elusive role of phosphorylation in nuclear import. – ComBio2003, Melbourne, Victoria, Australia, 29 September - 2 October.

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Richard Lewis

MOLECULAR PHARMACOLOGY

Research overview

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

Currently we are investigating conotoxins that selectively target the nicotinic acetylcholine and NMDA receptors, the voltage sensitive calcium and sodium channels, the noradrenaline transporter and the α_1-adrenoceptor. Complimentary interactions between conotoxins and their receptor are being established to better understand where and how they act. Research on characterising the toxins involved in ciguatera is also undertaken in the laboratory.

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

Projects

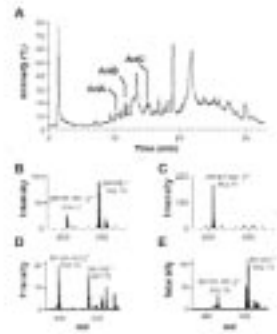
We are currently investigating conotoxins that selectively target:

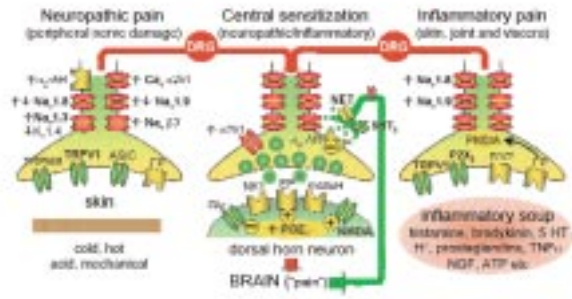
1. The nicotinic acetylcholine receptor, a non-selective cation channel stimulated by acetylcholine and nicotine, is selectively inhibited by α-conotoxins. We have discovered several new α-conotoxins using receptors expressed in oocytes to guide crude venom fractionation. Several had unusual structure and subtype selectivity. Homology modelling and docking studies are allowing us to understand at the molecular level how these selectivity differences arise;
2. The NMDA receptor, an important non-selective cation channel in the brain, is inhibited by conantokins. Using specific analogues of conantokin-G, we have recently found that specific subtypes of the NMDA receptor are lost in Alzheimer's disease. Currently we are trying to establish their identity to better understand how Alzheimer's disease develops;
3. The voltage sensitive N-type calcium, a neuronal calcium channel found in pathways involved in the transmission of painful stimuli, is inhibited by ω-conotoxins. We have recently identified a novel variant of this channel using ω-CVID. The nature and role of this variant is now being investigated to understand its role in chronic pain;(figure Lewis1.jpg)
4. The voltage sensitive sodium channels, particularly those found in neurons that are inhibited by μ-conotoxins, are also under investigation. We have established that μ-conotoxins selectively target persistent forms of the TTX-sensitive sodium channel. The nature and role of these sodium channels is currently under investigation.
5. The noradrenaline transporter (NET) is the primary route of noradrenaline removal from synapses. We have identified χ-conotoxins as the first peptide inhibitor of NET, which is effective in the treatment of neuropathic pain and depression. We are presently establishing the complimentary interactions between χ-conotoxins and NET to understand where and how they act at the molecular level.
6. We are also developing an understanding of where and how the ρ-conopeptides act on the α1-adrenoceptor, and important target for treating cardiovascular disorders and benign prostatic hyperplasia.
7. Finally, we are characterising the novel substrate specific proteases found in cone snail venom that have homology to pathogenesis related proteins and are up regulated in stress and diseases such as cancer.

Grants

NHMRC grant *Selectivity and Mode of Action of Rho-Conopeptide TIA: A Novel Inhibitor of Alpha1-Adrenoceptors*

ARC *Glycerotoxin, a unique tool to investigate the dynamic interactions between N-type Ca2+ channels and the exo-endocytic machinery (with Fredric Meunier, Physiology and Pharmacology, UQ).*





Collaborators

Professor Jean-Paul Vernoux, University of Caen, France

Professor Heinz Bönisch, University of Bonn, Germany

Professor Robert Graham, Victor Chang Cardiac Research Institute, Sydney

Professor MacDonald Christie, Pain Management Research Institute, University of Sydney

Professor Gustaaf Hallegraeff, Department of Botany, University of Tasmania

Professor David Adams, School of Biomedical Sciences, UQ

Dr Lesley Lluka, School of Biomedical Sciences, UQ

Professor Paul Alewood, IMB

Professor David Craik. IMB

Professor Robert Capon, IMB

Staff and Students

Research officers
Denise Adams
Marion Loughnan
Leonard Motin
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Tina Schroeder
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Trudy Bond
Sebastien Dutertre
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Lotten Ragnarsson
Dimitra Temelcos
Vicky Tsai
Taka Yasuda

Research assistants:
Trudy Bond
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Honours student
Nadeeka Dissanayaka

Visiting researcher
Patricia Hung

Visiting students
Jessica Larsson
Pia Larrson
Emma Larzenius
Sofie Singbrant
Angela Starke

Publications

Lewis RJ and Garcia ML (2003) Therapeutic potential of venom peptides. Nature Reviews Drug Discovery 2:790-802.

Nicke A., Loughnan M.L., Millard E.L., Alewood P.F., Adams D.J., Daly N.L., Craik D.J. and Lewis R.J. (2003) Isolation, structure and activity of GID, a novel 4/7α-conotoxin with an extended N-terminal sequence. *J. Biol. Chem.* 278:3137-3144.

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Milne, T.J., Abbenante, G., Tyndall, J.D., Halliday, J., Lewis, R.J. (2003) Isolation and characterization of a cone snail protease with homology to CRISP proteins of the pathogenesis-related protein superfamily. *J Biol Chem.* 278:31105-31110.

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Bryan-Lluka, L.J., Bonisch, H., Lewis, R.J. (2003) χ-Conopeptide MrIA partially overlaps the desipramine and cocaine binding sites on the human norepinephrine transporter. *J Biol Chem.* 278:40324-40329.

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Nicke, A., Samochocki, M., Loughnan, M.L., Bansal, P.S., Maelicke, A., Lewis, R.J. (2003) α-Conotoxins EpI and AuIB switch subtype selectivity and activity in native versus recombinant nicotinic acetylcholine receptors. *FEBS Lett.* 554:219-223.

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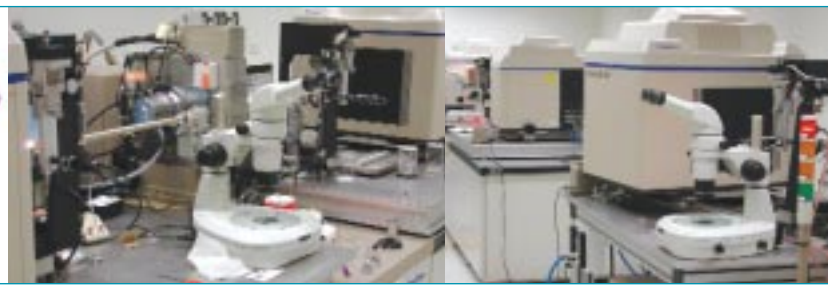
The aim of this research is to develop research tools and potential therapeutics for poorly treated diseases, such as chronic pain.



Jenny Martin

PROTEIN STRUCTURE AND PROTEIN INTERACTIONS

Research overview

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

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

Projects

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

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

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

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

SNARE proteins involved in insulin-regulated glucose transport.
In this collaboration with David James (Garvan) we have produced recombinant forms of all the SNARE proteins involved in the GLUT4 process as well as the regulatory SM protein Munc18c. We are currently investigating protein-protein interactions using the recombinant proteins.

Grants awarded for 2003

- **ARC Discovery Project** *Investigating the structure, function and inhibition of the adrenaline-synthesizing enzyme PNMT*
- **ARC Linkage Project** *Structural studies on carbohydrate modifying enzymes*
- **ARC Linkage Infrastructure and Equipment Funding** *Queensland high throughput structural biology screening facility*

Collaborations (not including those within IMB)

Gary Grunewald, Kansas University, USA

Michael McLeish, University of Michigan, USA

Linda Thöny-Meyer, ETH Zurich, Switzerland

Mick McManus, School of Molecular and Microbial Sciences, University of Queensland

Paul Young, School of Molecular and Microbial Sciences, University of Queensland

Judy Halliday, Alchemia Pty Ltd

David James, Garvan Institute for Medical Research, Sydney

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Niranjali Gamage
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Shu-Hong Hu

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Casey Pfluger
Maria Somodevilla-Torres

PhD students
Melissa Edeling
Cath Latham

Masters Students
Aditya Angadi
Frank Lin

Exchange Student
Danny Loveday

Honours students
Elizabeth Westbury

Undergraduate Students
Vivian Chan
Natalie Saez
Rosemary Harrison

Publications and papers in 2003

Heras, B., Edeling, M.A., Byriel, K.A., Jones, A., Raina, S., Martin, J.L. (2003) Dehydration converts DsbG crystal diffraction from low to high resolution. *Structure* 11:139-145

Gamage, N.U., Duggleby, R.G., Barnett, A.C., Tresillian, M., Latham, C.F., Liyou, N.E., McManus, M.E., Martin, J.L. (2003) Structure of a human carcinogen converting enzyme, SULT1A1: structural and kinetic implications of substrate inhibition. *J Biol Chem* 278:7655-7662

Hansford, K.A., Reid, R.C., Clark, C.I., Tyndall, J.D.A., Whitehouse, M.W., Guthrie, T., McGeary, R.P., Schafer, K., Martin, J.L., Fairlie, D.P. (2003) D-Tyrosine as a chiral precursor to potent inhibitors of human non-pancreatic secretory phospholipase A2 (IIA) with anti-inflammatory activity. *ChemBioChem.* 4:181-185

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Hu, S.-H., Gee, C.L., Latham, C.F., Rowlinson, S., Rova, U., Jones, A., Halliday, J.A., Bryant, N.J., James, D.E., Martin, J.L. (2003) Recombinant expression of Munc18c in a baculovirus system and interaction with syntaxin4. *Prot Expr Purif* 31:305-310.

Conferences

East Coast Protein Meeting, Coffs Harbour, June 2003 Nathan Cowieson, A. Aagaard, C. Wells, T. Ravasi, C. Gee, T. Huber, .P Listwan, D. Hume, B. Kobe, J.L. Martin. "Structural genomics of mouse macrophage proteins"

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

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

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

COMBIO 2003, Melbourne October 2003
A. Aagaard, P. Listwan, N. Cowieson, T. Huber, C. Wells, T. Ravasi, D.A. Hume, B. Kobe and J.L. Martin. "The crystal structure of latexin - a protease inhibitor upregulated in stimulated macrophages"

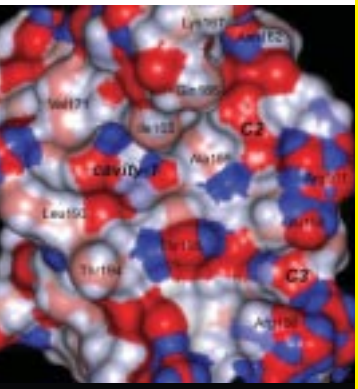
Christine Gee, M.J. McLeish, C.L. Grunewald, J.L. Martin. "Structural studies on PNMT, the adrenaline synthesising enzyme: improving crystallisation methods and diffraction resolution"

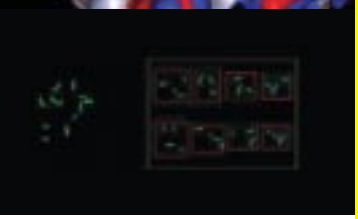
Begona Heras, M. Edeling, S. Raina, J.L. Martin "Crystal structure of oxidized and reduced DsbG"

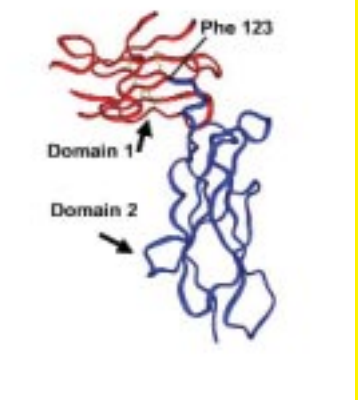
ASCEPT, Sydney December 2003-12-03
J.L. Martin "Focus on Queensland - the IMB and DDD"

Achievements in 2003

- Together with Bostjan Kobe and David Hume we succeeded in solving what we believe to be the first "high throughput" crystal structure, that of latexin a novel mammalian carboxypeptidease inhibitor (see picture on previous page).
- Installation of the first (and only) high brightness FR-E X-ray facility in Australia (see picture on previous page).
- Currently establishing with Bostjan Kobe and David Hume a high throughput facility for protein expression screening (pictures in next year's annual report).







Mark Smythe

COMBINATORIAL CHEMISTRY AND MOLECULAR DESIGN

Research Overview

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

Projects

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

Development of new molecular design tools

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

Synthetic Chemistry

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

Biology

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

Drug Discovery

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

Collaborators

Professor Garland Marshall. Washington University, St Louis, USA

Professor Mike Waters, IMB

Dr Kritaya Kongsuwan Livestock Industries, CSIRO

Dr Gene Wijffels, Livestock Industries, CSIRO

Dr Peter Adams, Department of Mathematics UQ

Dr Darryn Bryant, Department of Mathematics UQ

Staff and Students

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Andreas Ruhmann
Steve Love

PhD students
Andrew McDevitt
Doug Horton
Stephen Long
Gerald Hartig

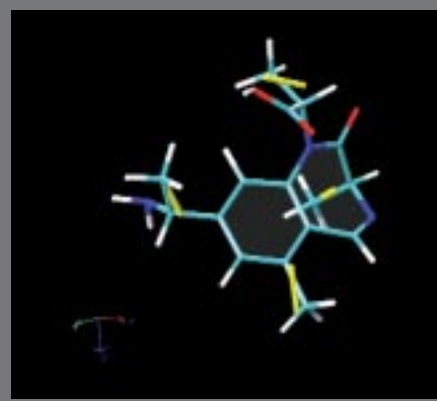
Research assistants
Justin Coughlan
Jill Turner
Ngari Teakle
Jonathon Nielson
Carolyn Jacobs
Warren Oliver

Publications

Meutermans, W.D.F., Bourne, G.T., Golding, S.W., Horton, D.A., Campitelli, M.R., Craik, D., Scanlon, M., Smythe, M.L. (2003) Difficult macrocyclizations: New strategies for synthesizing highly strained cyclic tetrapeptides *Org Lett.* 5: 2711-2714

Horton, D.A., Bourne, G.T., Smythe, M.L. (2003) The combinatorial synthesis of bicyclic privileged structures or privileged substructures *Chem Rev.* 103: 893-930

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

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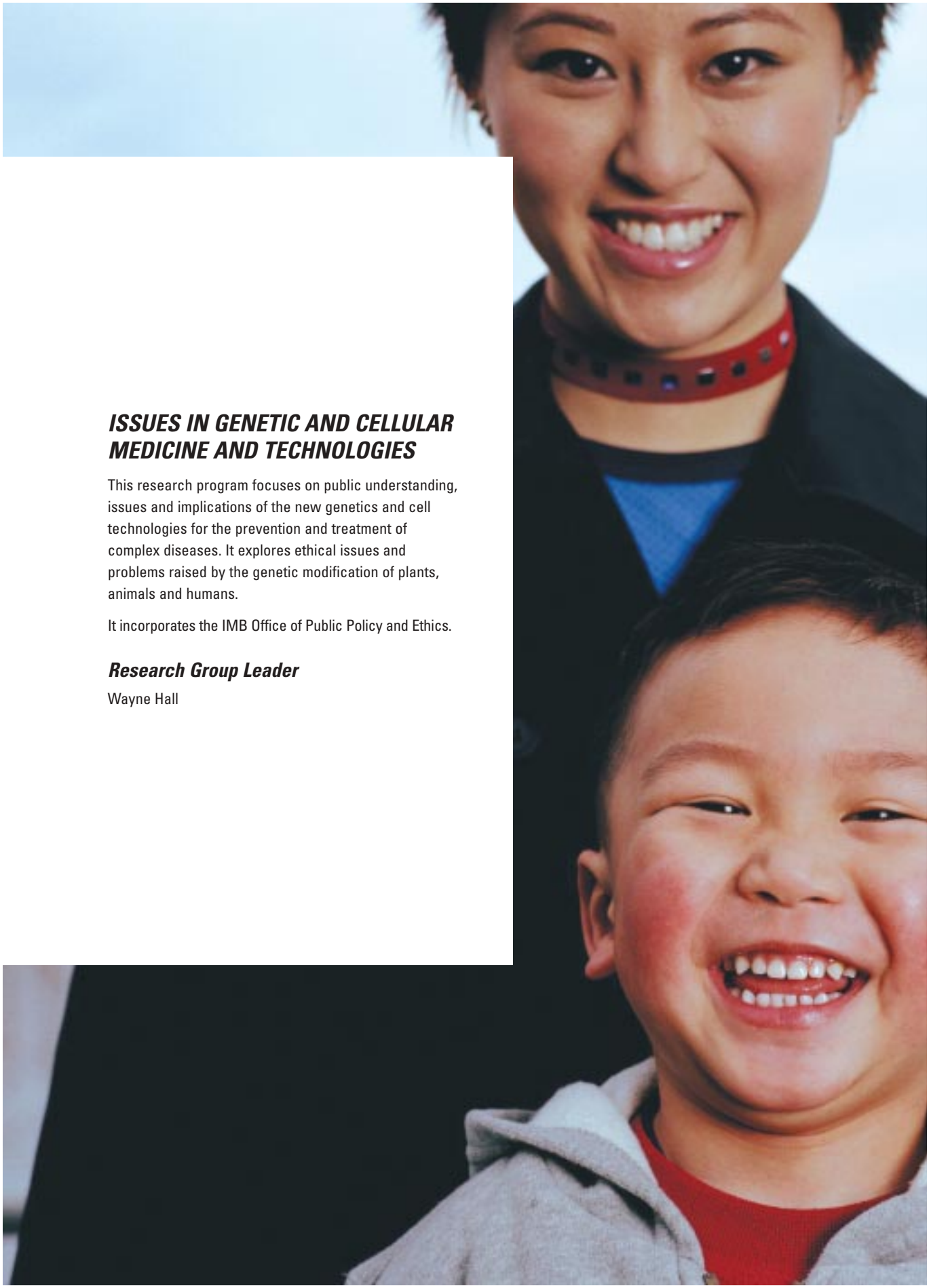


ISSUES IN GENETIC AND CELLULAR MEDICINE AND TECHNOLOGIES

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

It incorporates the IMB Office of Public Policy and Ethics.

Research Group Leader

Wayne Hall

Wayne Hall

OFFICE OF PUBLIC POLICY AND ETHICS

Research overview

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

Projects

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

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

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

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

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

Grants/funding

Australian Institute of Criminology / Criminology Research Council

Queensland Cancer Fund

School of Population Health, University of Queensland

beyondblue: the national depression initiative

UQ New Staff Research Start-up Fund

Staff and Students

Visiting professors
John Morgan
David Weisbrot

Adjunct senior research fellows
Susan Treloar
Kim Summers

Visiting research fellow
Martin Wilkinson

PhD students
Lucy Carter
Jennifer Fleming
David Turnbull
Katie Wilson

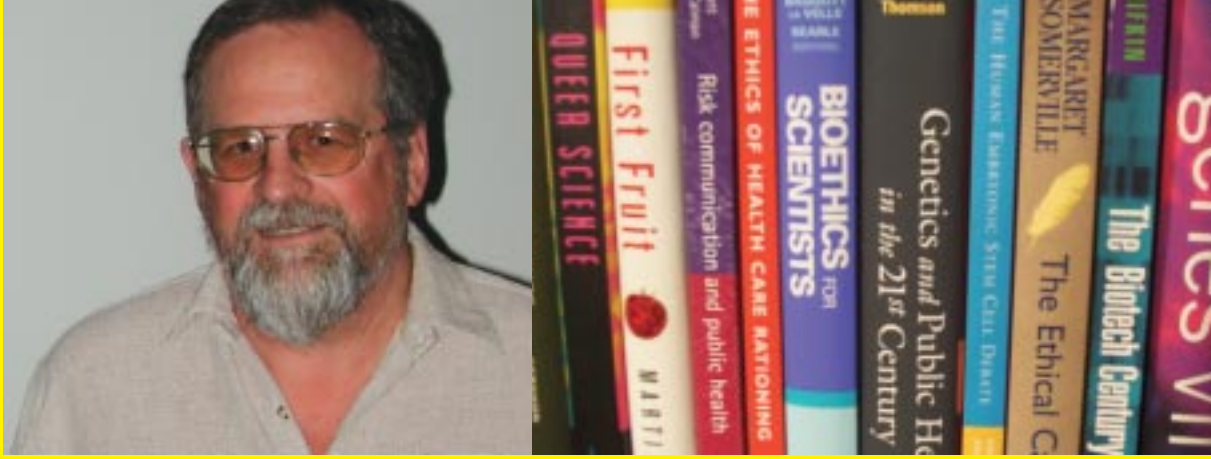
Masters student
Angela Wallace

Research assistants
Marla Gwynne
Katherine Morley

Specialist librarian
Sarah Yeates

Undergraduate research opportunities program student
Cerys Jones

URSS students
Moya Anne McCaskill
Cindy Rinehart



Collaborators

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

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

Dr Rick Harwood, National Institute on Drug Abuse, USA

Dr Jeff Dunn and Dr Joanne Aitken, Queensland Cancer Fund

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

Publications

Hall, W., Carter, L., Morley, K.I. (2003) Addiction, ethics and scientific freedom. *Addiction* 98:873-4.

Hall, W., Carter, L., Morley, K.I. (2003) Addiction, neuroscience and ethics. *Addiction* 98:867-70.

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Hall, W.D., Mant, A., Mitchell, P.B., Rendle, V., Hickie, I., McManus, P. (2003) Association between antidepressant prescribing and suicide in Australia, 1991-2000: trend analysis. *BMJ* 326:1008-1012.

Hall, W.D., Pacula, R. Cannabis use and dependence: public health and public policy: Cambridge University Press; (2003).

Day, C., Topp, L., Rouen, D., Darke, S., Hall, W., Dolan, K. (2003) Decreased heroin availability in Sydney in early 2001. *Addiction* 98:93-5.

Carter, L. (2003) The ethics of xenotransplantation. In: Healey J, editor. *Organ transplantation*. Rozelle, N.S.W: Spinney Press.

Degenhardt, L., Hall W.D., Lynskey M. (2003) Exploring the association between cannabis use and depression. *Addiction* 98:1493-1504.

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Morley, K.I., Hall, W.D. (2003) Is there a genetic susceptibility to engage in criminal acts? *Trends & Issues in Crime and Criminal Justice*;263 (September).

Fry, C.L., Hall, W.D. (2003) Key issues in determining the ethics of research subject payment: the special case of drug abuse epidemiology. *Australasian Epidemiologist* 10:41-47.

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

Degenhardt, L., Hall, W. D. (2003) Patterns of co-morbidity between alcohol use and other substance use in the Australian population. *Drug and Alcohol Review* 22:7-13.

Maher, L., Dixon, D., Hall, W.D., Lynskey, M. (2003) Property crime and income generation by heroin users. *Australian and New Zealand Journal of Criminology* 35:187-202.

Dolan, K.A., Shearer, J., MacDonald, M., Mattick, R.P., Hall, W., Wodak, A.D. (2003) A randomised controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system. *Drug and Alcohol Dependence* 72:59-65.

Morley, K.I., Carter, L. & Hall, W. (2003) Regulation of embryonic stem cell research and therapeutic cloning: the Australian debate. *Plaintiff* 55:20-23.

Taylor, D.R., Hall, W.D. (2003) Respiratory health effects of cannabis: Position Statement of The Thoracic Society of Australia and New Zealand. *Internal Medicine Journal* 33:310-313.

Hall, W.D., Mant, A., Mitchell, P., Rendle, V., Hickie, I., McManus, P. (2003) Responses to our critics. *BMJ Online* 326.

Degenhardt, L., Hall, W., Lynskey, M. (2003) Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and Alcohol Dependence* 71:37-48.

Research presentations

Carter, L. (2003) Consequentialist Objections to Transgenesis: GM Foods, Xenotransplantation and Germ Line Gene Therapy. *Issues in Animal Transgenesis:* A Symposium. Sydney, NSW.

Carter, L. (2003) Ethics of Somatic and Germ Line Gene Therapy. *Australian Gene Therapy Society Meeting.* Brisbane, Queensland.

Fleming, J. (2003) End of Life Session [Chair/Facilitator] *The Australian Institute of Health Law and Ethics 8th Annual Conference - "The Risk Society: Challenges in Health Law and Ethics.* Hobart, Tasmania.

Fleming, J. (2003) Questions of Balance: Multicentre Clinical Trials involving participants with impaired capacity. *Australian Ethics of Research Congress.* Canberra, ACT.

Fleming, J. (2003) Great Debate: Swimming in a Sea of Change - Regulation is Killing Innovation [Convenor]. *Hosted by Australian Institute of Health Law and Ethics and the Australasian Research Management Society.* Brisbane, Queensland.

Fleming, J., Lyons, A. (2003) Balancing risks and benefits: Legal and ethical dimensions in conducting clinical trials involving patients with impaired capacity. *28th International Congress on Law and Mental Health,* Sydney, NSW.

Hall, W. (2003) Addiction: What if it's genetic? [Panelist]. *CSIRO-World Genetics Congress Symposium.* Melbourne, Victoria.

Hall, W. (2003) Assessing health outcomes: the view from the Drug Utilisation Subcommittee of the Pharmaceutical Benefits Advisory Committee. *Health Outcomes Conference.* Canberra, ACT.

Hall, W. (2003), *Biotechnology, genetics and tobacco control: an ethical and policy analysis of some scenarios.* Stanford Centre for Bioethics. Stanford University Medical School, Palo Alto, California.

Hall, W. (2003) *Biotechnology, genetics and tobacco control.* Centre for Addiction and Mental Health, Toronto, Ontario.

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

Hall, W. (2003) *Ethical issues in neuroscience and genetic research on addiction.* Centre for Applied Bioethics, University of British Columbia, Vancouver, Canada.

Hall, W. (2003), *Ethical and social implications of cocaine and nicotine vaccines.* Center for Health Care Evaluation, Veterans' Affairs Hospital, Menlo Park, California.

Hall, W. (2003) Genetics of depression: ethical and policy implications. *Mental Health and Law Congress.* Sydney, NSW.

Hall, W. (2003) Great Debate: Swimming in a Sea of Change - Regulation is Killing Innovation [Panelist]. *Hosted by Australian Institute of Health Law and Ethics and the Australasian Research Management Society.* Brisbane, Queensland.

Hall, W., Carter, L., Morley, K. (2003) Genetics of depression: ethical and policy implications. Paper presented at *28th International Congress on Law and Mental Health,* Sydney, NSW.

Hocking, B., Campion, V., Fleming, J.. (2003) Mind games? Crime gene? Clueless in Hollywood? *28th International Congress on Law and Mental Health,* Sydney NSW.

7.

Community Engagement and Awareness

IMB OFFICE OF PUBLIC POLICY AND ETHICS – OPPE

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

'Attack of the Clones': Patent Law and Stem Cell Research	*Dr Matthew Rimmer,* Faculty of Law, Australian National University
Patently Justified? Gene Patents, Ethics and Public Policy	*Prof Wayne Hall,* Director, Office of Public Policy and Ethics, IMB
A Bigger Voice? Engaging Citizens with Life Science Questions	*Dr Tom Shakespeare,* Director of Outreach, PEALS Research Institute, UK
Biotechnology, genetics and tobacco control: an ethical and policy analysis of some feasible scenarios	*Prof Wayne Hall,* Director, Office of Public Policy and Ethics, IMB
Better People Through Better Technology	*A/Prof Carl Elliott,* Center for Bioethics, University of Minnesota
What are the Key Messages in Genetics and how can we Broadcast them?	*Dr Kristine Barlow-Stewart,* Director, Centre for Genetics Education, NSW Genetics Service
The Popular Press and Genetics Policies: The Nature and Impact of "Genohype"	*A/Prof Timothy Caufield,* Canada Research Chair in Health Law and Policy, University of Alberta, Canada
Genetic Risk Information – Can it motivate behaviour change?	*Prof Theresa Marteau,* Professor of Health Psychology and PDirector of the Psychology and Genetics Research Group, King's College, London

8.

Australian Collaborative Research



Further underlining the Institute's commitment to research excellence, IMB Group Leaders are core partners and participate in several Cooperative Research Centres (CRC) , a major National Research Facility, Australian Research Council (ARC) Centres of Excellence (COE) , an ARC Special Research Centre, and a new ARC Centre.

These programs are integral to building Australia's national and international research capabilities.

They aim to create the scale and focus necessary to maintain and develop Australia's world-class standing in priority areas through highly innovative research that addresses challenging and significant problems.

CRCs and COEs make vital contributions to Australia's research landscape and produce outcomes with economic, social and cultural benefit to the country.

Involvement in these ventures reflects very highly on the participating researchers, indicating the high value of their work in both scientific and commercial terms.

ARC SPECIAL RESEARCH CENTRE FOR FUNCTIONAL AND APPLIED GENOMICS

The ARC Special Research Centre for Functional and Applied Genomics provides and develops the latest technologies to enable internationally competitive research in the field of genomics. The SRC comprises an integrated network of core technologies including computational biology, structural biology, proteomics, animal transgenics service, as well as a microarray facility.

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

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

In terms of scientific outcomes, SRC affiliates provided the largest foreign group in the international consortium that provided functional annotation to the

mouse transcriptome project (FANTOM2) and subsequent analyses that made a major contribution to a special issue of *Genome Research* providing an overview of the FANTOM2 project. The close collaboration with Japanese colleagues at the RIKEN Genome Sciences Centre will continue with our strong involvement in FANTOM3 in 2004.

The new resources and common location provide a powerful foundation for the SRC to fulfil its aim of providing all of the links in the pipeline from gene discovery to functional assignment and application. The future will see the coordinated application of these resources to provide meaningful description of biological systems such as mammalian cells, from the structure, location and function of individual proteins to the control networks that allow the system to respond to its environment in development, differentiation and disease.

AUSTRALIAN PHENOMICS FACILITY

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

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

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

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

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

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

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

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

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

COOPERATIVE RESEARCH CENTRE FOR CHRONIC INFLAMMATORY DISEASES

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

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

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

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

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

NANO

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

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

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

ARC CENTRE OF EXCELLENCE IN BIOTECHNOLOGY AND DEVELOPMENT

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

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

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

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

CENTRE OF EXCELLENCE: THE NATIONAL STEM CELL CENTRE

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

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

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

ARC CENTRE IN GENOME/ PHENOME BIOINFORMATICS

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

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

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

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

Involvement in these ventures reflects very highly on the participating researchers, indicating the high value of their work in both scientific and commercial terms.

The AGRF is recognised as a truly national facility through the establishment of successful and complementary nodes at the University of Queensland, the Walter and Eliza Hall Institute and now at the Waite in South Australia.

AUSTRALIAN GENOME RESEARCH FACILITY

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

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

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

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

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

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

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

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

The AGRF is recognised as a truly national facility through the establishment of successful and complementary nodes at the University of Queensland, the Walter and Eliza Hall Institute and now at the Waite in South Australia.

9.

IMB Graduate Program

The IMB Graduate program, established in 2000, came to fruition in 2003, when the first PhD students fully enrolled through the IMB graduated alongside a number of their IMB colleagues, enrolled through other University departments. Additionally, the total number of enrolments in the Graduate Research Higher Degree programs of the IMB swelled to 80 students throughout 2003. The Program is now widely recognized in Australia and around the world and is attracting high quality students.

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

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

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

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

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

IMBcom also conducted a three day Bio-Entrepreneurism Retreat for third year PhD students, covering topics such as technology transfer, business planning, legal issues and communication (including people management, negotiation skills and dealing with the media). Wayne Hall and the Office of Public Policy and Ethics (OPPE) team ran a workshop for the first year students, discussing the topic of gene patenting. Particular attention was given to the implications of Genetic Technologies Ltd patent on non-coding DNA sequences prompting open discussion on the issues associated with the purpose and conditions of patents, IP and the ramifications for affordability of public health and medical research.

Melissa Little conducted an information session about applying for NHMRC Postdoctoral Fellowships, with a focus on the more popular fellowships such as the CJ Martin. This was greatly appreciated by students in the latter phases of their PhDs. It is intended that this information session become a regular feature of the IMB Graduate Program.

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

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

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

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

IMB GRADUATE FAST FACTS

Scholarships awarded to IMB for studies commencing 2004:

11 Australian Postgraduate Award/University of Queensland Postgraduate Research Scholarships (of which 9 were accepted)

8 IMB Scholarships

2 National Health and Medical Research Council Dora Lush Scholarships

2 International Postgraduate Research Scholarships (one with additional stipend scholarship)

2 University of Queensland Graduate School Scholarships

1 Australian Rotary Health Research Fund Scholarship

Honours Students

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

New Research Higher Degree students for 2003

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

PhD Completions 2003

1. Adolphe Christelle, *Examination of the in vivo effect or excess sonic in cuan and descre hedgehog.* Brandon Wainwright
2. Christopher Armishaw, *The Chemical Synthesis of Proteins.* Paul Alewood
3. Julie Dutton *Studies of novel disulphide-bonded cyclic peptides.* David Craik
4. Melissa Edeling, *Protein Folding: Structure-function studies on CycY, a reducing disulphide oxidoreductase.* Jennifer Martin
5. Juliet French, *Characterisation of G3BP and its implicated role in cancer.* John Mattick
6. Brett Hamilton, *Development of Detection Methodologies for Ciguatoxins.* Richard Lewis
7. Kelly Loffler, *Molecular Genetics of Sex Determination in Mice.* Peter Koopman
8. Asanka Karunaratne, *Molecular Genetics of Cell-Type Specification in Vertebrate Central Nervous System.* Peter Koopman
9. Wendy Ingram, *Discovery of novel downstream target genes regulated by the Hedgehog Pathway.* Brandon Wainwright
10. Gabriel Kolle, *Functional studies of a novel gene, S52 in the development of the central nervous system.* Melissa Little
11. Fiona McCarthy, *Bovine Enterovirus: Molecular characterisation and evaluation as a vaccine vector.* John Mattick
12. Michael Piper, *Functional analysis of slit2, a human homolog of the Drosphila slit gene, in CNS and kidney development.* Melissa Little
13. Ayanthi Richards, *Endocytosis and retrograde transport of Simian Virus 40 (SV40) and cholera toxin – a comparative study.* Rob Parton
14. Johan Rosengren, *Twists, knots and rings -topological features of antimicrobial peptides.* David Craik
15. Tedjo Sasmono, *Regulation of the C-FMS gene in macrophages and transgenic mice.* David Hume

    Annette Schewan *Molecular dissection of protein trafficking in eukaryotic cells.* David James

    Christina Schroeder *Probing calcium channel selectivity of peptide toxins.* Richard Lewis/David Adams
16. Annalese Semmler, *Biogenesis and function of Type 4 Fimbriae in Pseudomonas Aeruginosa.* John Mattick
17. David Sester, *Mechanism of action of bacterial DNA on macrophage activation.* David Hume
18. Manuela Trabi, *Circular, disulfide rich peptides – sources, properties structures.* David Craik
19. Nicole Walsh, *The Function and Regulation of Tartrate-Resistant Acid Phosphatase (TRAP).* David Hume

10.

IMB Speakers

IMB FRIDAY SEMINAR SERIES 2003

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

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

Speakers	Position	Seminar Topic
Dr David Manallack	Head of Applied Design De Novo Pharmaceuticals, Cambridge, UK	*Application of Quasi2 for drug discovery: an extended pharmacophore generation and database searching program*
Professor Gottfried Otting	Research School of Chemistry Australian National University, Canberra	*Structural biology, NMR, and paramagnetically labelled proteins*
Professor Ralph Bradshaw	Department of Physiology and Biophysics University of California, at Irvine, USA	*N-Terminal Processing: Role of Aminopeptidases and Transferases*
Professor Nobutaka Hirokawa	Department of Cell Biology and Anatomy University of Tokyo, Japan	*The Kinesin Superfamily Motor Proteins, KIFs and Intracellular Transport: Structures, Dynamics, Functions and Diseases*
Professor Mike Ostrowski	Department of Molecular Genetics Ohio State University, USA	*The microphthalmia transcription factor: coordinating signaling and transcription during osteoclast differentiation*
Professor Nigel Laing	Centre for Neuromuscular and Neurological Disorders Australian Neuromuscular Research Institute, Western Australia	*Gene and protein defects in muscle disease*
Professor Kevin Burrage	Department of Mathematics The University of Queensland	*Stochastic multiscale modelling of genetic regulatory networks*
Professor Alok Mitra	School of Biological Sciences The University of Auckland, NZ	*Membrane protein channels and macromolecular complexes at the membrane interface studied by electron cryo-microscopy - what can structure tell us about function*
Professor Bill Denny	Auckland Cancer Society Research Centre The University of Auckland, NZ	*Drugs that target tumour hypoxia: the promise and the challenge*
Associate Professor Roger Daly	Cancer Research Program Garvan Institute of Medical Research, Sydney	*Adaptor and scaffolding proteins in receptor tyrosine kinase signalling*
Dr Pritinder Kaur	Stem Cell Laboratory Peter MacCallum Cancer Institute, Melbourne	*Identification of a functional subset of dermal cells capable of regulating epithelial tissue regeneration*
Professor Chris Goodnow	Medical Genome Centre John Curtin School of Medical Research, Canberra	*Elucidating cellular and molecular pathways for human health by genome-wide mutagenesis in mice*

Speakers	Position	Seminar Topic
Dr Charlie Bond	Division of Biological Chemistry and Molecular Microbiology, School of Life Sciences Wellcome Trust Biocentre, University of Dundee, Scotland	*Structural Studies of Holliday Junction Resolution in the Archaea: the resolving enzymes Hjc and Hje.*
Dr Archa Fox	Division of Gene Regulation and Expression, School of Life Sciences Wellcome Trust Biocentre, University of Dundee	*New insights into nuclear organisation revealed by proteomic analysis of human nucleoli*
Professor Ross Coppel	Department of Microbiology Monash University, Melbourne	*Data, data everywhere, nor any chance to think*
Professor Simon Easteal	Centre for Bioinformation Science and John Curtin School of Medical Research, Canberra	*Complexity in diversity on the road to information-based medicine*
Professor Halina Rubinsztein-Dunlop	Department of Physics/Centre for Biophotonics and Laser Science The University of Queensland	*Catch, move and twist using optical tweezers*
Associate Professor Vic Nurcombe	Department of Anatomy and Developmental Biology The University of Queensland	*So long and thanks for all the fish; the answer is 42 ES cells. Reflections on UQ Developmental Biology, stem cell engineering, and the use of chopsticks for embryonic manipulation*
Dr Ian Atkinson	Information Technology and Resources James Cook University, Townsville, Australia	*Molecular self-assembly in supramolecular systems*
Mr Adam Lowe	Genomic Applications Research and Development Applied Biosystems Pty Ltd	*Combining content and technology in genomic research*
Professor Edward Baker	School of Biological Sciences The University of Auckland, NZ	*Targeting TB through structural genomics*
Professor Chris Abell	Department of Chemistry University of Cambridge Chemical Laboratory, UK	*Explorations in chemical and biological nanotechnology*
Dr Helen Cooper	Neural Migration Laboratory, School of Biomedical Sciences The University of Queensland	*Diverse roles of netrin receptors in central nervous system development*
Dr Tim Bailey	Advanced Computational Modelling Center The University of Queensland	*Seaching for statistically significant regulatory modules*
Professor Kathryn North	Neurogenetics Research Unit Children's Hospital at Westmead Clinical School, Sydney	*The evolution of the _-actinins and their role in human skeletal muscle muscle performance*
Dr Steve Gerondakis	Immunology Division The Walter and Eliza Hall Institute of Medical Research, Melbourne	*Mitogen-induced cell growth: B and T cells adopt different strategies in the exploitation of Rel/NF-kB*
Dr Matthew Rimmer	Faculty of Law The Australian National University, Canberra	*Myriad Genetics: patent law & genetic testing*

Speakers	Position	Seminar Topic
Dr Tom Garrett	Structural Biology Walter and Eliza Hall Institute of Medical Research, Melbourne	*Structure and signalling in the epidermal growth factor receptor family*
Professor David Vaux	Molecular Genetics of Cancer Walter and Eliza Hall Institute of Medical Research, Melbourne	*Apoptosis - biology to die for*
Dr Sigrid Lehnert	Livestock Applications of Biotechnology Program CSIRO Livestock Industries, Brisbane	*Transcriptional profiling of bovine muscle*
Professor Geoff McLachlan	Department of Mathematics and Institute for Molecular Bioscience The University of Queensland	*Classification of microarray gene-expression data*
Dr Peter Currie	Victor Chang Cardiac Research Institute Sydney	*Specification, morphogenesis and differentiation of skeletal muscle cells within the zebrafish embryo*
Professor Michael Johnson	Centre for Pharmaceutical Biotechnology University of Illinois at Chicago, USA	*Structural studies of spectrin - an ubiquitous protein*
Professor David Weisbrot	President, Australian Law Reform Commission, Sydney	*Essentially yours: the protection of human genetic information in Australia*
Dr Richard Bruskiewich	Bioinformatics International Rice Research Institute, Los Baños, Phillipines	*My genome is sequenced! So...what next?*
Dr Patrick Aloy	Biocomputing European Molecular Biology Laboratory – Heidelberg, Germany	*The third dimension for protein interactions and complexes*
Dr Martin Frith	Bioinformatics Program Boston University, USA	*Deciphering the Regulation of Human Genes: Motif Clusters in DNA and RNA*
Dr Nick Brown	Wellcome/Cancer Research UK Gurdon Institute and Department of Anatomy University of Cambridge , UK	*Genetic dissection of the integrin-cytoskeletal link in Drosophila*
Ms Anneliese Appleton	Accelrys Inc.	*Accelrys Information Seminar*
Dr Christine Vogel	MRC Laboratory of Molecular Biology Cambridge, UK	*Domain duplication and recombination in the evolution of the protein repertoire*
Dr Arnold Falick	Mass Spectrometry Laboratory Howard Hughes Medical Institute University of California at Berkeley, USA	*Protein identification with a MALDI Tandem Time-of-Flight mass spectrometer*
Professor Roger Tsien	Howard Hughes Medical Institute & Department of Pharmacology University of California at San Diego, USA	*Breeding molecules to spy on cells*

Speakers	Position	Seminar Topic
Dr Andrew Perkins	Monash University, Melbourne	*Making blood and kidneys: transcriptional programming and ES cell differentiation*
Professor Walter Birchmeier	Max-Delbrück Center for Molecular Medicine, Berlin, Germany	*b-catenin and Wnt signaling: implications for developmental programming and cancer*
Dr Margaret Frame	Beatson Cancer Center, Glasgow, Scotland	*New insights into the regulation and action of Src kinases*
Dr Matthew Cooper	Chief Scientific Officer Akubio Ltd, UK	*Drugs, bugs and biotech*
Dr Scott Weinberger	Director, Research Proteomics Ciphergen Biosystems Inc.	*Proteinchip arrays: advances in SELDI technologies for the discovery in identification and characterisation of biomarkers of clinical interest*
Professor Peter Roepstorff	Department of Biochemistry and Molecular Biology University of Southern Denmark	*Current strategies in expression proteomics and modification specific proteomics*
Dr Paul Trainor	Stowers Institute for Medical Research, Kansas, USA	*Neural crest cells: patterning and development of a stem cell population during craniofacial development and evolution*
Dr Anneliese Appleton	Accelrys Inc.	*Accelrys information seminar*
Dr Inke Nathke	School of Life Sciences University of Dundee, Scotland	*Recent advances in understanding the fundamental biology of the tumor suppressor, APC*
Dr David Sacks	Pathology, Brigham & Women's Hospital Harvard Medical School, Boston, USA	*IQGAP1 - a fundamental regulator of ca2+/calmodulin signalling and cytoskeletal architecture*
Dr Irina Mineyev	Caliper Technologies California, USA	*Caliper microfluidics technologies for drug discovery and genomics*
Dr Al Reynolds	Department of Cancer Biology Vanderbilt University, Tennessee, USA	*P120-catenin: a core regulator of cadherin function and potential tumour suppressor*
Dr David Hansen	SRS Software Development LION Bioscience Ltd, UK	*Providing integrated access to genomic data*

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

11.

IMB Systems and Administration



(Left) IMB Deputy Director (Systems and Administration) Ian Taylor; (Centre) Dr Steve Tay

Construction of the Queensland Bioscience Precinct (QBP) building was completed in early 2003 and followed by several weeks of systems testing and building cleaning prior to occupation by CSIRO and IMB.

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

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

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

- Two new 600MHz Nuclear Magnetic Resonance (NMR) machines extending IMB's ability to solve the three dimensional structures of biological molecules. The new magnets enable IMB to determine highly complex structures with greater confidence than ever before.
- Australia's most powerful X-Ray Crystallography machine. The high resolution and exquisite sensitivity of the new machinery can only be bettered by a synchrotron, currently unavailable in Australia. These facilities enable the determination of high resolution structures of the most difficult proteins.
- P690 supercomputer equipped with DiscoveryLink software as part of the IBM's Shared University Research program. This alliance provides an unparalleled level of excellence in an integrated research program combining the Institute's world-class bioinformatics expertise and IBM's state-of-the-art IT infrastructure for life sciences, as well as providing access to IBM's own research resources.

- A Sun fileserver greatly expanding IMB's capacity to provide storage space for staff and students
- Over $1 million high pressure liquid chromatography equipment to accelerate the effective exploration of Australian biodiversity as a means to discover new and improved drugs, with application in the areas of human and animal health, and crop protection.

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

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

Finally, the IMB was saddened by the sudden death of Level 7 Floor Manager, Dr Steve Tay in November. Steve joined the IMB as we took up residence in the new building and in his short time with the Institute he played a vital role in establishing the chemistry laboratories on Level 7. He will be sorely missed.

Research Support

Administration and finance
Teresa Buckley
Jodie Campbell
Robyn Craik
Barb Clyde
Mileta Duggleby
Barbara Feenstra
Angela Gardner
Jenny Greder
John Spooner

Animal House
Anne Hardacre
David McNeilly
Elena Piotto
Anita Swallow

Central Sterilising Facility
Robyn Baird
Wendy Campbell
Sherrell McCarthy
Karleen Marsh
Michael Tetley
Dawn Walsh

Graduate program
Amanda Carozzi
Patricia McCauley

IT services
Matthew Bryant
Brett Cravaliat
Calvin Evans
Ondrej Hlinka
Lindsay Hood
Ireneusz Porebski
Maria Maddison
Nelson Marques
Peter van der Heide
Calvin Wang
Kim Welch

Laboratory Management
Chris Barnett
Jill Bradley
Karl Byriel
Joanne Kelly
Colin MacQueen
Charles Nelson
Darren Paul
Lance Rathbone
Stephen Tay
Greg Young

Marketing and Communications
Russell Griggs
Tania Hudspith
Andrea Sackson

Workshop
Henk Faber
Wayne Kirby
Jeremy Kroes
Greg McHugh
David Scarce

Queensland Bioscience Precinct staff
Rebecca Brooks
Alan Gilligan
Efstratios Manolis
Barry Pitt
Nathan Steenstra
Maria Trubshaw
Ronda Turk

12.

Glossary of terms

Some readers may be unfamiliar with some of the scientific terms used in this Annual Report. Please check below for a short explanation to some of the more common terms. More information about current issues in biotechnology can be downloaded from the Office of Public Policy and Ethics pages in the IMB website.

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

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

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

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

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

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

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

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

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

Computational biology The study of living systems using computation.

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

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

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

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

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

Functional Genomics The use of genetic technology to determine the function of newly discovered genes by determining their role in model organisms.

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

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

Genome All DNA contained in an organism or cell.

Genomics The study of genes and their function.

Genotype Is the hereditary genetic constitute of an organism.

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

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

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

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

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

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

Phenome The physical characteristics of an organism.

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

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

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

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

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

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

X-ray Crystallography A technique of determining a molecule's three-dimensional structure by analysing the x-ray diffraction patterns of crystals made up of the molecule in question.

13.

Financial Statement – Statement of Operating Income and Expenditure Year Ended 31 December 2003

INCOME:

	Note	2000	2001	2002	2003
University of Queensland (Operating Grant)	1	2,942,718	6,664,365	6,023,929	8,122,858
University of Queensland Research Grants		200,990	100,000	269,358	277,337
State Government		5,500,000	2,500,000	6,000,000	8,500,000
SRC Grant (Australian Research Council)		1,631,153	1,039,320	1,148,975	1,005,151
Australian Research Council	2	1,131,271	1,668,000	1,599,576	3,218,103
Cancer Council South Australia					30,500
Clive and Vera Ramaciotti Foundation		43,545	9,545	0	
CRC for Discovery of Genes for Common Human Diseases		220,958	232,415	122,469	48,946
CRC for Chronic Inflammatory Diseases				943,401	968,800
Department of Primary Industries				98,040	0
Diabetes Australia Research Trust		33,409	35,791	37,700	0
Department of Industry Science and Technology		166,400	0	0	0
Human Frontiers Science Program		127,242	0	0	146,291
Glaxo Welcome Australia		670,000	62,000	0	0
Government Employees Medical Research Fund		45,000	0	0	0
Juvenile Diabetes Foundation International		299,626	267,704	77,084	0
Mayne Bequest Foundation		60,000	0	0	0
The Merck Genome Research Institute		261,559	0	0	0
National Institute of Health (US)				1,391,005	1,049,548
National Health and Medical Research Council	2	2,938,586	5,359,112	4,306,397	6,761,404
National Heart Foundation		45,000	0	50,000	42,735
Novartis					641,790
Post Graduate Scholarships		28,209	15,882	38,214	73,467
QIMR				53,908	60,575
Queensland Cancer Fund		230,072	116,447	92,750	72,590
Sylvia and Charles Viertel Charitable Foundation		165,000	165,000	165,000	0
Wellcome Trust		28,011	23,829	0	204,763
Commercial Income		1,371,664	2,589,861	2,127,649	1,517,449
Cross-Institutional contributions to LIEF		0	0	0	122,500
University of Newcastle (re ARC Centre)		0	0	0	127,727
QBP recoveries		0	0	0	331,594
Shared Grants		0	0	0	105,845
Conference Income		0	0	0	55,275
Miscellaneous Income		415,591	272,136	19,593	392,822
TOTAL INCOME:		18,556,004	21,121,405	24,565,049	33,878,069
Funds brought forward from previous year	3	1,009,031	3,843,597	3,594,479	7,545,101
TOTAL FUNDS AVAILABLE:		19,565,034	24,965,002	28,159,528	41,423,169
EXPENDITURE:					
Salaries-Research		6,549,841	7,809,255	9,066,745	12,238,779
Administration		1,090,220	1,117,375	1,342,520	1,365,120
Infrastructure		541,043	813,527	1,012,400	1,735,158
Research Services		2,635,745	6,034,723	4,865,433	6,938,972
Education Programs	4	317,726	378,436	500,939	484,360
Administration	5	937,703	550,574	452,021	519,046
Infrastructure	6	357,436	928,651	786,809	1,568,251
Capital Equipment	7	2,307,116	3,132,769	1,840,664	8,649,700
IMBcom		984,608	605,214	746,896	1,176,785
TOTAL EXPENDITURE:		15,721,437	21,370,523	20,614,427	34,676,171
Funds carried forward:	**8**	**3,843,597**	**3,594,479**	**7,545,101**	**6,746,999**

Explanatory Notes to Statement of Income and Expenditure Year Ended 31 December 2003

1. In-kind Contributions

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

	School	Percentage
S. Barker	Molecular & Microbial Sci.	80
D. Hume	Molecular & Microbial Sci.	20
J. Martin	Molecular & Microbial Sci.	10
S. Kelly	Molecular & Microbial Sci.	80
P. Koopman	Biomedical Sciences	10
J.Rothnagel	Molecular & Microbial Sci.	80
B.Wainwright	Molecular & Microbial Sci.	20
M.Waters	Biomedical Sciences	20
A.Yap	Biomedical Sciences	20
B.Kobe	Molecular & Microbial Sci.	80
J. Stow	Molecular & Microbial Sci.	20
A. McDowall	Microscopy & Microanalysis	80
W. Hall	Social Behaviourial Sci.	20
G. McLachlan	Mathematics	80
J. Hallinan	ITEE	20
T. Bailey	ACMC	80

2. Fellowship/Projects from Government Agencies

Australian Research Council	
Projects	2,707,459
Fellowships	510,644
	3,218,103
National Health and Medical Research Council	
Projects	5,936,844
Fellowships	824,559
	6,761,404

3. Funds brought Forward from 2002

University of Queensland Operating Grant	4,047,449
University of Queensland Research Grants	69,686
Post Graduate Scholarships	4,371
State Government	346,758
SRC Grant	373,794
Fellowships (as approved by funding bodies)	91,919
Project Grants (as approved by funding bodies)	2,611,123
	7,545,101

4. Education Programs

Postgraduate scholarships	328,357
Postgraduate recruitment & training	29,471
Public Policy & Ethics	126,532
Total Education Services	**484,360**

Explanatory Notes to Statement of Income and Expenditure Year Ended 31 December 2003

5. Administration	
Annual Report	20,698
Marketing	48,102
Personnel Recruitment and Training	126,680
Visiting Scientists/Seminars	21,687
Fees	61,071
Entertaining	6,875
Equip Lease	0
Photocopying	35,486
Postage and Freight	6,021
Printing & stationery	75,179
Telephone	61,008
Travel Expenses	12,247
Sundries	5,409
Cost Recovery	38,581
Total Administration	**519,046**
6. Infrastructure	
Building Maintenance	66,192
Rental -Demountables/Storage	17,092
Safety Equipment	67,730
Laundry	1,953
Minor Equipment & Furniture	32,378
Equipment Maintenance	173,956
Animals	72,950
Computer Services	824,462
Glass washing and replacement	40,854
Reticulated gases, RO water & dry ice	89,807
Sundries	69,746
Relocation Costs	84,060
Stores	27,072
Total Infrastructure	**1,568,251**
7. Capital Equipment	
Scientific Equipment	8,600,104
Minor Equipment	49,596
Total Capital Equipment	**8,649,700**
8. Funds carried forward to 2004	
University of Queensland Operating Grant	1,645,629
University of Queensland Research Grants	26,038
Post Graduate Scholarships	3,734
State Government	125,166
SRC Grant	374,734
Fellowships (as approved by funding bodies)	149,096
Overseas Grants funded mid year	1,709,903
Contract Research	1,270,789
Project Grants (as approved by funding bodies)	1,441,911
	6,746,999

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

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