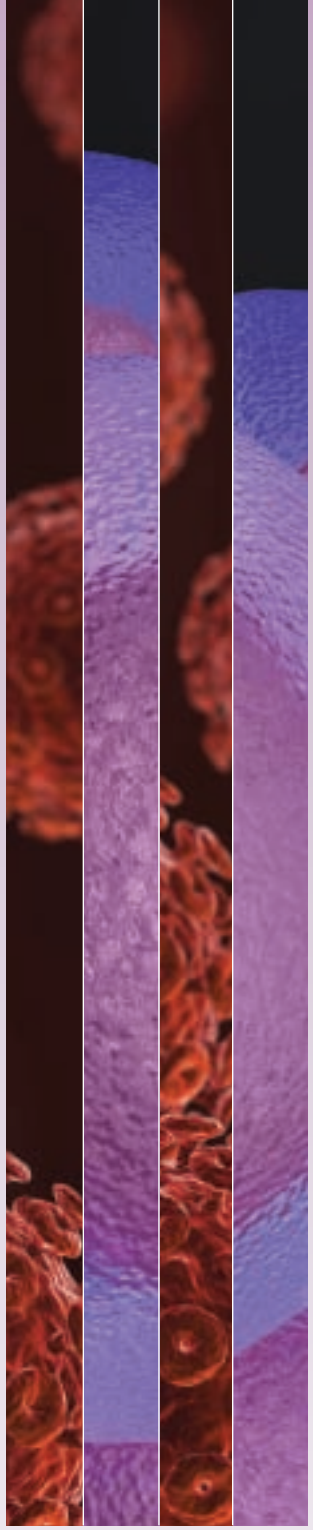
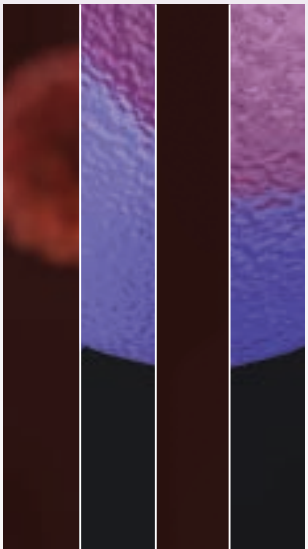


THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

# IMB Institute for Molecular Bioscience

## ANNUAL REPORT 2006



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

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

# *IMB VISION STATEMENT*

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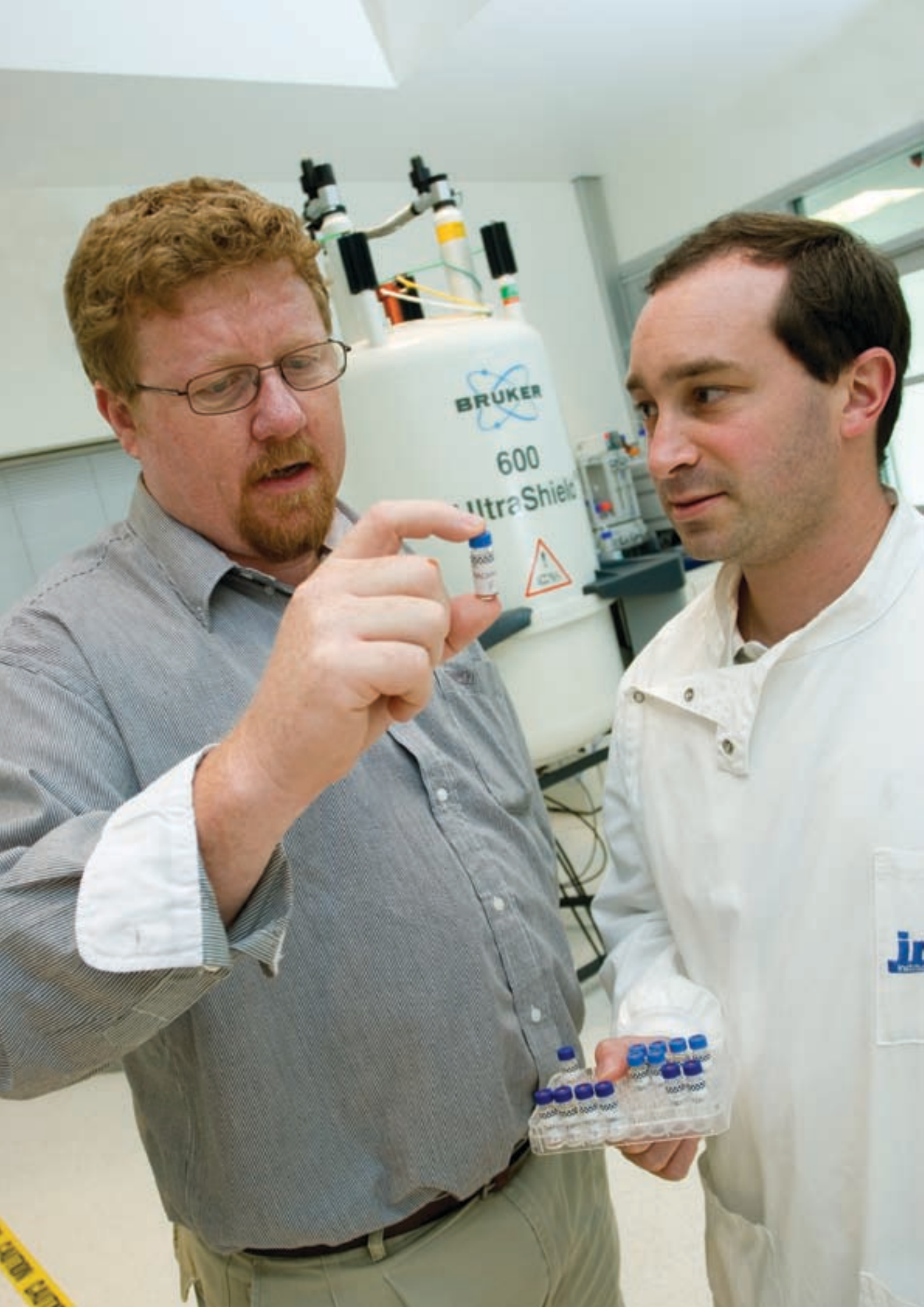
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2006 has been a significant year for The University of Queensland's Institute for Molecular Bioscience (IMB), with the appointment of a new Director. Professor Brandon Wainwright was chosen to lead the IMB late in the year, after becoming Acting Director when Professor John Mattick relinquished the position to spend more time on his research. Professor Wainwright conducts research into cancer and cystic fibrosis, and is internationally known within these fields. He was previously Deputy Director (Research) of the IMB, thus he already possesses a thorough comprehension of the workings of the Institute and its future priorities. I am confident that, under Professor Wainwright's guidance, the IMB will continue to produce outstanding research results of concrete worth to the community, thereby further consolidating its position as a leading bioscience research institute.

It has also been an important year for the wider UQ bio-research community. The $70 million Australian Institute of Bioengineering and Nanotechnology building opened in October, substantially supported by the Queensland Government and the Atlantic Philanthropies, as was the IMB. In 2007, the $64 million home of the Queensland Brain Institute will be opened, and the Diamantina Institute for Cancer, Immunology and Metabolic Medicine will be established. UQ's Centre for Clinical Research, jointly funded by the University, Atlantic Philanthropies and the State Government, will open in late 2007 at Herston. These additions will mean that by the end of the decade, when IMB celebrates its 10th birthday, more than 1700 UQ scientists will be conducting bio-research in new facilities. The IMB was the first of these, and in many ways its success paved the way for the establishment of these new UQ initiatives.

I thank everyone who has been involved in this success, including staff, students, the Advisory Board and the Scientific Advisory Committee. The Queensland and Federal governments and the Atlantic Philanthropies have also been instrumental in the success of the Institute, through their generous funding and the creation of an environment in South East Queensland where investment in scientific research is encouraged and the research itself is valued.

The specific achievements of the IMB in 2006 are detailed in this report, and I encourage you to peruse them.

***Professor John Hay, AC***

Vice-Chancellor
The University of Queensland

# CHAIR'S MESSAGE
## Professor John Hay AC

# DIRECTOR'S REPORT

## *Brandon Wainwright*

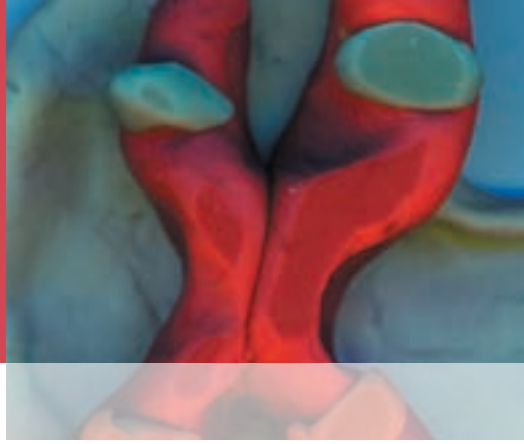
This is my first report as the new Director of the IMB. It is an honour to accept this position and I have no doubt I will face the same challenges as many of my colleagues around the world as I attempt to balance the administrative load of Director with the desire to continue my own scientific research. Fortunately I will be ably assisted in my directorial duties by the two Deputy Directors, Professor John Hancock (DD, Research) and Ian Taylor (DD, Systems and Administration), both of whom have provided invaluable support and advice during the directorial transition phase. I would like to acknowledge the outstanding contribution of outgoing Director, John Mattick, who stepped aside at the end of 2005 to take up his prestigious Federation Fellowship. John's vision and drive during the early years were responsible for the recruitment of our talented group of scientists as well as the construction of the magnificent building we now occupy. With the establishment phase of the Institute now well and truly behind us, I am looking forward to meeting the challenges of the future as we consolidate our position domestically and internationally as the one of the premier molecular bioscience research institutes in the country.

In her budget speech in June of this year, the Queensland Treasurer, the Hon. Anna Bligh, MP, announced a further five-year tranche of funding for the IMB which secures our future until the end of 2014. This funding support extends our current $10M per annum for a further five years and represents a total commitment by the Queensland State Government to the IMB of over $135M over a fifteen-year period. The funding from the State Government allows us to support IMBcom, retain key scientific staff and provide significant infrastructure support. This outcome followed a 2005 independent report addressing the economic impact of the IMB on the State, and a very positive Quinquennial Review Committee report.

Our success in the 2006 national competitive grant rounds will be outlined in greater detail in this report by our Deputy Director (Research), Professor John Hancock, but I would like to express my delight at our success in both the ARC and the NHMRC rounds for 2006. Two of our Group Leaders (Jenny Martin and Peter Koopman) were successful in obtaining professorial fellowships and in 2007 we will be in the happy position where sixteen of our Group Leaders, or approximately half of the total number of senior scientists, will have part or all of their salary paid from competitive fellowship schemes. This is a testament to the outstanding quality of our Group Leaders. In addition to Group Leader grant success, four of our postdoctoral staff members secured grants in their own right – a very pleasing indicator that the next 'wave' of successful IMB scientists is already emerging.

In May this year David Fairlie was awarded a Federation Fellowship. This brings to four the number of Federation Fellows at or closely associated with the IMB. Professor John Mattick, AO and Associate Professor Bostjan Kobe, an IMB affiliate appointee from the School of Molecular and Microbial Science were both awarded Federation Fellowships in last year's round and Professor Kevin Burrage, an IMB joint appointee from the School of Mathematics, was awarded a fellowship in 2003.

Other major prizewinners this year were John Mattick, who was awarded the 2006 CSIRO Eureka Prize for Leadership in Science at a ceremony in Sydney in August, Melissa



Little, who was awarded a Smart State Smart Women prize in September and David Craik who was awarded the HG Smith Memorial Award for outstanding contributions to Australian chemistry at Royal Australian Chemical Institute dinner in Adelaide in early December.

The 900 MHz NMR hosted by the IMB on behalf of the Queensland NMR Network was delivered in September and launched by the Premier, the Hon. Peter Beattie, MP, in late October. The 900 MHz NMR will give us the ability to take a high-resolution, high-throughput approach to structural biology and significantly enhance our drug discovery capability. Our newest Group Leader, Professor Glenn King, who joined us from the University of Connecticut in December of this year, will put this new machine to good use. Glenn has developed unique and innovative NMR techniques for rapid protein structure determination, and is one of the world's acknowledged leaders in the field of structural biology. He will add considerable depth to our expertise in this area and I look forward to reporting on Glenn's successes in forthcoming Annual Reports.

Dr. Rosamond Siemon established the Rosamond Siemon Postgraduate Renal Research Scholarship this year, to provide funding for postgraduate research into kidney disease and renal regeneration. Dr. Siemon is the author of 'The Mayne Inheritance', which traces the history of the Mayne family in Brisbane and the origins of their bequest to The University of Queensland. Her interest in renal research stems from family experience of kidney disease and she has been a strong advocate of the research work in renal regeneration being carried out by Professor Melissa Little at the IMB. The Rosamond Siemon Scholarship will be open to any UQ or other suitably qualified postgraduate student undertaking multidisciplinary, collaborative research into renal disease, repair and regeneration. We thank Dr. Siemon for her outstanding support of the IMB.

A successful research Institute is generated from more than the sum of its grant funding, commercialisation outputs and published research papers. It is shaped and driven by the people. The significant achievements of the research staff in 2006 have already been noted here and are described in detail within these pages. Perhaps slightly less visible but every bit as important are the administrative and research support staff who work long hours and often on weekends to ensure that we can deliver the research outcomes expected of us. I thank them for their essential contributions in 2006. The IMB culture is vibrant and challenging and the postgraduate students' association (SIMBA), representing our 120 PhD students, adds enormously to the morale of the IMB through its social functions and newsletter. Long may it continue (despite the occasional lampooning of the Director!). Emerging this year was the IMB Early Career Researcher Committee and it continues to grow and accept a number of responsibilities within the Institute.

I anticipate over the next few years we will see another wave of growth in the IMB and that will bring its own challenges. At its most basic we only expect two things from our researchers – the pursuit of excellence and the application of our research findings for the benefit of the people who paid for them – the taxpayers and charitable supporters. Given the quality of the staff and the magnitude of the support from the University, the State and Commonwealth Governments and the private sector we are well placed to achieve our goals.

***Professor Brandon Wainwright***

Director
Institute of Molecular Bioscience

This has been a significant year for the IMB. In addition to our ongoing research and strategic activities, there have been changes in the leadership of the Institute that will have implications for many years to come. Professor Brandon Wainwright was appointed Director in November, after acting in the position since Professor John Mattick stepped down to concentrate on his research in December 2005. I was pleased and honoured to be named the new Deputy Director (Research), taking over this position that Professor Wainwright's promotion had left vacant. I look forward to supporting him in cementing the IMB's position as one of Australia's leading bioscience research institutes.

Despite the changes in senior personnel over the past year, I am pleased to note that one thing that hasn't changed is the quality of our research. Our scientists published over 170 papers during the year, with Professor Peter Koopman and Professor Rob Parton each having a paper in *Science*. Our collaboration with the RIKEN Institute on the FANTOM (Functional Annotation of Mouse) project continued, and this resulted in a series of papers, including one in *Nature* in April. Several IMB researchers were authors on these papers, with Professor David Hume and Dr. Sean Grimmond being senior authors. For more details on the papers above, as well as other notable papers published during the year, please see the Highlights section on page 10.

Our research prospects for the future are also excellent, with our researchers recording very successful Australian Research Council (ARC) and National Health and Medical Research Council (NHMRC) grant rounds. Our success rate was double that of the national average for both grant rounds, and IMB grants made up a significant fraction of The University of Queensland total. Altogether, IMB researchers received over $18.5 million in ARC and NHMRC funding. Professor Mike Waters received one of the nation's top research fellowships, becoming an NHMRC Senior Principal Research Fellow, while Associate Professor Carol Wicking, Associate Professor Richard Lewis, Professor Jenny Martin and Dr. Sean Grimmond all received NHMRC Senior Research Fellowships. Dr. Fiona Simpson received a Career Development Award. To read more details on the grants awarded, please see the Highlights section of this report on page 11.

Another highlight for IMB research in 2006 was the installation of a 900 MHz Nuclear Magnetic Resonance spectrometer (NMR). Used to determine the structure of molecules and aid in the design of drugs, it is the centrepiece of the Queensland NMR Network, a partnership between The University of Queensland, the Queensland University of Technology, Griffith University and the Queensland State Government. The IMB was chosen to house the NMR, which, as I write, is the most powerful commercially-available NMR in the world today, and the only one of its kind in the Southern Hemisphere. The NMR will assist in retaining researchers who will now be able to conduct world-class research in this field without having to leave the country. It will also attract scientists from overseas, and indeed the IMB has already gained a group leader who moved back to Australia in order to use in the NMR in his research. Professor Glenn King arrived in Queensland in late December from the University of Connecticut in the United States. He has an excellent record in both research and teaching, and will be a welcome addition to the IMB. Professor King's research interests include cell division and signal transduction in bacteria, as well as combinatorial peptide libraries in spider venoms. For more details on the research conducted at the IMB during 2006, please see the individual group leader pages, beginning on page 20.

# *DEPUTY DIRECTOR (RESEARCH) REPORT*

## ***John Hancock***

Just over 60 staff support our researchers in a range of areas including administration and finance; reception; animal house; central sterilising; postgraduate student coordination; information technology services; laboratory management; marketing and communication; technical services and building maintenance. I would like to thank these staff for a job well done.

We have had a number of senior staff movements during the year with IT Manager, Lindsay Hood, and his partner, Institute Research Grants Officer, Patricia McCauley, moving to Canberra. They have been replaced, respectively, by Rowan Gronlund, from the University of Auckland, and Michelle Foley, from Griffith University. Meanwhile, Marketing Manager, Andrea Sackson, left in order to devote more time to her consulting business and to her growing family.

Level 7 Floor Manager, Steve Love, left mid-year to take up the position of Infrastructure Manager in the University's newly completed Australian Institute of Bioengineering and Nanotechnology and Level 3 Floor Manager, Colin McQueen, left at the end of this year to take up a "demanding" new role at nearby St Lucia Golf Course. Both Steve and Colin had been with us since our move into the QBP in 2003 and as part of the Institute's team of Floor Managers played an important role in the establishment of the Institute in the new building. They have been replaced by Ian Lane and Ross Dixon who joined us from other University Schools.

This year saw the installation of a $10 million 900 MHz Nuclear Magnetic Resonance spectrometer (NMR), more details of which can be found in Professor Hancock's report on the opposite page. Support for the funding of this equipment came in part from the Queensland State Government's Smart State Research Facilities Fund. The Institute also received funding from the ARC Linkage Infrastructure Equipment and Facilities Fund (LIEF) to support the purchase of the Australian Mirror of the UCSC Genome Database Browser, which will provide support to the newly formed Queensland Facility for Advanced BioInformatics (QFAB).

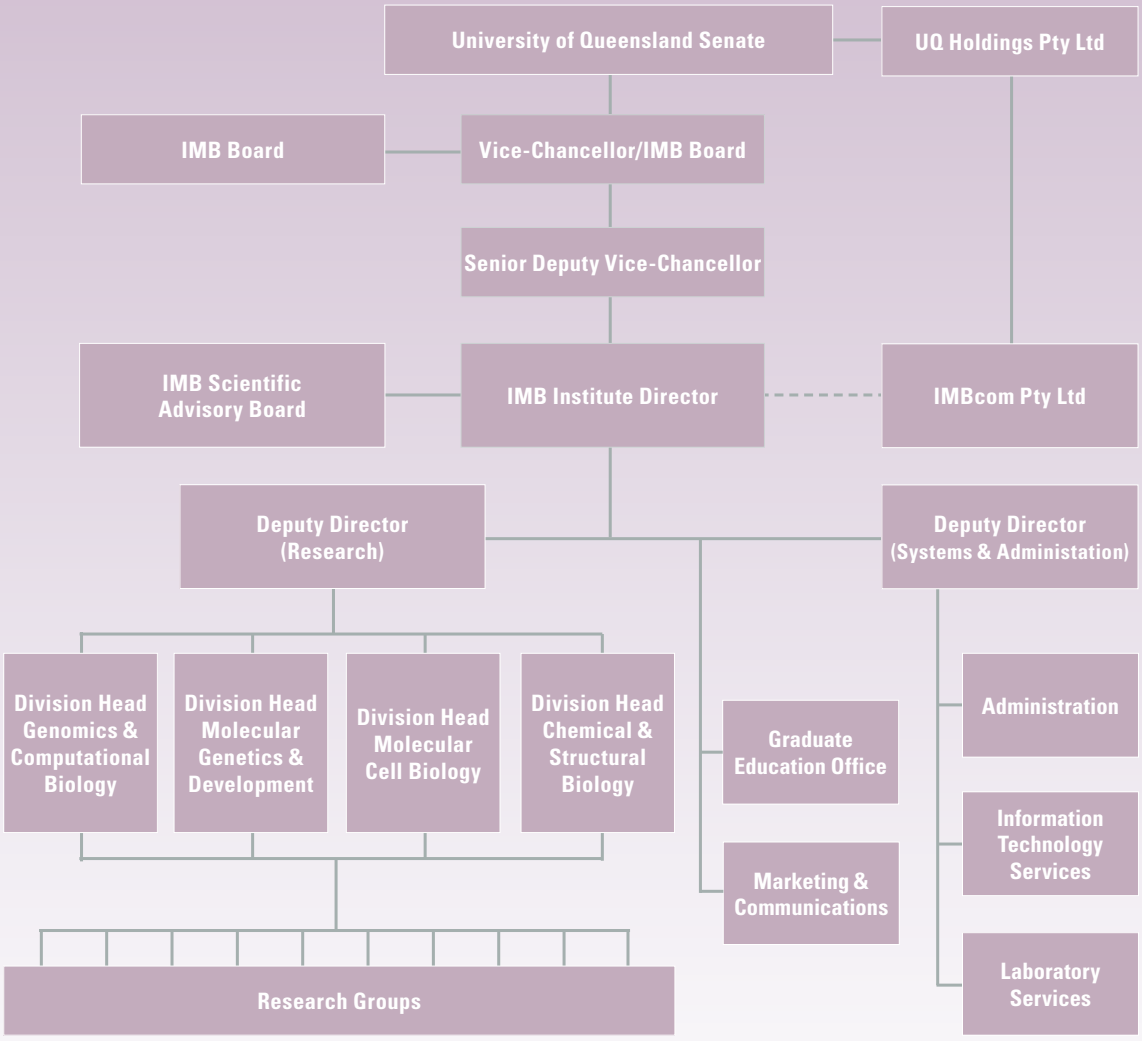
The IMB coordinated and/or hosted a number of research conferences and meetings in 2006. Notable amongst these was the third in the series of Winter Schools in Mathematical and Computational Biology, held in June, which attracted almost 150 delegates from around Australia and from overseas. The series of winter schools is designed to introduce mathematical and computational biology and bioinformatics to advanced undergraduate and postgraduate students, postdoctoral researchers and others working in the fields of mathematics, statistics, computer science, information technology, complex systems analysis, and biological, chemical and medical sciences and engineering.

The Tuesday Trade Off, introduced in 2004 in conjunction with CSIRO as a forum for companies to display the latest in scientific goods and services, has continued to be a successful format with sponsors for 2006 including PerkinElmer, Cambrex Bioscience, Genesearch, and HG Scientific.

The Queensland Bioscience Precinct continues to be a benchmark for many other laboratory construction projects throughout Australasia, resulting in a continuous stream of visits from interested scientists, architects and consultants  We also welcomed international scientific and government delegations from China, Germany, the UK, the USA, New Zealand, Malaysia, Singapore and Iraq. Delegations were briefed on IMB research and introduced to scientists in particular fields of interest. The IMB also hosted a number of visits by Australian government ministers and media.

# *DEPUTY DIRECTOR (SYSTEMS AND ADMINISTRATION) REPORT*

## ***Dr Ian Taylor***




# ORGANISATIONAL CHART

# IMB 2005 HIGHLIGHTS

## *The Year in Review*

# HIGHLIGHTS

## *New Director appointed for IMB*

Professor Brandon Wainwright began a five-year term as Director of the IMB late in the year, after acting in the position since the start of 2006.

"Professor Wainwright is an internationally-respected researcher who has detailed knowledge of the IMB and a clear view of its future priorities," UQ Vice-Chancellor, Professor John Hay, AC, said.

"I am confident that the Institute will continue to flourish under Professor Wainwright's guidance, producing outstanding research outcomes of tangible benefit to the national and international communities."

## *One big biology question solved*

An IMB research team solved one of biology's most fundamental questions – why males produce sperm and females produce eggs – in a breakthrough that could lead to improved infertility treatment, cancer therapy and pest management. The team, led by Dr. Josephine Bowles and Professor Peter Koopman, discovered that derivatives of Vitamin A trigger the beginning of egg and sperm production, a process known as meiosis.

The cells that eventually turn into either eggs or sperm, known as germ cells, are identical in male and female embryos, and whether a germ cell develops into an egg or a sperm depends on the time at which meiosis begins. In females, meiosis begins before birth and eggs are produced, whereas in males, meiosis begins after birth and the result is sperm.

Professor Koopman and his team found that retinoic acid, a derivative of Vitamin A, causes germ cells in female embryos to begin meiosis, leading to the production of eggs. They also discovered an enzyme present in male embryos that wipes out retinoic acid and so suppresses meiosis until after birth, resulting in sperm production. "This is an extremely important process that nobody has been able to figure out until now," Professor Koopman said.

## *Regenerating hope for liver disease*

A protein essential in the process of liver regeneration has been identified by a team of scientists from the IMB and the University of Barcelona, in a discovery that could lead to treatments for serious liver diseases such as hepatitis.

"The liver has an amazing capacity to regenerate and repair itself after damage, such as a heavy session of drinking," Professor Robert Parton, one of the team leaders, said. "But in some diseases, such as hepatitis and cirrhosis, the liver is so damaged that it loses this regeneration capacity.

"Identifying that this protein, caveolin-1, is an essential ingredient in the process of liver regeneration brings us a step closer to finding treatments for people whose livers are not able to heal themselves."

## *Learning the language of DNA*

An international consortium of scientists, including a team from the IMB, is a step closer to the next generation of treatments to combat disease, after publishing a comprehensive analysis of the human and mouse transcriptomes.

A senior member of the consortium and IMB researcher Professor David Hume said the transcriptome describes all of the information read from the genome by a cell at any given time. "Essentially, we need to understand the language that cells use to read DNA in order to know how processes in the body are controlled," Professor Hume said. "This knowledge will be a major resource to the biomedical research community."

## *Socking it to cancer*

An IMB research team has identified a gene that could be used to stop tumours growing by blocking their blood supply. A study led by Professor Peter Koopman showed that tumours in mice with a mutant form of the gene SOX18 actually stopped growing and became benign, unlike the lethal tumours that grew in normal mice.

Tumours only grow and spread if they can form a blood supply, and SOX18 is a key regulator of blood vessel formation. Mice with the mutant form of the gene were unable to develop blood vessels to feed the tumour. "Tumours of an equivalent size in humans would not be fatal, so if this discovery could be transferred to people, we could basically starve tumours before they could do much harm," Professor Koopman said.

## *Sea snail key to future of pain relief*

Associate Professor Richard Lewis was part of a study that could eventually lead to a treatment for sufferers of chronic pain. The study found that a conotoxin from the marine snail *Conus marmoreus* produces pain relief without apparent side effects.

The drawback to drugs that are currently available to treat pain, such as morphine, is that they sometimes only offer marginal relief, patients can build up a tolerance to them and they come with other side effects.

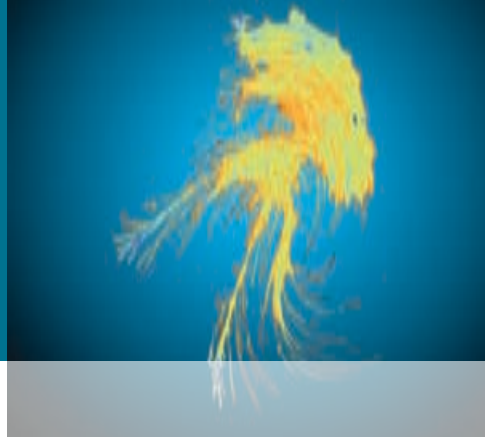
## *Proteins boost natural barrier to cancer*

An IMB PhD graduate has aided in pinpointing two proteins in cancer that could eventually halt the spread of tumours throughout the body. These proteins help the body's natural tumour suppressor called E-cadherin. Tumours usually lose the E-cadherin protein from their surface allowing cancer to spread.

Graduate Dr. Bo Wang, who was supervised by Professor Jenny Stow, said using proteins to boost E-cadherin levels could minimise or stop cancer spreading to other tissues.

## *Software speeds up the discovery process worldwide*

Biomedical and computational scientists from IMB and UQ's Queensland Brain Institute combined forces to create a powerful new tool that will greatly increase the amount of data that scientists can expect to process in a week.



The software, SwarmPS, speeds up the painstaking and often laborious process of selecting scientifically-significant images from the thousands of non-significant images that routinely accompany them. Screening processes that once demanded hundreds of hours from a skilled operator can now be done by a less-skilled operator in a fraction of the time, and will allow scientists to spend more time on the important aspects of their work, rather than the mundane, repetitive task of selecting images.

### *Mega-magnet adds to UQ's research attraction*

One of the world's most powerful magnetic instruments was officially commissioned at The University of Queensland, helping pave the way for research and development into the next wave of life-saving drugs.

Queensland Premier Peter Beattie launched the instrument, a 900MHz Nuclear Magnetic Resonance high-resolution spectrometer, which is housed at the IMB. It is the centrepiece of the $17 million Queensland Nuclear Magnetic Resonance Network (QNN), based at UQ. The State Government contributed $5 million through the Smart State Research Facilities Fund to help establish the QNN.

### *Inheritance may change history's course for kidney disease families*

An historian who chronicled one of Brisbane's most intriguing families in *The Mayne Inheritance* will leave a legacy that offers hope for families affected by a genetic kidney disease.

Dr. Rosamond Siemon has turned her focus from the past to the future by supporting kidney research at the IMB through a generous bequest and a scholarship, which begins in 2007. Dr Siemon's aim is to aid Professor Melissa Little and her team in researching polycystic kidney disease – an inherited condition affecting more than 60,000 Australians.

### *US$9 million raised for QLD biotech*

A Queensland biotechnology company whose technology is based on research from the IMB raised US$9 million in funding through Series A financing.

Protagonist, which targets disorders such as asthma, rheumatoid and psoriatic arthritis, gastro-intestinal disorders and diabetes-related conditions, will use the money to fund the development of new types of therapeutic drugs.

### *Memorial lecture attracts distinguished scientist from Japan*

The IMB, along with UQ's Queensland Brain Institute, marked International Brain Awareness Week with a memorial lecture for a celebrated neurobiologist on March 15. Professor Masatoshi Takeichi, Director of the Centre for Developmental Biology at the Riken Institute, Japan, presented the 2006 Toshiya Yamada Memorial Lecture. The lecture was named for the late Dr. Toshiya Yamada, who passed away in 2001. Dr. Yamada was an IMB researcher whose discoveries formed much of the basis of modern neurobiology.

## GRANTS

### *IMB research strengthened in latest NHMRC funding*

The IMB received more than $8 million in funding for 18 projects in National Health and Medical Research Council (NHMRC) funding, announced in October. The IMB also garnered five out of seven of UQ's research fellowships, which included Professor Mike Waters, who was granted one of the nation's top research fellowships, becoming a Senior Principal Research Fellow. Professor Waters leads a team of scientists studying growth hormone, which has important roles in determining a person's final height, body composition, strength and lifespan.

### *Intersex babies and skin cancer risk studies share in $6 million funding at IMB*

The genetics behind intersex babies, and improved prediction of skin cancer risk are two of the projects from the IMB that will receive funding from the latest round of Australian Research Council grants. The IMB will receive $6.34 million in total, spread over 11 projects.

### *Prestigious Federation Fellowship for IMB researcher*

Professor David Fairlie was awarded one of the country's most prestigious fellowships, a five-year Australian Research Council Federation Fellowship. Federation Fellows are regarded as exceptional researchers of world renown in their fields.

Professor Fairlie is undertaking pioneering work developing molecules that mimic selected functions of proteins, an approach that could present new ways of influencing infection and diseases of the aged, and could enhance preventative medicine in the form of drugs, vaccines and diagnostics.


*Professor John Mattick (centre) with CSIRO Chief Executive Dr. Geoff Garrett and CSIRO Chair Catherine Livingstone, after receiving the CSIRO Eureka Prize for Leadership in Science.*

*Professor Melissa Little (second from right) wins the Smart Women – Smart State: Research Scientist Award. Pictured with Professor Alan Lawson, Director of the UQ Graduate School and Dean of Postgraduate Students, and other UQ winners Bronwyn Galletly, Student Encouragement Award (left), and Lin Fielding (right), mother of Postgraduate Student Award winner Naomi Diplock.*

### *QLD Government grants IMB over $2.5 million in funding*

The IMB was awarded $2.7 million in Smart State grants announced in April by Deputy Premier Anna Bligh. IMB's Professor Mark Ragan and Dr. Anthony Maeder from the e-Health Research Centre received $1.9 million to establish the Queensland Facility for Advanced Bioinformatics, which supports the bioinformatics requirements of research-intensive organisations. The IMB and Bio-Layer Pty Ltd were awarded an $800 000 Research-Industry Partnerships Program grant to foster local development and international commercialisation of new biotechnology products for the detection and treatment of human diseases.

### *IMB gets tremendous boost from State Budget*

The IMB received $50 million over five years in the Queensland State Government Budget, handed down in June. The IMB is currently funded by the State Government until 2009, and this new funding will begin when the current funding agreement expires.

"The continuation of this funding for another five years will give the IMB the security it needs to conduct research which will lead to improvements in the lives of Queenslanders and people around the world," UQ Vice-Chancellor Professor John Hay, AC, said. "Without the Queensland Government's support, the IMB and UQ's other world-renowned institutes would not be able to achieve their incredible potential."

### *KOALA to fight childhood obesity*

A new research program will tackle the problem of childhood obesity using one of Australia's most loved animals – the koala. Dr. Gary Leong, a paediatric endocrinologist and basic researcher who divides his time between the IMB and the Mater Children's Hospital, will lead the KOALA Childhood Obesity Program, established with a $266 792 grant from the Golden Casket Medical Foundation. KOALA will bring together UQ and Mater researchers to investigate the genetic, environmental and behavioural reasons behind childhood obesity.

### *Cool fellowship for IMB researcher*

Dr. Janelle Keys, from the laboratory of Associate Professor Andrew Perkins, was awarded a prestigious international research fellowship to help cure the world's most common single-gene disorder. The Cooley's Anaemia Fellowship, worth US$40 000 a year, provides support to young scientists who are researching Cooley's Anaemia, a genetic blood disease that occurs when adult red blood cells cannot produce haemoglobin – the molecule that carries oxygen around the body.

Dr. Keys is investigating Ikaros, one of the proteins that controls haemoglobin production, and hopes that knowledge of how it works will be useful in developing novel treatments for the disorder.

## AWARDS

### *IMB researcher awarded for leadership in science*

A researcher who played a major role in the emergence of Brisbane as a centre of biological research was recognised for his achievements, being awarded the $10 000 CSIRO Eureka Prize for Leadership in Science.

Professor John Mattick, AO, was the driving force behind the establishment of the IMB and the Australian Genome Research Facility.

"John's initiatives have not only benefited Queensland, their flow-on effects have been the realisation for many key opinion leaders of the importance of investing in biotechnology for Australia's future – a realisation that has seen a much-needed increase in support for the science enterprise in many states," the prize committee said.

## Finding a smart way of treating renal disease

Professor Melissa Little won the Smart Women – Smart State (Research Scientist) Award for her work on renal disease. Professor Little established the Renal Regeneration Consortium, a national collaborative and multidisciplinary research team, and has defined six possible long-term therapies that may be pursued to treat renal disease. This is the second win in two years for IMB researchers, after Associate Professor Jenny Martin took out the award in 2005.

## Women in Biotech recognised

Associate Professor Jenny Martin won the inaugural Women in Biotech Outstanding Researcher award. Associate Professor Martin is a multi-award winning Principal Research Fellow who is working on the development of a new broad-spectrum anti-bacterial drug that would overcome the resistance being seen by some bacteria to existing antibiotics and on finding new compounds with anti-diabetic properties.

Professor Melissa Little received the Honourable Mention in the same category, again for her work on renal disease.

## Professor awarded for advancement of chemical science

Professor David Craik won the 2006 HG Smith Memorial Award from the Royal Australian Chemical Institute, given to a member of the Institute who, in the opinion of its Boards, has contributed most to the development of some branch of chemical science. Professor Craik uses NMR spectroscopy to determine the structure of proteins that are important in drug design programs and agriculture, and discovered cyclotides, novel circular proteins from plants.

## UQ staff honoured in Australia Day Awards

Two senior members of The University of Queensland who are connected with the IMB were honoured in the 2006 Australia Day Honours List. Professor Paul Greenfield, Senior Deputy Vice-Chancellor and IMB Board member, was appointed an Officer in the General Division of the Order of Australia (AO) for his services to science and engineering. Dr Peter Isdale, Chief Executive Officer of IMBcom, was appointed a Member in the General Division of the Order of Australia (AM) for service to marine science through research and contributions to the development and commercialisation of biotechnology.

## IMB student in an Ivy League of her own

IMB honours graduate Katey Robinson was awarded a six-year Harvard PhD scholarship worth US$60 000 a year. Ms Robinson's PhD will examine the early patterning of embryos, which could have applications to stem cell techniques or tissue engineering.

It is an area of science in which she became interested while investigating a gene, KLF12, in zebrafish development for her honours thesis under the supervision of Associate Professor Andrew Perkins.

## Smart PhD student rewarded

IMB researcher Jane Lattin, from the laboratory of Professor David Hume, was awarded a Smart State PhD scholarship worth up to $21 000 for her work on macrophages, a type of white blood cell, and their role in controlling chronic inflammation in diseases such as rheumatoid arthritis. The scholarships are designed to attract and retain promising researchers, such as Mrs Lattin, in Queensland.

## Taking science to schools

IMB PhD student David Ireland won a Young Science Ambassador Award from the Australian Academy of Technological Sciences and Engineering. The award aims to encourage talented young researchers to promote science and science education, and are chosen based on personal qualities and scholarly excellence.

Mr Ireland, who studies in the laboratory of Professor David Craik, won a certificate and $1000, and visited four schools as well as attending a Science in Parliament Day as part of his role.

## Developing a research career

Peter van der Heide, a PhD student studying in Dr. Brad Marsh's laboratory, was the inaugural winner of the Roche Award for Postgraduate Career Development (RAPCD). RAPCD allows a postgraduate to further their career by awarding them $1500 to take their work to the wider research community.

The judges viewed presentations from each of the finalists about their research before making their decision. Mr van der Heide's presentation was titled, "Towards a visible cell… reconstructing mammalian cells in 3D at 40-50Å resolution."

## Picturing the benefit of research

IMB PhD student Simon Wilkins won the inaugural Olympus Life Science Research Postgraduate Travel Award. Mr Wilkins, from the laboratory of Associate Professor Andrew Perkins, received travel funds to the value of $1000 to allow him to present his work at a relevant scientific conference.

Entries must represent part of a life science project on which the student is working, and Mr Wilkins won with his image, "Dark side of the moon – Visualising the yolk syncytial layer of early stage zebrafish embryos by fluorescence and scanning electron microscopy."

## Study of the cell's central sorting office takes out Amgen Prize

Luke Hammond took out the 2006 Amgen Australia Prize for being the best IMB honours student with his thesis, "Budding of membrane-bound carriers from the trans-Golgi network". The Golgi is the central sorting office of the cell, which handles all incoming material such as proteins, and also controls all outgoing material. Mr Hammond, who was supervised by Professor Jenny Stow, found that a dynamic population of actin microfilaments is required at the Golgi for efficient carrier detachment.

***Members of the IMB Advisory Board:***

*Professor John Hay AC, Professor Brandon Wainwright, Professor Frank Gannon, Professor Paul Greenfield AO, Dr Russell Howard, Dr Peter Isdale AM, Professor Mick McManus, Mr Ross Rolfe*

## *Professor John Hay, AC (Chair)*

Professor John Hay, AC, was appointed the Vice-Chancellor of The University of Queensland in 1996 and was previously Vice-Chancellor of Deakin University. Under his leadership, both UQ and Deakin were named Australia's University of the Year by the Good Universities Guide. UQ has now won far more teaching awards than any other university.

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

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

## *Professor Brandon Wainwright (Director)*

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

Professor Wainwright completed his undergraduate and postgraduate studies at the University of Adelaide, after which he took up a postdoctoral fellowship at St Mary's Medical School, the University of London. He remained at St Mary's for six years,

# IMB ADVISORY BOARD

eventually becoming a Medical Research Council Senior Research Fellow. In 1990, he moved back to Australia, joining the Centre for Molecular and Cellular Biology (CMCB) at The University of Queensland. Professor Wainwright stayed with the CMCB when it was merged with another UQ Centre (the Drug Design and Development Centre) in 2000 to create the Institute for Molecular Bioscience.

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

## Professor Frank Gannon

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

## Professor Paul Greenfield, AO

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

## Dr. Russell Howard

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

## Dr. Peter Isdale, AM

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

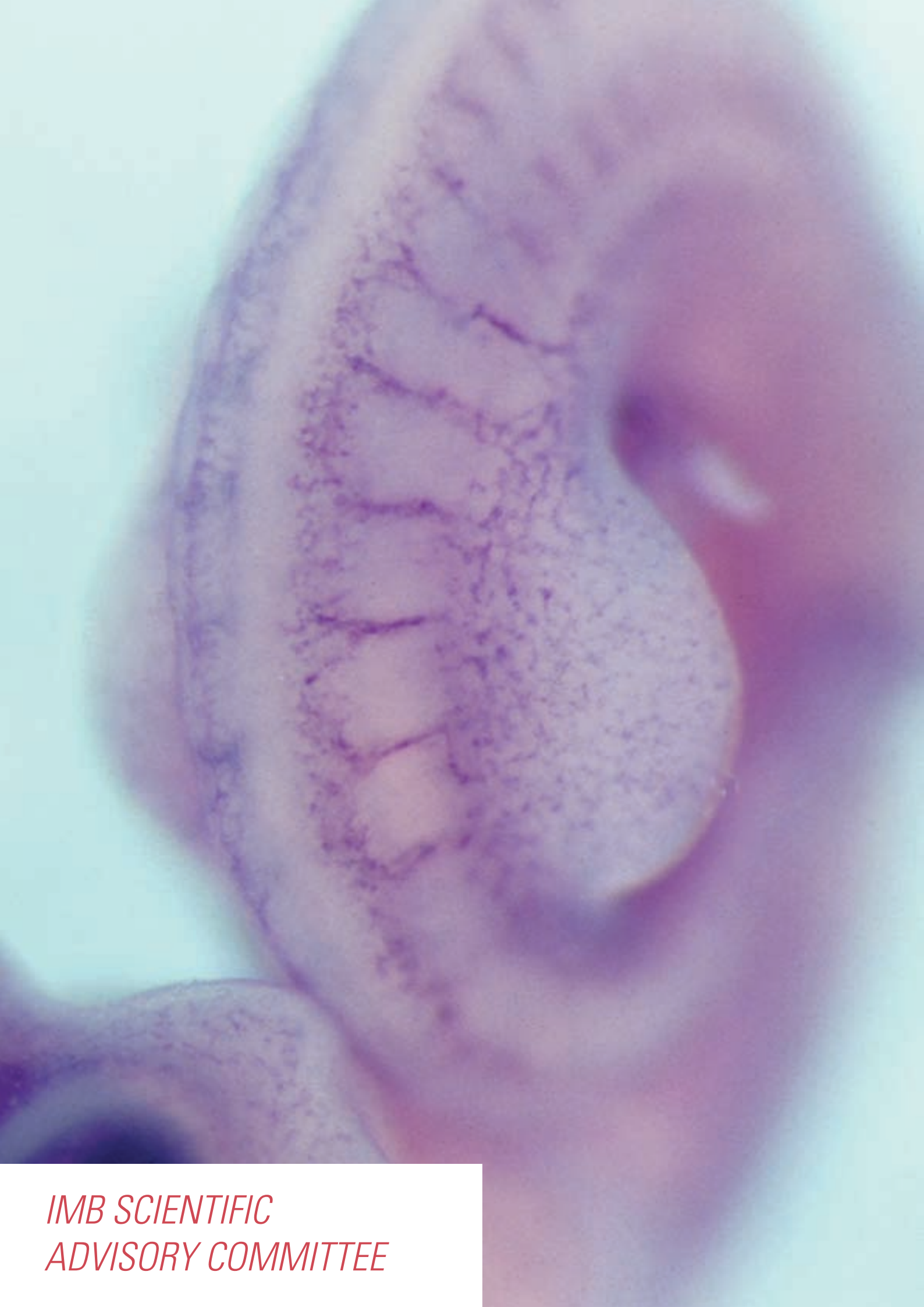
In 2006 he was awarded as a Member in the General Division of the Order of Australia (AM) for service to marine science through research and as a contributor to the development and commercialisation of biotechnology.

## Professor Mick McManus

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

## Mr Ross Rolfe

Ross Rolfe is Director-General of the Department of the Premier and Cabinet for Queensland. He was appointed to the Queensland Government in July 2005, prior to which he was Chief Executive Officer of Stanwell Corporation. Between 1995 – 2002 he was the Director-General of the Department of State Development and Coordinator-General. In 1996, he was the Director-General of the Department of Environment and Heritage. 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. He has held a range of board positions in the resources, energy and education sectors including Director of the Queensland Resources Council, Member of the Queensland Centre for Low Emissions Technologies, the Council of the Queensland University of Technology and the Board of Tennis Queensland.



# IMB SCIENTIFIC ADVISORY COMMITTEE

### *Professor Ken-ichi Arai*

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

### *Professor Wah Chiu*

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

### *Professor David Gallas*

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

### *Professor Robert Graham*

Executive Director
Victor Chang Cardiac Research Institute, Sydney

### *Professor Peter Gunning*

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

### *Professor Steve Kent*

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

### *Professor Edison Liu*

Executive Director
Genome Institute of Singapore
National University of Singapore

### *Professor Chris Marshall*

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

### *Professor Garland Marshall*

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

### *Professor Anne McLaren*

The Wellcome Trust/Cancer Research UK Institute of Cancer and Developmental Biology
University of Cambridge, UK

### *Professor Ira Mellman*

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

### *Professor Nicos Nicola*

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

### *Professor Greg Petsko*

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

### *Professor Robert Saint*

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

### *Professor Patrick Tam*

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

### *Professor Marino Zerial*

Max Planck Institute of Molecular Cell Biology
Dresden, Germany

***Members of the IMB Scientific Advisory Committee:***

*(Top Row) Professor Ken-ichi Arai, Professor Wah Chiu, Professor David Gallas, Professor Robert Graham, Professor Peter Gunning, Professor Steve Kent, Professor Edison Liu, Professor Chris Marshall.*

*(Bottom Row) Professor Garland Marshall, Professor Dame Anne McLaren , Professor Ira Mellman, Professor Nicos Nicola, Professor Greg Petsko, Professor Robert Saint, Professor Patrick Tam, Professor Marino Zerial.*

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

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

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

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

# *IMB RESEARCHERS*
## *The people and their passion*

## DIVISION OF GENOMICS AND COMPUTATIONAL BIOLOGY

***Research Focus:***

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

***Research Group Leaders:***

- Tim Bailey
- Sean Grimmond
- John Mattick
- Mark Ragan
- Rohan Teasdale

## DIVISION OF MOLECULAR GENETICS AND DEVELOPMENT

***Research Focus:***

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

***Research Group Leaders:***

- Peter Koopman
- Melissa Little
- George Muscat
- Andrew Perkins
- Rick Sturm
- Brandon Wainwright
- Carol Wicking

## DIVISION OF MOLECULAR CELL BIOLOGY

***Research Focus:***

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

***Research Group Leaders:***

- John Hancock
- Ben Hankamer
- David Hume
- Brad Marsh
- Alan Munn
- Rob Parton
- Jennifer Stow
- Mike Waters
- Alpha Yap

## DIVISION OF CHEMICAL AND STRUCTURAL BIOLOGY

***Research Focus:***

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

***Research Group Leaders:***

- Paul Alewood
- Robert Capon
- David Craik
- David Fairlie
- Richard Lewis
- Jenny Martin
- Mark Smythe

## JOINT APPOINTMENTS OF THE IMB

***Joint Appointments:***

Kevin Burrage – Professor, School of Physical Sciences (Mathematics) and Advanced Computational Modelling Centre
Geoff Goodhill – Professor, Queensland Brain Institute
Alan Mark – Professor, School of Molecular and Microbial Sciences
Alasdair McDowall – Associate Professor, Centre for Microscopy and Microanalysis
Geoff McLachlan – Professor, School of Physical Sciences (Mathematics)

# PATTERN RECOGNITION AND MACHINE LEARNING IN BIOLOGY

## Tim Bailey

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

Our recent work has focused mainly on analysing protein, DNA and RNA sequence data. We have developed tools for making predictions in several biological domains:

- Comparing and clustering transcription factor binding site motifs
- Motif discovery algorithms that allow gaps in the motifs
- Motif discovery algorithms that use negative and positive examples to discover motifs
- Detecting transcription factor binding sites
- Discovering protein domains
- Predicting clusters of interacting transcription factors
- Predicting secondary structure, flexibility and accessible surface area
- Detecting errors in protein databases

We have applied existing bioinformatics tools in recent work to answer several biological questions:

- Discriminating between coding and non-coding RNA transcripts
- Predicting short proteins in the transcriptome
- Detecting "pseudo-messenger RNA"

One current focus is on using the evolutionary signal present in orthologous genes from multiple species to improve the sensitivity and accuracy of prediction and discovery algorithms for transcription factor binding sites.

We place a strong emphasis in delivering useful computational tools to biologists. We make the algorithms we develop available as interactive tools over the web. We support these tools via websites located at IMB, UCSD, Boston University and the Pasteur Institute. These include MEME, a tool for discovering motifs (sequence patterns) in protein and DNA sequences; MAST, a tool for scanning sequence databases for matches to known patterns; MCAST, Comet and Clusterbuster, tools for scanning sequences for clusters of transcription factor binding sites; and Meta-MEME, a general-purpose sequence modelling tool. Some of these tools are among the most widely-used bioinformatics algorithms. For example, the MEME algorithm is used via the USCD website by over 800 biologists around the world each month. Maintaining these websites and supporting the biologists who use them is an important commitment for us.

## Research projects

- Developing motif discovery algorithms that use positive and negative examples; applications include looking for signals in DNA (splice junctions) and protein patterns that determine thermal stability
- Investigating genetic regulatory networks using protein-protein interaction data
- Identifying tissue-specific promoters
- Developing HMMs and scanning algorithms that utilise evolutionary information to improve detection of regulatory modules
- Finding ways of improving motif discovery algorithms

## Key Publications


Bailey, T.L., Williams, N., Misleh, C., and Wilfred, W.L. (2006). MEME: Discovering and analyzing DNA and protein sequence motifs. *Nucleic Acids Research* **34:** W369-W373.

Bodén, M., and Bailey, T.L. (2006). Identifying sequence regions undergoing conformational change via predicted continuum secondary structure. *Bioinformatics* **22**: 1809-1814.

Frith, M.C., Wilming, L.G., Forrest, A.R., Kawaji, H., Tan, S.L., Wahlestedt, C., Bajic, V.B., Kai, C., Kawai, J., Carninci, P., Hayashizaki, Y., Bailey, T.L., and Huminiecki, L. (2006). Psuedo-Messenger RNA: Phantoms of the Transcriptome. *PLoS Genetics* **2**: e23.

Stanley, S.M., Bailey, T.L., and Mattick, J.S. (2006). GONOME: measuring correlations between GO terms and genomic positions. *BMC Bioinformatics* **7:** 94.


### Lab members

Research Officer:
Dr. Martin Frith

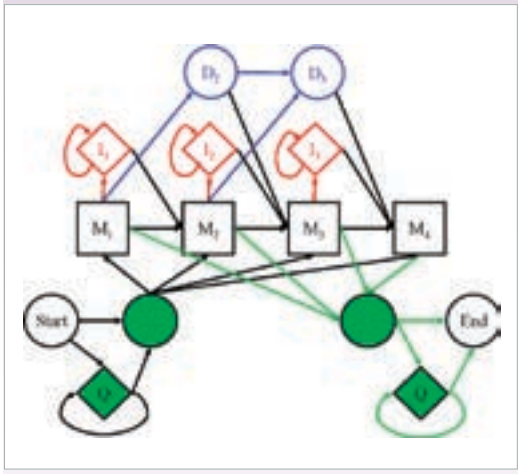
Research Assistant:
Tom Whitington

PhD Student:
Denis Bauer

Honours Student:
Emma Redhead

Visiting Professor:
Dr. Osamu Maruyama (Kyushu University)

Student Interns:
Rolv Seehus (Norway)
Zuzanna Cienikova (France)
Liang Ma (UNSW)




*(Above) Hidden Markov model.*

# EXPRESSION GENOMICS

## Sean Grimmond

The central theme to my research to date has been the capture of information contained within the transcriptome and the study of transcriptome dynamics to identify key genes or transcriptional programs. In collaboration with the FANTOM consortium and Japanese Genome Program, we have recently re-defined transcriptional output for each locus in mouse and man, with particular attention paid to: genes whose products are associated with developmental pathways, the phosphoregulators network, and the extracellular space. The next five years will build upon on these recent efforts and focus on:

Integrating transcriptome dynamics with functional annotations to identify candidate gene products driving key phenotypes in model systems: Gene expression profiling is a particularly powerful tool for defining candidate genes capable of driving specific outcomes. We are continuing to use these approaches to identify: 1) novel secreted factors or ligand-receptor interactions controlling ES cell-directed differentiation and survival, 2) the identification of renal morphogens or secreted factors that promote renal regeneration and 3) expression markers associated with different subtypes of breast cancer.

Accurately surveying transcriptional complexity of key systems in models of development and pathology: We have recently made inroads toward creating a temporal and spatial gene expression atlas for the developing mouse kidney. A combination of arrays, automated section and WMISH (as part of the NIDDK GUDMAP Program) and splicing array profiling of transcripts is being used to create a detailed molecular map of urogenital organogenesis.

Creating genetic networks of the mammalian phosphoregulator network: Previously, we have defined all protein kinases and protein phosphatases in the mouse and set out to functionally annotate them. This resulted in the creation of the phosphoregulator database providing a summary of the sub-cellular localisation, tissue distribution, classification, disease associations, substrates, ligands, interactions, nomenclature, and peptide sequence for each phosphoregulator locus. We are now using systems biology approaches to model the phosphoregulator network in the normal cell cycle and/or tumour progression. This is being done by identifying all of the expression patterns of all components of the network in normal and transformed cell types throughout the cell cycle, and includes both canonical and variant phosphoregulators generated by alternative transcription events (see the phosphoregulator variant database for details on novel phosphoregulator isoforms). We are also predicting and functionally screening key network components for an ability to regulate normal cell division. Finally we are also studying the role of alternate phosphoregulator promoter usage in the regulation of cell division and melanoma cell line progression.

### Lab members

Senior Research Officer:
Dr. Tina Maguire (SRC Microarray Facility)

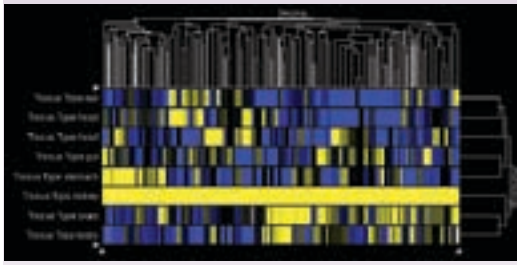
Research Officers:
Dr. Gabriel Kolle, Dr. Brooke Gardiner, Dr. Al Forrest, Dr. Nicole Cloonan

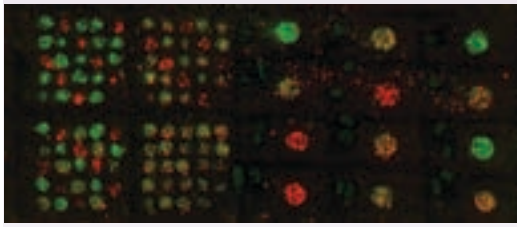
Bioinformaticians:
Darrin Taylor, Milena Gongora (SRC Computational Biology)

Research Assistants:
Ben Wilson, Ehsan Nourbakhsh, Melissa Brown

PhD Student:
Geoff Faulkner

Honours Student:
Michelle Chan





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

*(Above) Photomicrograph of HEK cells transfected using a robotically generated cell microarray.*

## Research projects

- Creating a transcriptome atlas for the mammalian kidney
- Transcriptional complexity of the mammalian phosphoregulator network
- Transcriptional programs in ES differentiation and organogenesis
- Transcriptome analysis of the extracellular space in mammalian development

## Key Publications


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

Forrest, A.R.R., Waddel, N., Taylor, D., Gongora, M., Flegg, C., Aturaliya, R., Teasdale, R., Wells, C.A., Hayashizaki, Y., Suzuki, H., and Grimmond, S.M. (2006). Role of alternate transcripts in the regulation of protein phosphorylation networks. *Genome Biology* **7:** R5.

Wells, C.A., Chalk, A., Forrest, A.R.R., Faulkner, G., Taylor, D., and Grimmond, S.M. (2006). Dominant negative alternate splicing events regulate the Toll4 signalling pathway. *Genome Biology* **7:** R10.

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

# RNA-BASED GENE REGULATION IN MAMMALIAN DEVELOPMENT

John Mattick

Only 1.2% of the human genome codes for proteins. The vast majority of the human genome, and that of other complex organisms, consists of vast tracts of sequences within and between genes that are widely thought of as evolutionary debris, or junk. However most of these sequences are in fact transcribed into RNA that is not translated into protein. Therefore the human genome is either replete with useless transcription, or these non-coding RNAs are fulfilling some unexpected functions.

Many of these transcripts are processed to smaller RNAs, called microRNAs, which control many aspects of development. MicroRNAs also regulate a variety of developmental processes in plants, and regulatory RNAs are clearly involved in chromosome dynamics and epigenetic modification in all multicellular organisms. Most, if not all, complex genetic phenomena in the eukaryotes appears to be connected to RNA signalling. In addition, a significant proportion of the mammalian genome appears to be under evolutionary selection, both positive and negative, including thousands of ultra-conserved sequences and transposon-free regions, which have remained essentially unchanged throughout mammalian evolution.

We are testing the hypothesis that the non-coding sequences constitute a hidden regulatory system that uses RNA signals to direct and coordinate complex suites of gene expression during our growth and development. We have shown that regulatory signals scale non-linearly with genome size and that simple organisms have reached a complexity limit based on analogue (protein) controls alone, implying that the more complex eukaryotes must have breached this limit, presumably by converting to a digital regulatory system based on RNA. If this is correct, our current conceptions of the genomic information content and programming of complex organisms will have to be radically reassessed, with implications for many aspects of biology, medicine and biotechnology.

Our recent findings include the discovery of large numbers of non-coding RNAs that are dynamically regulated during differentiation and development, including in embryonal stem cells, neuronal cells and the brain, muscle, gonads and immune cells.

## Research projects

- Comparative genomic analysis of non-coding sequence evolution in animals
- Bioinformatic analysis and computational modelling of RNA regulatory networks in differentiation and development
- Bioinformatic identification and laboratory validation of microRNAs, snoRNAs and other classes of regulatory RNAs
- Analysis of ultraconserved elements, transposon-free regions and other unusual features of the mammalian genome
- Analysis of the expression and functions of non-coding RNAs in mammalian differentiation and development
- Analysis of dynamic changes in RNA:DNA complexes during differentiation using whole-genome tiling arrays
- Proteomic identification of proteins interacting with RNA signalling complexes

## Key Publications

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

Carninci, P., *et al.* (2005). The transcriptional landscape of the mammalian genome. *Science* **309**: 1559-1563.

Gagen, M.J., and Mattick, J.S. (2005). Accelerating networks. *Science* **307**: 856-858.

Mattick, J.S., and Makunin, I.V. (2005). Small regulatory RNAs in mammals. *Human Molecular Genetics* **14**: R121-R132.

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

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

### Lab members

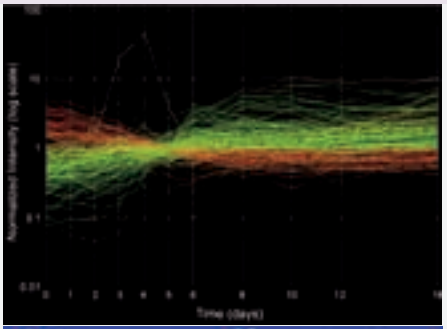
Senior Research Officers:
Dr. Igor Makunin
Dr. Larry Croft (UQ Postdoctoral Fellow)
Dr. Michael Gagen (Visiting Fellow)

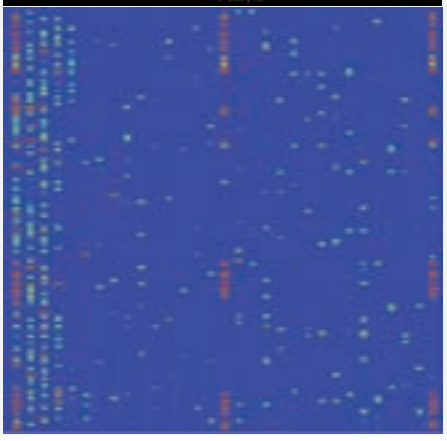
Research Officers:
Dr. Marjan Askarian Amiri
Dr. Marcel Dinger (New Zealand FoRST Fellow)
Dr. Evgeny Glazov
Dr. Lorenzo Malquori
Dr. Michael Pheasant
Dr. Giulia Solda (University of Milan Fellow)

Senior Research Assistant:
Ke-Lin Ru

PhD Students:
Paulo Amaral, Chol Hee Jung, Darren Korbie, Tim Mercer, Satu Nahkuri, Ken Pang (joint with Ludwig Institute Melbourne), Oliver Purcell, Ryan Taft, Cas Simons, Stuart Stephen, Stefan Stanley

Honours Student:
Sylvia Tippmann





*(Right Top) Dynamic expression of non-coding RNAs during embryonal stem cell differentiation.*
*(Right Bottom) Validation of bioinformatically-predicted small RNAs from mice using high-density arrays.*

# COMPUTATIONAL GENOMICS

## Mark Ragan

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

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

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

Our group also develops software and data infrastructure for the Visible Cell™ e-research project (http://www.visiblecell.com), a collaboration between IMB and the ARC Centre in Bioinformatics (http://bioinformatics.org.au). We have developed approaches for the management of terabyte data, implemented data grid technologies including Storage Resource Broker, and are learning to embed network models in reconstructed 3D image data. Core data infrastructure is being developed within the Queensland Facility for Advanced Bioinformatics (http://www.qfab.com).

## Research projects

- Automated inference of vertical and lateral gene transmission, genetic recombination and breakpoints in pathogenic bacteria
- Genome dynamics and the evolution of new protein functions in fish
- Fine-scale mapping of orthologous and paralogous regions of mammalian genomes
- Protein-protein interaction networks in cellular context
- Computational discovery of novel miRNA targets in mammalian genomes
- Integrating bioinformatic information using Semantic Web technologies
- Visible Cell™ Project: software and data infrastructure
- Data grid for very large molecular and image datasets

## Key Publications


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

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

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

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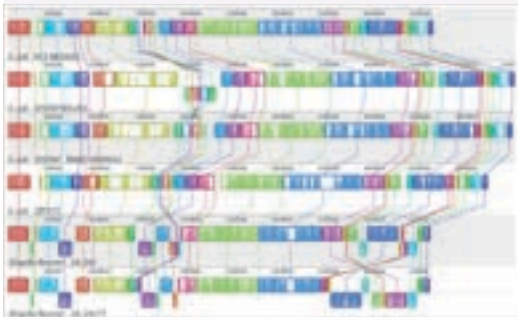

*(Above) A multiple whole-genome alignment of six strains of* Escherichia coli *consists of 34 rearranged pieces larger than 1 kb (Dr. Aaron Darling).*

# COMPUTATIONAL CELLULAR BIOLOGY

## Rohan Teasdale

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

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

**Subcellular Localisation:**
Individual proteins have "signals" that are responsible for their intracellular localisation and efficient distribution of these proteins throughout the cell occurs via membrane transport or trafficking. Determining organelle association or subcellular localisation is therefore an essential step in characterising the protein's function across all types of biomedical research, and its modulation needs to be considered when developing pharmaceutical agents. Our major long-term objective is to document the subcellular localisation of every protein within the mouse proteome. This will be achieved by a combination of experimental evidence, computational prediction and data mining.

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

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## Research projects

- Annotation of the membrane organisation of mammalian secretory pathway proteins
- Determination of the Subcellular Localisation of the entire mouse proteome
- LOCATE: A Mouse Protein Subcellular Localisation Database - http://locate.imb.uq.edu.au
- Algorithm development for prediction of protein features
- Development of computational approaches to analyse image and real-time microscopy data
- Endosome Dynamics, Macropinocytosis and Retromer

## Key Publications


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

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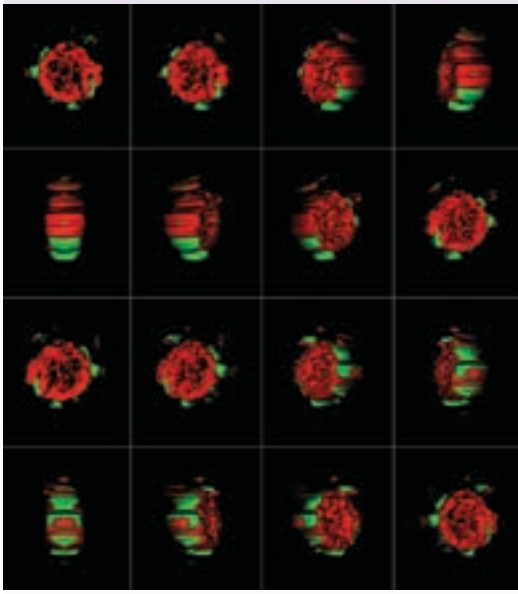

*(Above) Macropinosome gallery.*

# IDENTIFICATION AND STUDY OF GENES REGULATING EMBRYO DEVELOPMENT

Peter Koopman

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

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

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

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

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

## Research projects

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

## Key Publications:

Beverdam, A., and Koopman, P. (2006). Expression profiling of purified mouse gonadal somatic cells during the critical time window of sex determination reveals novel candidate genes for human sexual dysgenesis syndromes. *Human Molecular Genetics* **15**: 417–431.

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

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Schepers, G.E., Teasdale, R.D., and Koopman, P. (2002). Twenty pairs of Sox: Extent, homology and nomenclature of the mouse and human Sox transcription factor gene families. *Developmental Cell* **3**: 167–170.

Koopman, P. (2001). The genetics and biology of vertebrate sex determination. *Cell* **105**: 843–847.

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# RENAL DEVELOPMENT, DISEASE AND REGENERATION

## Melissa Little

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

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

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

The long-term aim of our laboratory is to develop novel cell-based, factor-based or bioengineering-based therapies for both acute and chronic renal disease. 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.

### Research projects

- Functional characterisation of potential adult renal stem cells
- Molecular characterisation of the cap mesenchyme
- Creation of an atlas of gene expression during urogenital development
- Investigating the role of the resident tissue macrophage in renal regeneration
- Analysis of the role of specific growth factors in renal development, repair and regeneration
- Lentiviral screen for the directed dedifferentiation of proximal tubule cells
- Characterisation of the role of Crim1 in kidney and vascular development

### Key Publications


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

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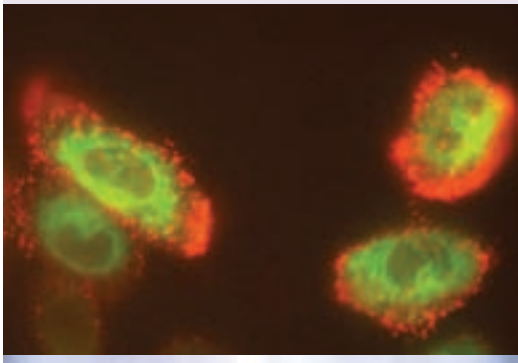

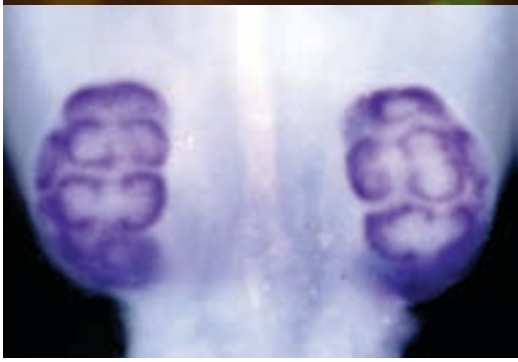

*(Right Top) Fluorescent imaging of cultured cells expressing Crim1-GFP fusion protein. Double fluorescent imaging shows cultured Chinese hamster ovary cells expressing recombinant Crim1-green fluorescent protein. Green shows the protein on the inside of the cells, while red shows its presence on the external cell surface.*

*(Right Bottom) Wholemount* in situ *hybridisation of the crim gene on 12.5dpc kidneys, with MRNA expression in blue in the cap mesenchyme.*

# NUCLEAR HORMONE RECEPTORS AND SKELETAL MUSCLE

## George Muscat

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

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

Surprisingly, the function of these orphan NRs in skeletal muscle metabolism has not been examined. Nevertheless, given the data on the dietary lipid-dependent NRs and skeletal muscle, and their utility as therapeutic targets for the treatment of disease, the contribution of this tissue to orphan NR action must be defined. The objective of our current research is to examine the role of orphan NRs in skeletal muscle cell and animal models. Furthermore, we are examining the roles of adrenergic and TGF-beta signalling, in the context of crosstalk with NR signalling in the control of lipolysis and muscle mass. We will test the hypothesis that the orphan NR subgroups regulate lipid and energy homeostasis.

## Research projects

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

## Key Publications


Allen, T., Zhang, F., Moodie, S.A., Clemens, L.E., Smith, A., Gregoire, F., Bell, A., Muscat, G.E., and Gustafson, T.A. (2006). Halofenate is a selective peroxisome proliferator-activated receptor gamma modulator with antidiabetic activity. *Diabetes* **55**: 2523-2533.

Maxwell, M.A., and Muscat, G.E. (2006). The NR4A subgroup: immediate early response genes with pleiotropic physiological roles. *Nuclear Receptor Signaling* **4**: e002.

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

Ramakrishnan, S.N., and Muscat, G.E. (2006). The orphan Rev-erb nuclear receptors: a link between metabolism, circadian rhythm and inflammation? *Nuclear Receptor Signaling* **4**: e009.

Smith, A.G., and Muscat, G.E. (2006). Orphan nuclear receptors: therapeutic opportunities in skeletal muscle. *American Journal of Physiology: Cell Physiology* **291**: C203-217.

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


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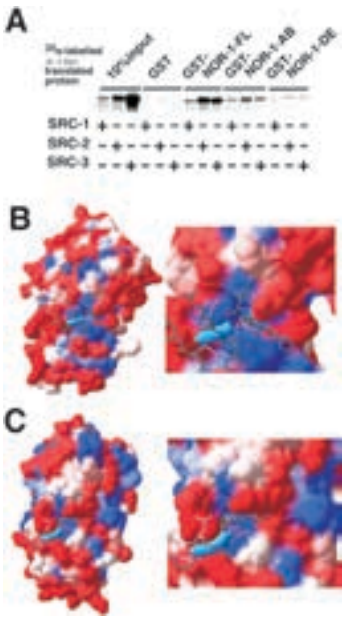


*(Top) GST pulldown analysis of NOR-1 cofactor recruitment.*

*(Above) Molecular Modeling of the NOR-1 ligand binding domain.*

# BLOOD DEVELOPMENT

## Andrew Perkins

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

We have three primary focus areas:

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

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

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

### Research projects

- Analysis of mesoderm transcriptional programs within embryonic stem cells, with the aim of generating adult-type stem cells for repair and regeneration of damaged adult organs, particularly the kidney and bone marrow
- Dissection of the transcriptional regulation of human haemoglobin switching in order to develop new drugs to reactivate foetal haemoglobin in people with sickle cell disease and beta-thalassaemia
- Analysis of the role of the transcription factors in mesoderm patterning and organogenesis in zebrafish

### Key Publications


Keys, J.R., Tallack, M.R., Hodge, D.J., Cridland, S.O., David, R., and Perkins, A.C. (2007). Genomic organisation and regulation of murine alpha haemoglobin stabilising protein by erythroid Kruppel-like factor. *British Journal of Haematology* **136**: 150–157.

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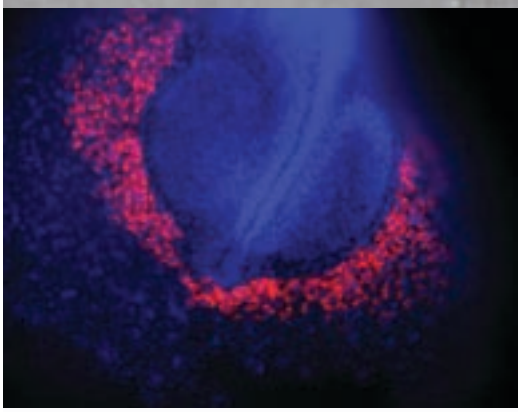

*(Top) Tol2 eGFP transgenic zebrafish at 6 weeks (photo by Christine Neyt).*

*(Above) Fluorescent* in situ *for zebrafish hatching gland (photo by Stephen Bruce and Melissa Gardiner).*

# MELANOCYTE BIOLOGY, MELANOMA AND PIGMENTATION GENETICS

Rick Sturm

The traits of skin, hair and eye colour combined with high levels of environmental UV exposure have been recognised as potential modulators of an individual's risk of developing skin cancer. We are investigating the genes within the human genome that are involved in directing pigmentation phenotype and identifying polymorphic alleles which underlie a person's skin cancer risk. A number of proteins essential to normal melanin biosynthesis have so far been identified and include the enzymes tyrosinase, tyrosinase-related protein-1 and dopachrome tautomerase (TYR, TYRP1 and DCT), the P-protein (OCA2) associated with blue eye colour, and the melanocortin-1 receptor (MC1R) responsible for red hair colour. Recently, population-specific polymorphisms within the MATP (SLC45A2) and NCKX5 (SLC24A5) protein-coding regions have been associated with the degree of pigmentation in human skin.

Our group has found that variation within the MC1R coding region can result in altered receptor activity and this underlies the association with the red hair and fair skin phenotype (RHC). We have quantified the contribution of individual MC1R alleles to the RHC phenotype using allelic modelling with four common (D84E, R151C, R160W and D294H) and two rare (R142H and I155T) alleles, designated as R, shown to be strongly associated with the RHC phenotype. A further three alleles (V60L, V92M and R163Q), designated as r, had lower penetrance. Using immunofluorescence and ligand binding studies, we have found that melanocytic cells expressing MC1R show strong surface localisation of the wildtype, R142H and D294H receptors but markedly reduced cell surface expression of the other R variants. Conversely r alleles were expressed with normal or intermediate cell surface receptor levels.

Investigations into pigment cell biology have utilised cultures of both murine and human melanocytes, and numerous melanoma cell lines. More recently, we have published conditions for the isolation and propagation of precursors of human epidermal melanocytes, termed melanoblasts, using medium supplemented with a range of growth factors, and which we have shown have the capacity to differentiate into melanocytes upon mitogen withdrawal. To investigate the molecular and cellular consequences of MC1R, SLC45A2 and SLC24A5 variant alleles on melanocyte function and response to UV irradiation, we have established a bank of over 400 primary human melanocyte and melanoblast cultures of defined genotype. We have also established a serum-free melanocyte-keratinocyte coculture system to examine the behaviour and functional abilities of melanocytes possessing variant MC1R activity and make comparison to wildtype strains. Using this model, melanocytes of similar MC1R genotype displayed differences in morphological appearance when cocultured with keratinocytes under various calcium conditions.

## Research projects

- Interaction of genes for skin, hair and eye colour in determining skin cancer risk phenotypes
- Parallel genetic and cellular analysis of human melanogenesis
- Melanocyte-keratinocyte coculture systems to study gene responses after UV exposure
- Eye colour as a genetic trait

## Key Publications

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

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

Cook, A.L., Smith, A.G., Smit, D.J., Leonard, J.H., and Sturm, R.A. (2005). Co-expression of SOX9 and SOX10 during melanocyte differentiation in vitro. *Experimental Cell Research* **308**: 222-235.

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

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

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Tim Bladen
Kimberley Beaumont

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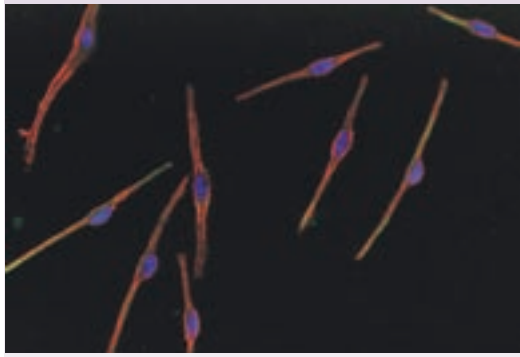

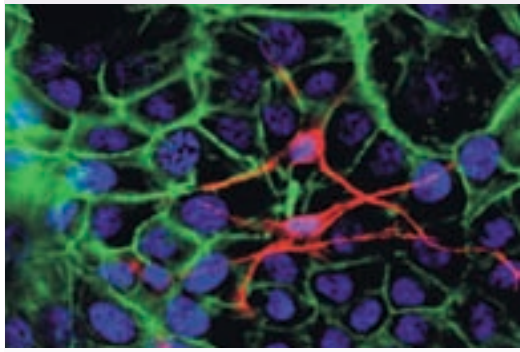

*(Top) Monoculture of human melanocytes (red).*

*(Above) Coculture of human melanocytes (red) with keratiocytes (green).*

# TISSUE REPAIR AND CANCER

## Brandon Wainwright

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

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

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

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

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## Research projects

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

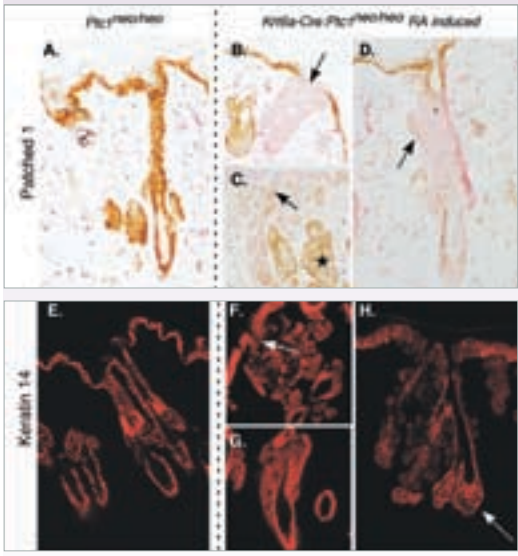
## Key Publications


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

Kunzelmann, K., Scheidt, K., Scharf, B., Ousingsawat, B., Schreiber, R., Wainwright, B., and McMorran, B. (2006). *Pseudomonas* inhibits $Na^+$ transport in airway epithelia. *FASEB Journal* **20:** 545-546.

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

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


*(Above) Loss of Patched leads directly to skin tumours.*

# DEVELOPMENTAL GENES AND HUMAN DISEASE

## Carol Wicking

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

Using genomics-based approaches we have identified a number of novel or poorly characterised genes with potential roles in embryonic development, particularly of the limb and face. For those genes of interest we are undertaking a more detailed characterisation at both the cell and whole-organism level. We employ standard cell, biological and biochemical techniques to shed light on the cellular role of these molecules, and in some cases are using transgenic or knockout approaches in the mouse to elucidate function. We are currently pursuing analysis of a protein involved in the cellular response to UV-induced DNA damage, and another that appears to regulate cell migration. Our ultimate aim is to correlate the genes we identify with human disease, and we are analysing a number of novel genes in human disease cohorts.

The Hedgehog signalling pathway is pivotal to embryonic development and is perturbed in a range of developmental anomalies as well as in several common tumours. We are further investigating the fine regulation of Hedgehog signalling at the cellular level, with particular emphasis on the receipt and transduction of the Hedgehog signal. We are also investigating the role of the Hedgehog receptor, *patched*, in limb development, based on a conditional knockout of this gene in the mouse limb.

### Research projects

- Regulation of the Hedgehog pathway by intracellular trafficking and sterol levels
- Conditional knockout of the Hedgehog receptor *patched* in the developing mouse limb
- Identification and analysis of genes regulated by the transcription factor Gli3 in the developing limb
- Identification and analysis of genes expressed in the facial primordia
- Cellular analysis of a novel regulator of cell migration in development
- Conditional mouse knockout of a novel Gli3 regulated gene expressed in the developing palate

### Key Publications


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

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

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

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

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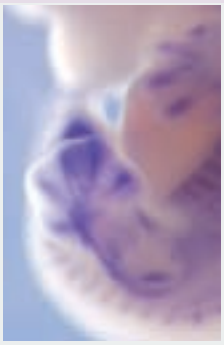
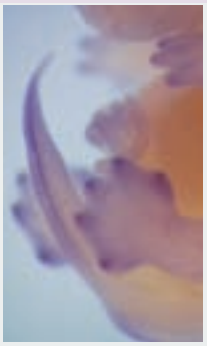
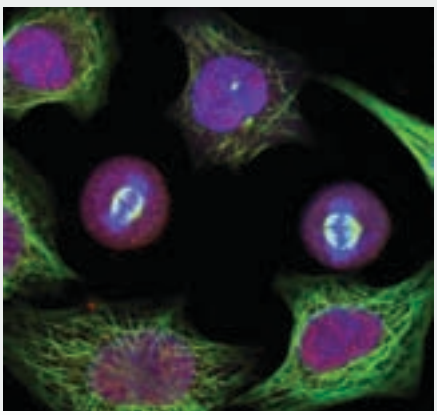
*Part of the year







*(Top Left and Right) Gene expression in the developing mouse limb as determined by whole mount* in situ *hybridisation analysis.*

*(Above) HeLa cells stained for a-tubulin (green), DAPI (blue) and a novel protein (red).*

# PLASMA MEMBRANE MICROSTRUCTURE AND SIGNAL TRANSDUCTION

## John Hancock

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

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

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

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

### Research projects

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

### Key Publications


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

Hancock, J.F. (2003). Ras proteins: Different signals from different locations. *Nature Reviews Molecular Cell Biology* **4:** 373-385.

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

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

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

Hancock, J.F., and Parton, R.G. (2005). Ras plasma membrane signalling platforms. *Biochemical Journal* **389:** 1-11.

Prior, I.A., Muncke, C., Parton, R.G., and Hancock, J.F. (2003). Direct visualisation of Ras proteins in spatially distinct cell surface microdomains. *Journal of Cell Biology* **160:** 165-170.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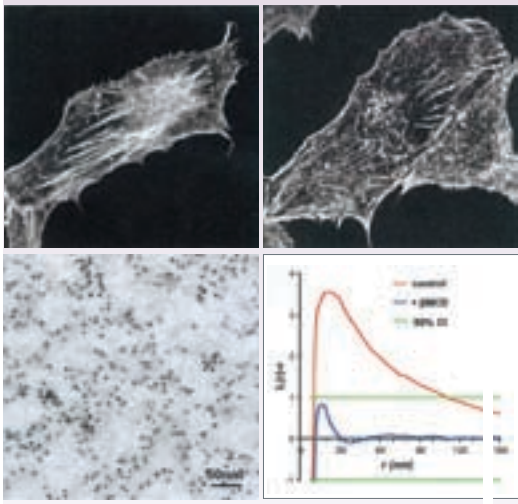

*(Top Right) Depleting plasma membrane cholesterol with the drug MCD reorganises the actin cytoskeleton: compare the control panel (top left) with a cholesterol-depleted cell.*

*(Bottom Right) Cholesterol depletion also causes the lipid raft marker protein GFP-tH, imaged on intact plasma membrane sheets by immunogold labelling (bottom left) to de-cluster: immunogold-point patterns are analysed using spatial statistics.*

# STRUCTURAL BIOLOGY OF MEMBRANE PROTEINS, MACROMOLECULAR ASSEMBLIES & VIRUSES

## Benjamin Hankamer

**Membrane proteins and macromolecular assemblies** make up a large proportion of the cellular proteome and present a rich area for structural biology. Membrane proteins account for ~20-30% of the proteome and form the responsive interface between cellular and subcellular compartments and their environment. They mediate material and information transfer, and include a wide range of protein families such as receptors, signal transducers, channel-forming proteins, active transport pumps, electron transport systems and adhesive proteins, as well as a considerable number of enzymes. Despite their importance, to date only ~100 unique, near-atomic resolution (< 4 Å) membrane protein structures have been deposited in the Protein Data Bank. This is a vanishingly small fraction of the global proteome identified to date (> 3,500,000 entries in the Protein Information Resource) and in a large part this is due to their amphipathic nature and the difficulty that this imposes on crystal production. Macromolecular assemblies (e.g. ribosome, proteosomes, spliceosomes) are also abundant in every cell. Yet, despite their importance and large copy number, the molecular details of their dynamic structural reorganisation *in vivo* are only beginning to be characterised and continue to be of intense scientific interest.

**Cryo-electron microscopy, single particle analysis and electron crystallography:** Cryo-electron microscopy has advanced rapidly to the point that it can yield membrane proteins' structures in a lipid bilayer environment to a resolution of 1.8Å (Gonen, T. *et al.* (2005). *Nature* **438**: 633-638). In the first phase of the project, state-of-the-art cryo-EM facilities at the IMB were coupled to a semi-automated single particle analysis pipeline and new template-mediated 2D crystallisation systems for high-throughput protein structure determination (see figure on right). These are facilitating the structural analysis of a whole range of important membrane proteins (e.g. photosynthetic membrane protein complexes, ATPases, mechanosensitive channels), macromolecular assemblies (AAA ATPases related proteins, ferritin and macrophage proteins), and whole viruses.

**The Solar Bio-$H_2$ project:** The structure determination of the photosynthetic complexes and ATPases is part of the Solar Bio-$H_2$ project which is focused on the development of solar-powered $H_2$ production from water. The development of zero-$CO_2$ emission fuels for the future is one of the greatest challenges facing our society. There are two main reasons for this: global oil production is increasingly reported to be close to its peak and $CO_2$ emissions from the combustion of fossil fuels are exacerbating global warming. Extensive scientific evidence now indicates that it is of the utmost importance to maintain atmospheric $CO_2$ levels below 450ppm, a target that will require the installation of a clean energy production capacity of ~11TW/yr by 2025 (current global energy demand is ~13 TW/yr). $H_2$ is considered to be one of the most promising clean fuels for the future by the US, EU and Japan. Advances in fuel cell technology, the fact that the combustion of $H_2$ produces only $H_2O$, and the potential to reduce national dependence on external petroleum reserves, all contribute to its attractiveness.

## Research projects

- Single Particle Analysis: High-resolution single-particle analysis of biological macromolecules
- Electron Crystallography: Structural analysis of membrane proteins using template-mediated crystallisation
- The Solar Bio-$H_2$ project: Solar-powered $H_2$ production from $H_2O$ using engineered green algal cells

## Key Publications


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

Landsberg, M.J., Bond, J., Gee, C.L., Martin, J.L., and Hankamer, B. (2006). A method for screening the temperature dependence of three-dimensional crystal formation. *Acta Crystallographica Section D Biological Crystallography* **62**: 559-562.

Pantelic, R., Rothnagel, R., Huang, C., Muller, D., Woolford, D., Landsberg, M., McDowall, A., Pailthorpe, B., Young, P., Banks, J., Hankamer, B., and Ericksson, G. (2006). The discriminative bilateral filter: An enhanced denoising filter for electron microscopy data. *Journal of Structural Biology* **155**: 395-408.


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Radosav Pantelic
Cameron Votan

# MACROPHAGES AND OSTEOCLASTS

## David Hume

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. Macrophages and osteoclasts are closely-related cells but have distinctly different activities. Macrophages have critical roles in regulating not only immune response but also tissue development and homeostasis, and they also contribute to the pathology of many human diseases, including chronic inflammatory diseases, atherosclerosis and cancer. Osteoclasts have specialised roles in resorbing bone and in maintaining bone and mineral homeostasis. These cells mediate the pathology of a number of bone diseases including osteoporosis.

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.

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 (LPS) and CpG-containing DNA. We adopt a systems biology approach, combining gene expression profiling, proteomics, protein-interaction and cellular imaging to infer control networks. The group collaborates closely with the RIKEN Genome Sciences Centre in Japan, and the international FANTOM consortium. 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.

### Research projects

- Development and validation of transcriptional network models to explain processes of gene regulation in macrophages on a genome-wide scale
- Characterisation of the role of macrophages in chronic inflammatory diseases, with the aim of developing novel therapeutic approaches to their treatment
- The structure and function of macrophage-specific and inducible promoters
- The function and transcriptional control of genes expressed specifically in osteoclasts
- The role of bone surface macrophages on bone remodelling and repair
- Osteoclast and macrophage activity towards a novel bone biomaterial

### Key Publications


Carninci, P., *et al.* (Hume, D.A. Joint Corresponding Author.) (2006). Genome-wide analysis of mammalian promoter architecture and evolution. *Nature Genetics* **38**: 626-635.

Himes, S.R., Sester, D.P., Cronau, S., Sasmono, T., Mulford, C., and Hume, D.A. (2006). The c-jun N-terminal kinases are important for the development and survival of macrophages. *Journal of Immunology* **176**: 2219-2228.

Carninci, P., *et al.* The FANTOM Consortium; RIKEN Genome Exploration Research Group and Genome Science Group (Genome Network Project Core Group). (Hume, D.A. cited as a core author.) (2005). The Transcriptional Landscape of the Mammalian Genome. *Science* **309**: 1559-1563.

Himes, S.R., Cronau, S., Mulford, C., and Hume, D.A. (2005). The Runx1 transcription factor controls CSF-1-dependent and -independent growth and survival of macrophages. *Oncogene* **24**: 5278-5286.

Roberts, T.L., Sweet, M.J., Hume, D.A., and Stacey, K.J. (2005). Cutting edge: species-specific TLR9-mediated recognition of CpG and non-CpG phosphorothioate-modified oligonucleotides. *Journal of Immunology* **174**: 605-608.

Sasmono, R.T., Oceandy, D., Pollard, J., Tong, W., Himes, S.R., and Hume, D.A. (2003). Definition of the mononuclear phagocyte system of the mouse using a macrophage colony-stimulating factor receptor (CSF-1R)-green fluorescent protein transgene. *Blood* **101**: 1155-1163.


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# STRUCTURE-FUNCTION STUDIES OF THE ENDOCRINE PANCREAS – COMPARATIVE STUDIES OF MOUSE & HUMAN PANCREATIC ISLET BIOLOGY

Brad Marsh

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

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

To complement our move toward an integrated or more *holistic* approach to understanding cells as examples of complex systems, we have undertaken a multi-scale/multi-resolution approach whereby we have started reconstructing entire mammalian (beta) cells in 3D at both high (≤5nm) and intermediate (15-20nm) resolutions. This work requires the parallel development and implementation of new algorithmic/mathematical tools for identifying/extracting/annotating useful structural/biological information from the data in a rapid, reliable and quantifiable manner.

Importantly, these kinds of data underpin the Visible Cell™ project based here at the IMB and the Australian Centre in Bioinformatics (ACB) at The University of Queensland. This project represents a large-scale, cross-disciplinary, multi-institutional and international e-Science initiative founded on the provision of complete sets of 3D spatio-temporal coordinates for entire mammalian cells at a range of resolutions that will uniquely inform advanced *in silico* studies of 3D cell and molecular organisation using the mammalian cell as a unitary example of an ordered complex system. Embedded within this broader research program to study and simulate mammalian molecular biology *in situ* - *in silico* - is the concept of developing the world's first navigable 'Visible Cell™ atlas': a single high-resolution map of the 3D landscape for an entire insulin-secreting pancreatic beta cell imaged and reconstructed by cellular tomography at ~40-50Å resolution. This high-resolution atlas will be complemented by a high-throughput cellular tomography pipeline for whole cells at 15-20nm resolution and parts of cells at ≤5nm under different physiological conditions/disease states, and will serve as a unique framework for protein and organelle annotation, database integration, 3D visualisation and 4D animations of cells at pseudo-molecular resolution. Such a Visible Cell™ atlas looks set to play a key role in modelling and predicting the pathophysiology of chronic diseases like diabetes and cancer.

## Research projects

Understanding how insulin granule contents are modified as the granules "mature" after exit from the Golgi complex; characterising the spatio-temporal coordinates of insulin granule interaction with the cytoskeleton *in situ* to facilitate granule exocytosis and insulin release into the bloodstream to regulate blood glucose homeostasis

The Visible Cell™ project

## Key Publications

van der Heide, P., Xu, X., Marsh, B.J., Hanein, D., and Volkmann, N. (2006). Efficient automatic noise reduction of electron tomographic reconstructions based on iterative median filtering. *Journal of Structural Biology* doi:10.1016/j.jsb.2006.10.03

Marsh, B.J. (2006). Toward a "Visible Cell"... and beyond. *Australian Biochemist* **37:** 5-10.

Marsh, B.J. (2005). Lessons from tomographic studies of the mammalian Golgi. *Biochimica et Biophysica Acta* **1744:** 273-292.

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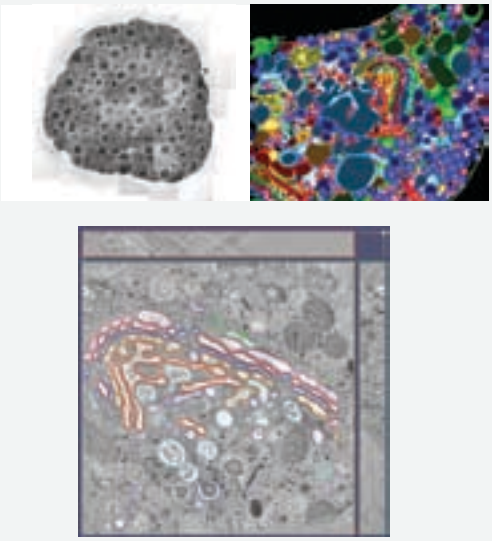
PhD Students:
Andrew Noske
Peter van der Heide

Visiting Scholar:
Zemin Pan



*(Top Left) A low magnification (2,000x) digitally-tiled overview of a thick (~350nm) section cut from a pancreatic islet isolated from a healthy adult mouse.*

*(Top Right) Model of the Golgi region in a glucose-stimulated, insulin-secreting, mouse islet beta cell reconstructed in 3D by dual-axis EM tomography.*

*(Bottom) 3D tomographic reconstruction of the Golgi region in a beta cell. Shown are views around the x, y and z axes.*

# YEAST AS A TOOL FOR UNDERSTANDING HUMAN DISEASE

Alan Munn

Yeast is widely used as a powerful experimental tool to understand complex biological processes that occur in all cells but are difficult to study in other cell types. Indeed, much of modern medicine, from cancer biology to neurobiology, has been built upon a foundation of basic knowledge provided by studies of analogous processes in yeast. There are obvious differences between yeast cells and human cells, yet as we learn more about how cells function at the molecular level it is striking how many molecular processes have been conserved. Like humans, yeast cells harbour retroviruses and prions. They secrete hormones and respond to hormones. They differentiate into distinct cell types. Moreover, they age and undergo programmed cell death. Yeast is already used extensively in the pharmaceutical industry to produce therapeutic proteins. The growing appreciation of the level of conservation of key processes between yeast and human cells has led to a rapidly-emerging second role for yeast in elucidating the mode-of-action of novel human therapeutics.

## Research projects

**1) Understanding the role of the actin cytoskeleton in health and disease**

The actin cytoskeleton is a dynamic framework of proteins that gives cells their form and is important for their ability to respond to changes in their environment. The actin cytoskeleton is implicated in a broad spectrum of human diseases, including Alzheimer's Disease, cancer, immune deficiency, and both viral and bacterial infections. Our studies in 2006 have provided the first detailed understanding of how one critical actin cytoskeletal protein functions at the molecular level. This finding provides an opportunity to test whether we can restore function to cells that are afflicted by disease.

**2) Identifying novel targets for antiviral compounds**

Viruses such as the human immunodeficiency virus (HIV) make extensive use of cellular machinery during their infective cycle, i.e. they "hijack" key host machinery and use it for their own ends. We have been investigating the regulation and function of host machinery hijacked by numerous types of viruses known as the endosomal sorting machinery. In healthy cells this machinery works at endosomes to regulate cell growth. In virus-infected cells this machinery is used to release viruses from the infected cells. Our studies have revealed targets for the design of novel anti-viral compounds.

**3) Understanding how fungal pathogens infect wheat plants**

A new collaborative project with CSIRO Division of Plant Industry commenced in 2006. The aim of this project is to understand how filamentous fungi (in particular *Fusarium graminearum*) infect wheat plants. *F. graminearum* infection not only results in severely reduced crop yields, but also contamination of the grain with fungus-produced mycotoxins that are a serious hazard to animal and human health. We have identified genes in *F. graminearum* that may represent possible targets for identification of novel anti-fungal compounds.

## Key Publications

Vajjhala, P.R., Catchpoole, E., Nguyen, C.H., Kistler, C., and Munn, A.L. (2007). Vps4 regulates a subset of protein interactions at the multivesicular endosome. *FEBS Journal* In Press.

Vajjhala, P.R., and Munn, A.L. (2007). Host Factors in Virus Budding- Insights from Yeast. *Microbiology Australia* In Press.

Wiradjaja, F., Ooms, L.M., Tahirovic, S., Kuhne, E., Munn, A.L., Piper, R., Mayinger, P., and Mitchell, C.A. (2007). PtdIns(4,5)P2 accumulates on vacuole membranes upon inactivation of the phosphoinositide phosphatases Sac1p and Inp54p. *Journal of Biological Chemistry* In Press.

Brinkworth, R., Munn, A.L., and Kobe, B. (2006). Protein kinases associated with the yeast phosphoproteome. *BMC Bioinformatics* **7:** 47.

Ren, G., Vajjhala, P., Lee, J.S., Winsor, B., and Munn, A.L. (2006). The BAR domain proteins: molding membranes in fission, fusion, and phagy. *Microbiology and Molecular Biology Reviews* **70:** 37–120.

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### Lab members

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Amber Stephens

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Elizabeth Catchpoole

Undergraduate Students:
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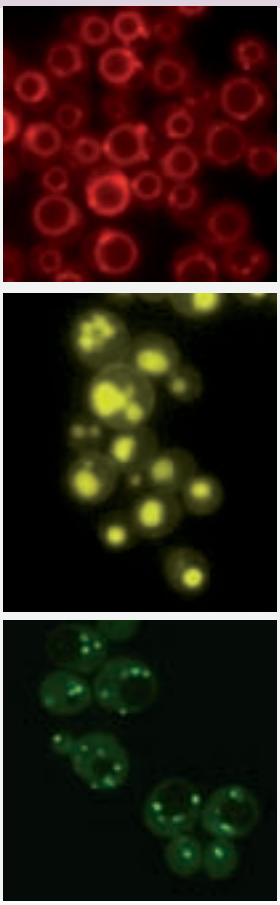

*(Top) Yeast cells labelled with the membrane-bound endocytic dye FM4-64.*

*(Middle) Yeast cells labelled with the aqueous endocytic dye Lucifer Yellow.*

*(Bottom) Yeast cells showing endosomes labelled with green fluorescent protein.*

# THE CELL SURFACE IN HEALTH AND DISEASE

## Rob Parton

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

### Research projects

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

### Key Publications


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

Hernandez-Deviez, D.J., Martin, S., Laval, S.H., Lo, H.P., Cooper, S.T., North, K.N., Bushby, K., and Parton, R.G. (2006). Aberrant dysferlin trafficking in cells lacking caveolin or expressing dystrophy mutants of caveolin-3. *Human Molecular Genetics* **15**: 129-142.

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

Martin, S., Driessen, K., Nixon, S.J., Zerial, M., and Parton, R.G. (2005). Regulated localization of Rab18 to lipid droplets: effects of lipolytic stimulation and inhibition of lipid droplet catabolism. *Journal of Biological Chemistry* **280**: 42325-42335.

Matsuo, H., Chevallier, J., Mayran, N., Le Blanc, I., Ferguson, C., Faure, J., Blanc, N.S., Matile, S., Dubochet, J., Sadoul, R., Parton, R.G., Vilbois, F., and Gruenberg, J. (2004). Role of LBPA and Alix in multivesicular liposome formation and endosome organization. *Science* **303**: 531-534.

Miaczynska, M., Christoforidis, S., Giner, A., Shevchenko, A., Uttenweiler-Joseph, S., Habermann, B., Wilm, M., Parton, R.G., and Zerial, M. (2004). APPL proteins link Rab5 to nuclear signal transduction via an endosomal compartment. *Cell* **116**: 445-456.


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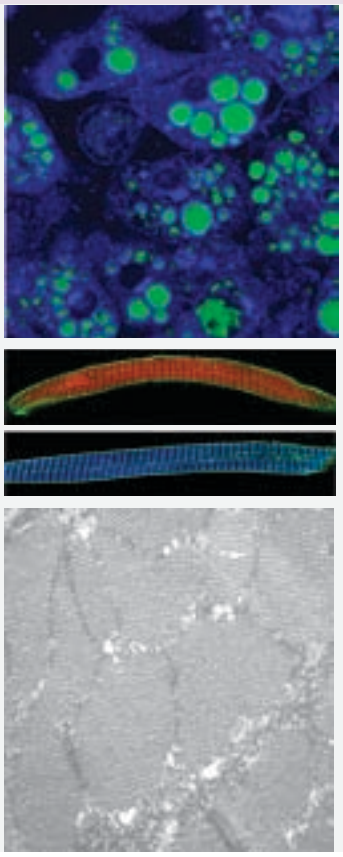
*Part of year



*(Top) Lipid droplets (green) in an adipocyte. Blue staining indicates Rab18, a small GTPase recruited to lipid droplets when lipolysis is stimulated.*

*(Middle) Expression of GFP-Cav3 in zebrafish muscle fibres (green). Red staining indicates T-tubules (upper panel) and blue indicates intracellular endogenous caveolin (lower panel).*

*(Bottom) Electron micrograph of zebrafish muscle.*

# PROTEIN TRAFFICKING IN HUMAN DISEASE

## Jennifer Stow

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

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

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

### Research projects

- Live cell imaging; fluorescence imaging and 4D computer modelling to map trafficking pathways
- E-cadherin trafficking: morphogenesis, tubulogenesis and tumorigenesis in cyst cultures
- Regulated endocytosis of E-cadherin for growth factor signalling in cancer cells
- Protein sorting and cell polarity in epithelial cells
- Trafficking and secretion of inflammatory cytokines in macrophages
- Phagocytosis in macrophages

### Key Publications


Kay, J.G., Murray, R.Z., Pagan, J.K., and Stow, J.L. (2006). Cytokine secretion via cholesterol-rich lipid raft-associated SNAREs at the phagocytic cup. *Journal of Biological Chemistry* **281**: 11949-11954.

Stow, J.L., Manderson, A.P., and Murray, R.Z. (2006). SNAREing immunity: the role of SNAREs in the immune system. *Nature Reviews Immunology* **6**: 919-929.

Bryant, D.M., Wylie, F.G., and Stow, J.L. (2005). Regulation of endocytosis, nuclear translocation, and signaling of fibroblast growth factor receptor 1 by E-cadherin. *Molecular Biology of the Cell* **16**: 14-23.

Lock, J.G., and Stow, J.L. (2005). Rab11 in recycling endosomes regulates the sorting and basolateral transport of E-cadherin. *Molecular Biology of the Cell* **16**: 1744-1755.

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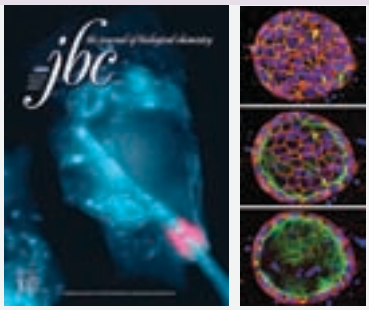


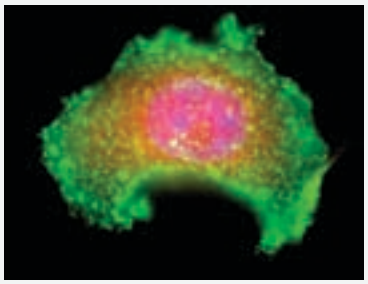

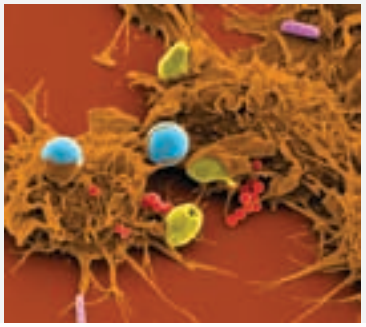

*(Right Top) JBC cover of a macrophage (left) and confocal microscopy sections through a mini-organ culture (right).*

*(Right Middle) Immunofluorescence image of E-cadherin in a breast cancer cell.*

*(Right Bottom) Scanning electromicroscopy of macrophages attacking bacteria.*

# ROLE OF GROWTH HORMONE AND RELATED CYTOKINES IN GROWTH, CANCER, METABOLISM AND OBESITY

Mike Waters

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

By creating targeted knock-in mutations to signalling domains within the GH receptor cytoplasmic domain, we have shown that enhancement of postnatal somatic growth by GH is dependent on its ability to activate the transcription factor Stat5. Because these mice become strikingly obese after 6 months of age, we are currently investigating the role of Stat5a/b in control of lipid and carbohydrate metabolism using tissue-targeted gene deletion of Stat5a/b.

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

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

## Research projects

- Mechanism of activation of growth hormone and related cytokine receptors
- Role of nuclear localised growth hormone receptor in cell proliferation and oncogenesis
- Role of GH-dependent Stat5 in lipid and carbohydrate metabolism
- Role of suppressors of cytokine signalling in prolactin and GH physiology

## Key Publications

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

Waters, M.J., Hoang, H.N., Fairlie, D.P., Pelekanos, R.P., and Brown, R.J. (2006). New insights into growth hormone action. *Journal of Molecular Endocrinology* **36**: 1-7.

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

Rowland, J.E., Lichanska, A.M., Kerr, L.M., White, M., D'Aniello, E., Maher, S.L., Brown, R.J., Teasdale, R., Noakes, P.G., and Waters, M.J. (2004). In vivo analysis of growth hormone receptor signalling domains and their associated transcripts. *Molecular and Cellular Biology* **25**: 66-77.

Wan, Y., McDevitt, A., Shen, B., Smythe, M.L., and Waters, M.J. (2004). Increased Site 1 affinity improves biopotency of porcine growth hormone: Evidence against diffusion dependent receptor dimerization. *Journal of Biological Chemistry* **279**: 44775-44784.

Jiang, J., Wang, X., He, K., Li, X., Chen, C-M., Sayeski, P.P., Waters, M.J., and Frank, S.J. (2004). A conformationally sensitive GHR antibody: impact on GH signaling and GHR proteolysis. *Molecular Endocrinology* **18**: 2981-2996.

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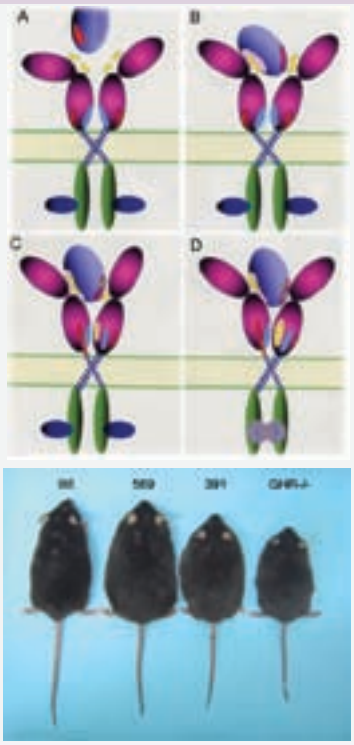
Carolyn Nelson



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

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

# CADHERIN ADHESION AND TISSUE ORGANISATION: MOLECULAR MECHANISMS AND MORPHOGENETIC CONSEQUENCES

## Alpha Yap

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

By understanding the basic biological mechanisms of cadherin-mediated cell recognition we thus hope to provide vital insights into the basis of developmental patterning and common human diseases. Currently we focus on understanding how cadherins cooperate with the actin cytoskeleton, long believed to be central to cadherin function. Our experience makes it increasingly clear that this cooperation involves a complex interplay between adhesion receptors and diverse distinct states of the cytoskeleton that are coordinated by a variety of signalling pathways at the cell membrane.

### Research projects

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

### Key Publications


Scott, J.A., Shewan, A.M., den Elzen, N.R., Loureiro, J.J., Gertler, F.B., and Yap, A.S. (2006). Ena/VASP proteins critically determine distinct modes of actin organization that can coexist at cadherin adhesive contacts. *Molecular Biology of the Cell* **17**: 1085-1095.

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

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

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

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

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


### Lab members

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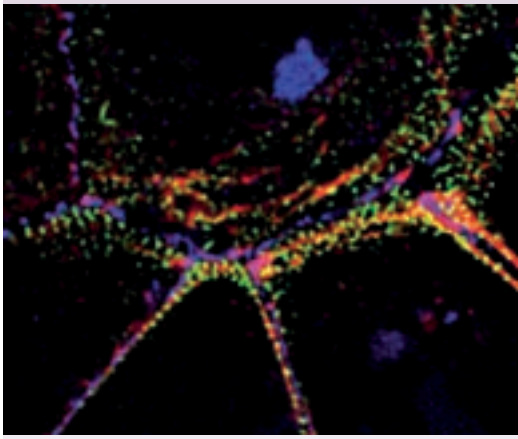

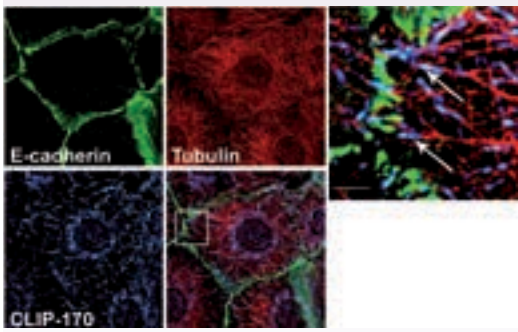


*(Top) Myosin II (green) accumulates with actin filaments (red) at E-cadherin cell-cell adhesions (blue).*

*(Bottom) Microtubules (red) decorated at the ends with CLIP170 (blue) extend into E-cadherin adhesions (green).*

# DESIGN AND DISCOVERY OF BIOACTIVE PEPTIDES AND PROTEINS

## Paul Alewood

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

### Research projects

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

### Key Publications


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

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

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

Hogg, R.C., Hopping, G., Adams, D.J., Alewood, P.F., and Bertand, D. (2003). Alpha conotoxins PnIA and [A10L]PnIA stabilize different states of the alpha7 L247T nicotinic acetylcholine receptor. *Journal of Biological Chemistry* **278**: 26908-26914.

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


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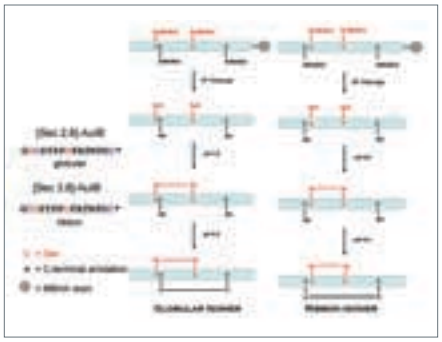
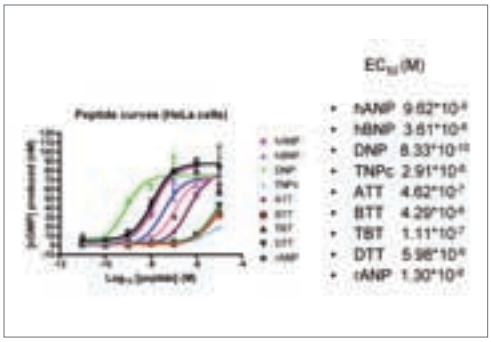
Corinna Voll
Angelika Christ







*(Above) Exploring nature's laboratory.*

*(Far left) Direct synthesis of alpha-conotoxin selenocysteine isomers.*

*(Left) Potency of designed and native natriuretic peptides.*

# AUSTRALIAN BIODISCOVERY: BIOACTIVES FROM BIODIVERSITY

## Robert Capon

The Centre for Molecular Biodiversity (CMB) is a thematic research unit within the IMB, with a mission to explore the chemical potential of Australian biodiversity (marine and terrestrial, plants, animals and microbes) to discover and develop valuable molecular products with applications in the fields of human and animal health, crop protection, and basic science. As specialists in the detection, isolation, structure elucidation and synthetic manipulation of naturally-occurring bioactive molecules, CMB is well equipped with modern chromatographic and spectroscopic instrumentation, and has developed effective protocols to streamline the biodiscovery process. We work in close collaboration with colleagues across academia, industry and government, to identify and address key areas of opportunity and need, and to assemble focused research teams with complementary expertise and infrastructure. Areas of research currently under investigation include the discovery and development of next-generation antibacterials, antiparasitics, antivirals and anticancer agents, as well as therapeutics to treat neurodegenerative diseases and pain. In addition to pharmaceutical objectives, with support from the Queensland Government we are actively researching molecular solutions to the control of cane toads in Australia.

### Research projects

- Anticancer agents from Australian marine biodiversity
- Microbial biodiscovery @ IMB
- Australian marine biodiversity as a source of new drugs to control neurodegenerative disease
- Novel sodium ion channel modulators from Australian cephalopods
- Inhibitors of host proteins as a new paradigm for controlling viral replication
- Controlling bacterial infection by inhibiting key virulence determinants
- New antiparasitics with application in animal health
- Toad busting: discovering a molecular solution to control cane toads

### Key Publications


Provisional Patent 20006900980 - Polyketide xanthones and uses thereof. 2006

Capon, R.J., Hayes, R.A., and Grigg, G.C. (2006). In Cane toad chemical ecology: getting to know your enemy., Cane Toad Workshop, Brisbane, **2006** accepted.

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

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

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

Miller, R.E., Stewart, M., Woodrow, I.E., and Capon, R.J. (2006). A galloylated cyanogenic glycoside from the Australian endemic rainforest tree *Elaecarpus sericopetalus* (Elaeocarpaceae). *Phytochemistry* **67**: 1365-1371.

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

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


### Lab members

Senior Research Officer:
Dr. Frank Fontaine

Research Officers:
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Dr Ertong Wang
Dr. Xin Liu
Dr Cedric Dooms
Dr. Hua Zhang
Dr. Andrew Hayes

Administrative Assistant:
Nadine Coleman

PhD Students:
Ranjala Ratnayake
Leith Fremlin
Mohamed El-Naggar

*(Above) HPLC installation.*

# NMR AND PROTEIN STRUCTURE IN DRUG DESIGN

David Craik

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

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

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

## Research projects

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

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

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

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

## Key Publications

Craik, D.J. (2006). Seamless proteins tie up their loose ends. *Science* **311**: 1563-1564.

Craik, D.J., Cemazar, M., and Daly, N.L. (2006). The cyclotides and related macrocyclic peptides as scaffolds in drug design. *Current Opinion in Drug Discovery and Development* **9**: 251-260.

Mulvenna, J.P., Bharathi, R., Mylne, J.S., Burton, R.A., Shirley, N.J., Fincher, G.B., Anderson, M.A., and Craik, D.J. (2006). Discovery of cyclotide-like protein sequences in graminaceous crop plants: Ancestral precursors of circular proteins? *The Plant Cell* **18**: 2134-2144.

Rosengren, K.J., Lin, F., Bathgate, R.A.D., Tregear, G.W., Daly, N.L., Wade, J.D., and Craik, D.J. (2006). Solution structure and novel insights into the determinants of the receptor specificity of human relaxin-3. *Journal of Biological Chemistry* **281**: 5845-5851.

Clark, R.J., Fischer, H., Dempster, L., Daly, N.L., Rosengren, K.J., Nevin, S.T., Meunier, F.A., Adams, D.J., and Craik, D.J. (2005). Engineering stable peptide toxins by means of backbone cyclisation: Stabilization of the conotoxin MII. *Proceedings of the National Academy of Sciences USA* **102**: 13767-13772.

Simonsen, S.M., Sando, L., Ireland, D.C., Colgrave, M.L., Bharathi, R., Göransson, U., and Craik, D.J. (2005). A continent of plant defense peptide diversity: Cyclotides in Australian Hybanthus (Violaceae). *The Plant Cell* **17**: 3176-3189.

### Lab members

Senior Research Officers:
Dr. Richard Clark, Dr. Michele Colgrave, Dr. Norelle Daly, Dr. Justine Hill, Dr. Ute Marx

Research Officers:
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Undergraduate Students:
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*(Right Top) David Craik with the recently installed 900MHz NMR spectrometer at IMB, which is the centrepiece of the Queensland NMR Network. The instrument is the largest NMR spectrometer in the Southern Hemisphere and is being used for a range of drug design studies.*

*(Right Bottom) PhD students Christian Gruber, Kathryn Greenwood and research assistant Rekha Bharathi join group leader David Craik and local botanists on field work in equatorial Africa.*

# CHEMISTRY AND HUMAN THERAPEUTICS

## David Fairlie

We work at the interface of chemistry, biology and disease. Chemistry researchers in our group study computer-assisted molecular and drug design, solid & solution-phase organic synthesis, structure determination using NMR techniques, and bioassays for ligand-protein interactions. We use rational chemical intervention to inhibit enzymes, antagonise receptors, or mimic proteins that are pivotal in normal human physiology, aberrant in human disease, or crucial mediators of infection. Outcomes include new drug leads, new knowledge of molecular recognition, and new chemistry. Biology researchers in our group use novel compounds to interrogate cellular processes, inhibit enzymes, block or mimic protein-protein interactions, and to unravel mechanisms of protein activation, biological and physiological processes, disease development, and drug action. Researchers gain interdisciplinary skills and knowledge in diverse fields including enzymology, biochemistry, cell biology, immunology, pharmacology, neurobiology, oncology, virology and parasitology. We aim to better understand the biological roles of proteins in life, ageing, disease and death.

### Research projects

- Chemical synthesis (organic, medicinal, inorganic, biological)
- Drug design using computers, structure determination using NMR spectroscopy
- Enzyme inhibition, cell activation, molecular pharmacology
- Protein surface mimics
- Disease mechanisms & drug action for inflammatory disorders, viral and parasitic infections, cancers, and neurodegenerative diseases

### Key Publications


Chappell, K.J., Nall, T., Stoermer, M.J., Fang, N.-X., Tyndall, J.D.A., Fairlie, D.P., and Young, P.Y. (2005). Site-directed Mutagenesis and Kinetic Studies of the West Nile Virus NS3 Protease Identify Key Enzyme-Substrate Interactions. *Journal of Biological Chemistry* **280**: 2896-2903.

Shepherd, N.E., Hoang, H.N., Abbenante, G., and Fairlie, D.P. (2005). Single Turn Alpha Helical Peptides With Exceptional Stability In Water. *Journal of the American Chemical Society* **127**: 2974-2983.

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

Tyndall, J.D.A., Pfeiffer, B., Abbenante, G., and Fairlie, D.P. (2005). Over 100 Peptide-Activated G Protein-Coupled Receptors Recognize Ligands with Turn Structure. *Chemical Reviews* **105**: 793-826.

Glenn, M.P., Kahnberg, P., Boyle, G.M., Hansford, K.A., Hans, D., Martyn, A.C., Parsons, G.P., and Fairlie, D.P. (2004). Anti-Proliferative And Phenotype-Transforming Antitumor Agents Derived From Cysteine. *Journal of Medicinal Chemistry* **47**: 2984-2994.

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


### Lab members

Senior Researcher Officers:
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Research Officers:
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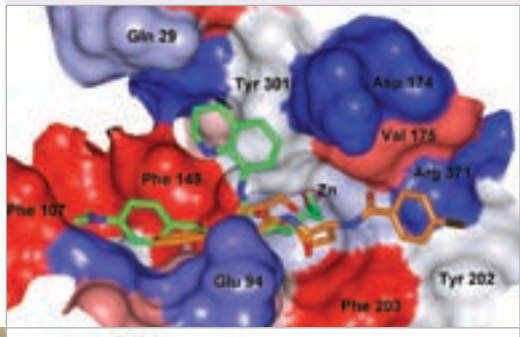
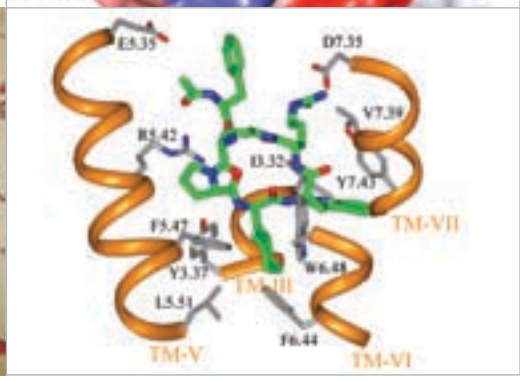
Masters Student:
Praveer Gupta

Honours Students:
Heng Boon Low, WeiJun Xu

Occupational Trainee:
Eric Letouze

Undergraduate Students:
Jasmine Davis, David Eviston




*Top Far Right: Human histone deacetylase bound to novel anticancer inhibitors.*
*Bottom Far Right: Human C5a receptor bound to novel anti-inflammatory antagonist.*
*Right: Human MM96L melanoma cells treated with novel differentiating drug.*

# MOLECULAR PHARMACOLOGY OF TOXINS

## Richard Lewis

My group's research focuses on the discovery and characterisation of conotoxins produced in the venom duct of the predatory cone snail. These highly-structured peptides (mini-proteins) act at ion channels, receptors and transporters found in the membranes of most cells, especially cells of the nervous system. Conopeptides make exquisite molecular tools, with some being developed as novel treatments for chronic diseases. A major focus of the group is to discover new protein targets and develop peptides able to act at these targets to reduce pain sensation. This research involves assay-guided isolation of venom peptides, peptide synthesis, tissue pharmacology, radioligand binding and electrophysiological studies, peptide structure elucidation by NMR, receptor mutagenesis, modelling, and finally docking simulations of the peptide target interaction. Several of the group's discoveries are being commercially developed. Currently, AMRAD is developing AM336 (ωC-CVID) for chronic pain and Xenome Ltd is developing Xen2174 (an analogue of χ-MrIA) for chronic neuropathic and cancer pain. High-content screening approaches will be introduced into the program in 2007 with the acquisition of a BD Pathway 855.

### Research projects

- Discovery of conopeptides useful in the treatment of pain (NHMRC)
- Determining sites of conotoxin action at the $\alpha_1$1-adrenoceptor and noradrenaline transporter (NHMRC)
- Interactions of conotoxins at nicotinic acetylcholine receptors, and calcium and sodium channels (NHMRC)
- Identification of novel anti-cancer agents from marine biodiversity (ARC)
- Identification and characterisation of novel sodium channel toxins in squid and octopus (ARC)
- Discovery and characterisation of novel bioactives using high-content screening

### Key Publications


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

Lewis, R.J., Schroeder, C.I., Ekberg, J., Nielsen, K.J., Loughnan, M., Thomas, L., Adams, D.A., Drinkwater, R., Adams, D.J., and Alewood, P.F. (2006). Isolation and structure-activity of mu-conotoxin TIIIA, a potent inhibitor of TTX-sensitive voltage-gated sodium channels. *Molecular Pharmacology* **71**: 676-685.

Loughnan, M., Nicke, A., Jones, A., Schroeder, C.I., Nevin, S.T., Adams, D.J., Alewood, D.J., and Lewis, R.J. (2006). Identification of a novel class of nicotinic receptor antagonists: dimeric conotoxins VxXIIA, VxXIIB and VxXIIC from *Conus vexillum*. *Journal of Biological Chemistry* **281**: 24745-24755.

Dutertre, S., Nicke, A., and Lewis, R.J. (2005). ß2 subunit contribution of 4/7 ß-conotoxin binding to the nicotinic acetylcholine receptor. *Journal of Biological Chemistry* **280**: 30460-30468.

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

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


### Lab members

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Dr. Aijun Yang
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Thea Monks

PhD Students:
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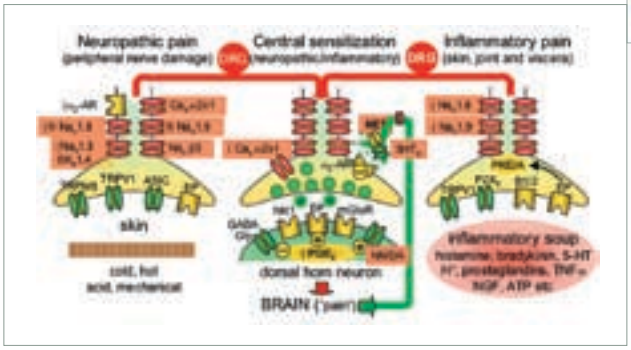
Claudia Zapata
Christina Yan


*(Above) Venomous species yield peptides with clinical potential.*

*(Left) Conotoxins inhibit pain at a diverse range of targets in ascending excitatory and descending inhibitory pathways.*

# PROTEIN STRUCTURE AND DRUG DESIGN

## Jenny Martin

We are interested in understanding the role of proteins in disease and in developing novel chemicals to modify the functions of disease-causing proteins. We use a range of biochemical and biophysical techniques to investigate the structure, function and interactions of proteins, with a particular emphasis on high-throughput protein crystallography and structure-based approaches for inhibitor design.

Achieving complementary shapes is a fundamental principle of enzyme inhibitor design. Our work on the enzyme PNMT (phenylethanolamine N-methyltransferase), that catalyses adrenaline biosynthesis, showed that it has a cryptic binding site that is not revealed until large substituted inhibitors are bound. These large inhibitors are not complementary in shape to the previously defined binding site in that they protrude through the accessible surface, yet they are potent inhibitors of the enzyme. In collaboration with Prof. Grunewald in Kansas and Dr. Michael McLeish in Michigan, we found, using protein crystallography, that the volume of the active site doubles upon the binding of the large inhibitors. The energetic cost of the conformational changes to accommodate the large inhibitors is modest, estimated by kinetic analyses at 2-3 kcal/mol. These findings have important implications for protein dynamics studies and for understanding the energetics of enzyme catalysis and protein flexibility. For drug discovery studies such as *in silico* screening, the results underline the necessity of including significant enzyme flexibility.

We have made significant advances in our understanding of the regulation of SNARE proteins involved in insulin-stimulated trafficking of the GLUT4 glucose transporter. This process, which is critical to the regulation of blood glucose levels, is affected in Type II Diabetes. Our recent results, in collaboration with Prof. David James (Garvan Institute), show that the Sec/Munc (SM) protein Munc18c binds to a short N-terminal region of the SNARE syntaxin4 protein, and that this interaction positively regulates the formation of SNARE ternary complex thereby promoting vesicle trafficking (Latham *et al.* 2006). These findings are in direct contrast to the highly homologous synaptic SNARE protein system, for which the homologous Munc18 protein has been reported to play a negative regulatory role.

## Research projects

- Structure, Function and Inhibition of Transferase Enzymes involved in disease
- Structure, Function and Interactions of SNARE proteins associated with insulin action
- Structure, Function and Inhibition of Redox Folding Factors involved in disease
- Novel inflammation drug targets using high-throughput structure approaches

## Key Publications


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

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

Aagaard, A., Listwan, P., Cowieson, N., Huber, T., Ravasi, T., Wells, C., Flanagan, J.U., Kellie, S., Hume, D.A., Kobe, B., and Martin, J.L. (2005). An inflammatory role for the mammalian carboxypeptidase inhibitor latexin: relationship to cystatins and the tumour suppressor TIG1. *Structure* **13**: 309–317.

Cowieson, N.P., Listwan, P., Kurz, M., Aagaard, A., Ravasi, T., Wells, C., Huber, T., Hume, D.A., Kobe, B., and Martin, J.L. (2005). Pilot studies on the parallel production of soluble mouse proteins in a bacterial expression system. *Journal of Structural and Functional Genomics* **6**: 13-20.

Heras, B., Edeling, M.A., Schirra, H.J., Raina, S., and Martin, J.L. (2004). Crystal structures of the DsbG disulfide isomerase reveals an unstable disulfide. *Proceedings of the National Academy of Sciences USA* **101**: 8876-8881.

Martin, J.L., and McMillan, F.M. (2002). SAM (dependent) I AM; The S-adenosyl methionine dependent methyltransferase fold. *Current Opinion in Structural Biology* **12**: 783-793.


### Lab members

Senior Research Officers:
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Research Officers:
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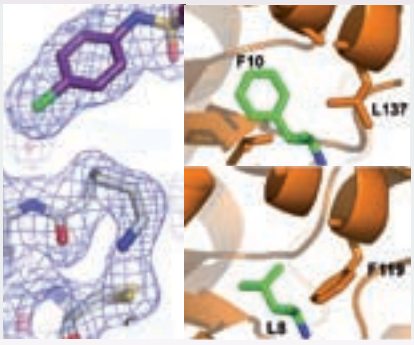
Research Assistant:
Russell Jarrott

Masters Student:
Kai-En Chen

Honours Student:
Arief Mulyadi

Undergraduate Student:
Andrew Fahey

Visitor:
Natalie Saez




*(Left) An unusual and conformationally unfavourable Lys-Cys interaction, observed in the crystal structure of a PNMT:inhibitor complex, enables large inhibitors to bind at the active site.*

*(Right Top) Close-up of the interaction between a yeast SM protein and its cognate syntaxin from the crystal structure of yeast Sly1p:Sed5p (Bracher and Weissenhorn (2002).* EMBO Journal **21**:*6114-24).*

*(Right Bottom) A model, based on this crystal structure, of the equivalent interaction for Munc18c:Syntaxin4. Note that the interaction in both cases involves Phe and Leu side chains, but that the residues are reversed (Latham* et al. *2006).*

# COMBINATORIAL CHEMISTRY AND MOLECULAR DESIGN

## Mark Smythe

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

Given a pharmaceutical industry that is currently categorised by a decrease in discovery of new chemical entities and escalating costs of research and development, approaches that improve the efficiencies of drug discovery are desperately required.

The industry has been biased by a trend that is focused on sampling increasingly narrow regions of well-trodden chemical structure space, at the expense of searching for new chemical structure space with biological relevance. This is pertinent given the almost infinite size of the chemical universe and that biologically-relevant space would appear to be small islands within this space. This leads to inefficient drug discovery that is plaguing the pharmaceutical sector.

Using a combination of mathematics, software development, drug design and combinatorial chemistry, we are developing new approaches to identify these islands of biologically-relevant chemistries. Arrays of compounds are then synthesised using combinatorial chemistry approaches and resulting compounds are screened in various biological assays to identify new drug candidates and to validate a new discovery paradigm.

### Research projects

- Exploitation of biologically-relevant scaffolds
- Improving the efficiency of drug discovery
- The development of new computational algorithms and strategies for sampling biologically-relevant chemistries
- The development of synthetic process for the combinatorial synthesis of biologically-relevant compounds
- The development of *in vitro* and cell-based assays for screening arrays of compounds
- The development of antipathogenic compounds to treat microbial infections. Such strategies do not kill microbes but arrest infection and should lead to less resistance
- Exploiting the scaffold nature of natural products in discovery

### Key Publications


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

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

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

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

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


### Lab members

Senior Research Officer:
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Christina Kulis

PhD Students:
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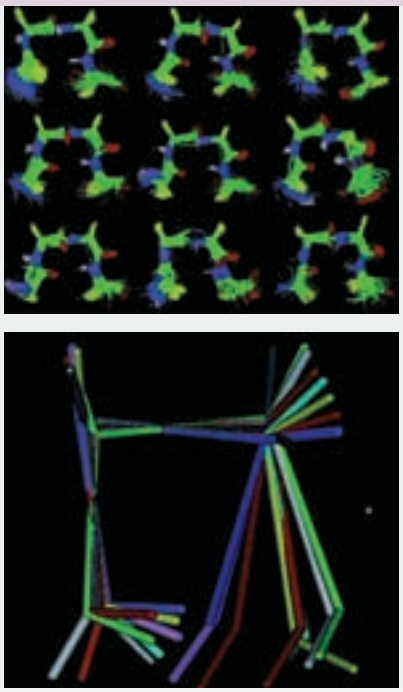
Andrew McDevitt



*ß-turns are important topological motifs for biological recognition of proteins and peptides. Nine clusters represent the topology of the side chain scaffold architecture of the vast majority of ß-turns.*
*(Top) The ß-turns within each of the nine clusters are superimposed onto the cluster's mean structure. The colouring schemes are: N: blue, O: red, H: white, C: green and $C_{\beta}$: yellow.*
*(Bottom) Superimposition of the mean structures of the nine clusters. The superimposition is based on the three atoms $C_{\alpha}1$, $C_{\alpha}2$ and $C_{\alpha}3$. The colour code for each cluster is: 1-magenta, 2-red, 3-yellow, 4-green, 5-orange, 6-dark blue, 7-white, 8-light blue and 9-grey.*

# MODELLING AND VISUALISING CELLULAR PROCESSES

## Kevin Burrage

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

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

### Research projects

- Developing new Monte-Carlo Simulation techniques in conjunction with the group of John Hancock that allow us to model the behaviour of lipid rafts and to investigate the effects of anomalous diffusion
- Modelling the effects of transcriptional and translational delays in the Hes1 gene in Mouse to produce models that are more accurate than extant models
- Developing models for quorum sensing that describe bi-modal populations effects better than previous deterministic models

### Key Publications


Barrio, M., Burrage, K., Leier, A., and Tian, T. (2006). Oscillatory Regulation of Hes1: Discrete Stochastic Delay Modelling and Simulation. *PLoS Computational Biology* **2**: 1017-1030.

Nicolau Jr., D., Burrage, K., Parton, R.G., and Hancock, J. (2006). Identifying Lipid Raft Characteristics required to promote nanoscale protein-protein interactions on the plasma membrane. *Molecular and Cellular Biology* **26**: 313-323.

Song, J., Wang, M., and Burrage, K. (2006). Exploring synonymous codon usage preferences of disulfide-bonded and non-disulfide bonded cysteines in the *E. coli* genome. *Journal of Theoretical Biology* **241**: 390-401.

Tian, T., and Burrage, K. (2006). Stochastic models for regulatory networks of the genetic toggle switch. *Proceedings of the National Academy of Sciences USA* **103**: 8372-8377.

Burrage, K., and Burrage, P.M. (2004). Numerical methods for strong solutions of stochastic differential equations: an overview. *Proceedings of the Royal Society of London Series A* **460**: 373-402.

Burrage, K., Tian, T., and Burrage, P. (2004). A multi-scaled approach for Chemical Reaction Systems Modelling Cellular and Tissue Function. *Progress in Biophysics and Molecular Biology* **85**: 217-234.

Tian, T., and Burrage, K. (2004). Binomial leap methods for simulating stochastic chemical kinetics. *Journal of Chemical Physics* **121**: 10356-10364.

Tian, T., and Burrage, K. (2004). Bistability and switching in the lysis lsogeny genetic regulatory network of Bacteriophage lambda. *Journal of Theoretical Biology* **227**: 229-237.

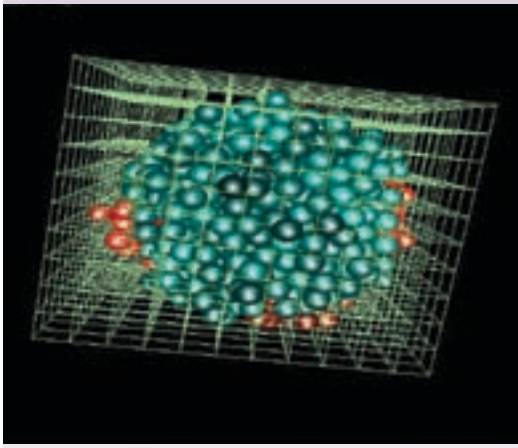
Turner, T.E., Schnell, S., and Burrage, K. (2004). Stochastic approaches for modelling *in vivo* reactions. *Computational Biology and Chemistry* **28**: 165-178.

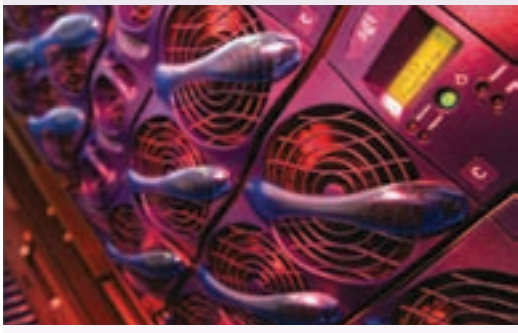
Croft, L., Schando, S., Clark, F., Burrage, K., Actander, P., and Mattick, J.S. (2000). ISIS: the intron information system reveals the frequency of alternative splicing in the human genome. *Nature Genetics* **24**: 340-341.


### Lab members

Research Officers:
Dr. Tianhai Tian
Dr. Nick Hamilton
Dr. Andre Leier
Dr. Jiangning Song
Dr. Tatiana Marquez Lago

PhD Students:
Daniel Nicolau Jr.
Shevarl McNamara
Farah Abdullah





*(Top) 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.*

*(Bottom) SGI Origin supercomputer.*

# COMPUTATIONAL NEUROSCIENCE

## Geoff Goodhill

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

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

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

### Lab members

Senior Research Officer:
Dr. William Rosoff

Research Officers:
Dr. Zac Pujic
Dr. David Smith
Dr. Julia Feldner

Research Assistants:
Clare Giacomantonio

PhD Student:
Duncan Mortimer
Jonathan Hunt

## Research projects

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

## Key Publications


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

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

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

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

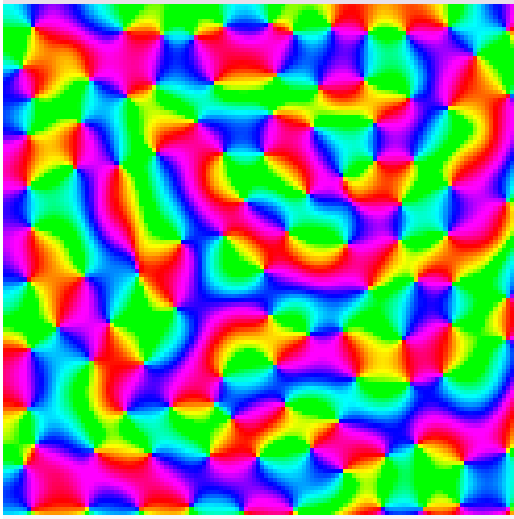
Carreira-Perpinan, M.A., and Goodhill, G.J. (2004). The influence of lateral connections on the structure of cortical maps. *Journal of Neurophysiology* **92**: 2947-2959.

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

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

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

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

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

# MOLECULAR DYNAMICS OF BIOMOLECULAR SYSTEMS

Alan Mark

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

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

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

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

## Research projects

- Protein and peptide folding
- Simulation of membrane-protein interactions
- Modelling the nucleation and growth of amyloid fibrils
- Atomic simulation of self-organisation in biomolecular systems

## Key Publications

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

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

Fan, H., and Mark, A.E. (2004). Mimicking the Action of Folding Chaperones in Molecular dynamics Simulations: Application to the Refinement of Homology Based Protein Structures. *Protein Science* **13**: 992-999.

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

Marrink, S.J., and Mark, A.E. (2003). Molecular dynamics simulation of the formation, structure, and dynamics of small phospholipid vesicles. *Journal of the American Chemical Society* **125**: 15233-15242.

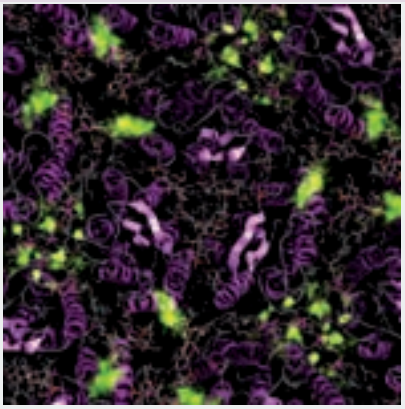
### Lab members

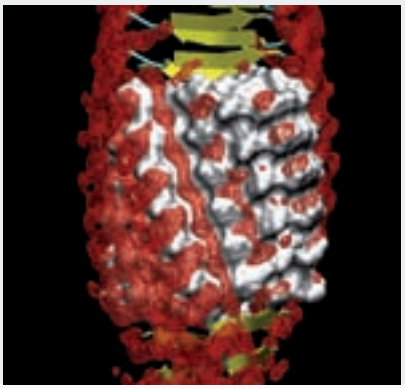
Research Officers:
Dr. David Poger (UQ), Dr. Itamar Kass (UQ), Dr. Xavier Periole (RUG), Dr. Aldo Rampioni (RUG)

Research Assistant:
Dr. In-Keun Oh (UQ)

Administration:
Kim Nguyen (UQ)

PhD Students:
Matthew Breeze (UQ), Ajinkya Joshi Daniela Mueller (RUG), Ying Xue (RUG), Magdelena Siwko (RUG), Tsjerk Wassenaar (RUG), Fan Hao (RUG), Hari Leontiadou (RUG), Jelger Risselada (RUG)





*(Top) A model of part of the light-harvesting purple membrane. Locations where $Ca^{+2}$ ions are predicted to bind preferentially to the central Bacteriorhodopsin molecule are highlighted (yellow).*

*(Bottom) A model for the cross-beta structure of the amyloid fibril-forming peptide GNNQQNY showing the ordering of water observed in molecular dynamics simulations.*

# CELL AND MOLECULAR ARCHITECTURE

## Alasdair McDowall

Our research group investigates biological structures using cryotechniques, in particular, high-pressure freezing or cryo-sectioning vitreous bulk material. Cryo-electron microscopy (cryo-EM) involves cutting cells into ultra-thin 40nm–200nm-thick sections, and cryo-EM observation of the perfectly preserved details is a goal favoured in current structural biology. In collaboration with the IMB group of A. Prof. Ben Hankamer, we are using high-pressure freezing and cryosectioning to investigate bulk structure systems of chloroplast organelles in high hydrogen-producing green algae, *C. reinhardtii.*

In this research field, electron microscopy of high-pressure frozen, freeze-substituted sections demonstrates full potential when combined with computerised electron tomography and 3-D reconstruction of organelles. In brief, our work here has provided new structural information on the *C. reinhardtii* organism and the high $H_2$-producing mutant Stm6. The data collected supports more recent claims that the thylakoid membrane of the WT only has stroma lamellae. Another finding is the close relationship between the mitochondria and the chloroplast when undergoing the circadian regulation. Structural comparisons between the Stm6 mutant and the WT show significant variation between the two organisms. Under temporal lighting conditions, the grana lamellae stacking adapts in a similar manner to higher plants. Other variations seen are in the locations of the Stm6 mitochondria, which are found along the perimeter following of the cell wall. This is opposed to the WT's mitochondria being placed centrally within the cell. See figures.

We are also using cryo-electron microscopy together with thin film (<1000nm) cryopreparations to investigate whole-cell and isolated plasma membrane protein packing arrangements in collaboration with the IMB group of Prof. Parton.

The IMB electron microscopy (EM) suite is supported through UQ's Centre of Microscopy and Microanalysis (CMM). This facility is a Commonwealth-funded Major National Research Facility, a node of the national Nanostructural Analysis Network Organisation.

The Advanced Cryo-electron Microscopy Facility promotes the techniques of single-particle 3D reconstruction, protein electron crystallography and cryo-electron tomography (CET). The facility specialises in investigating the architecture of cellular organelles and molecular complexes by rapid freezing, or vitrification of structures followed by (for bulk samples) ultra-thin sectioning and electron imaging of frozen hydrated sections (CEMOVIS). This technique reveals fascinating ultrastructural detail from native cells and is posing a new image for biology.

In addition, the Facility, as a node of the Nanostructural Network Analysis Organisation in Australia, has hosted a number of research projects from around Australia and overseas; the NANO report for 2006 may be downloaded at http://www.nano.org.au/ar.htm

### Research projects

- Electron microscopy of cellular organelles and complexes
- The Visible Cell Project

### Key Publications


Finnigan, B., Halley, P., Jack, K., McDowall, A., Truss, R., Casey, P., Knott, R., and Martin, D. (2006). Effect of the Average Soft-Segment Length on the Morphology and Properties of Segmented Polyurethane Nanocomposites. *Journal of Applied Polymer Science* **102**: 128-139.

Hodge, D., Coghill, E., Keys, J., Maguire, T., Hartmann, B., McDowall, A., Weiss, M., Grimmond, S., and Perkins, A. (2006). A global role for EKLF in definitive and primitive erythropoiesis. *Blood* **107**: 3359-3370.

Pantelic, R.S., Rothnagel, R., Huang, C-Y., Muller, D., Woolford, D., Landsberg, M.J., Marsh, B., McDowall, A., Pailthorpe, B., Young, P., Banks, J., Hankamer, B., and Ericksson, G. (2006). *Journal of Structural Biology* **155:** 395-408.

Fong, C., Krodkiewska, I., Wells, D., Boyd, B.J., Booth, J., Bhargava, S., McDowall, A., and Hartley, P.G. (2005). Submicron Dispersions of Hexosomes based on Novel Glycerate Surfactants. *Australian Journal of Chemistry* **58**: 683-687.

Al-Amoudi, A., Chang, J-J., Leforestier, A., McDowall, A., Michel Salamin, L., Norlén, L.P.O., Richter, K., Sartori Blanc, N., Studer, D., and Dubochet, J. (2004). Cryo-electron microscopy of vitreous sections. *EMBO Journal* **23**: 3583-3588.


### Lab members

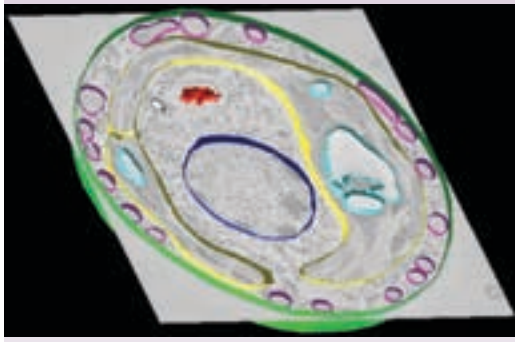
Research Officer:
Dr. Jamie Riches

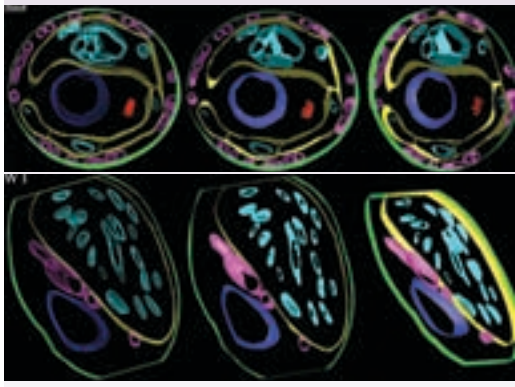
Research Assistants:
Robyn Webb (Part time),
Wendy Armstrong (Part time)

Honours Student: Alexander Foo

Undergraduate Students:
Robyn Kaye, Emily Knauth

Administrative Officer:
Kay Hodge





*(Top) Tomographic overlay image of* C. reinhardtii *mutant Stm6 green algae, high-pressure frozen, 350nm sectioned and imaged at 300keV in the cryoelectron microscope. The fine membrane chloroplast structure (yellow) contrasts the starch granules (light blue), mitochondria (purple), nucleus (blue) and golgi (red).*

*(Bottom) Segmentation, contour modelling and volume rendering of* C. reinhardtii *WT and Stm6 tomograms at a magnification of 9,400x. The colours depict the structures: green outlines the cell wall, yellow: chloroplast, light blue: starch granules, dark blue: nucleus, purple: mitochondria, and red is the golgi. Note the association and location of organelles.*

# APPLIED STATISTICS AND BIOINFORMATICS

## Geoff McLachlan

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

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

### Lab members

Research Officers:
Dr. Richard Bean
Dr. Liat Jones
Dr. Kui Wang

PhD Students:
Soong Chang
Justin Zhu
Katrina Monico

## Research projects

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

## Key Publications


Ambroise, C., and McLachlan, G.J. (2002). Selection bias in gene extraction on the basis of microarray gene expression data. *Proceedings of the National Academy of Sciences USA* **99**: 6562-6566.

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

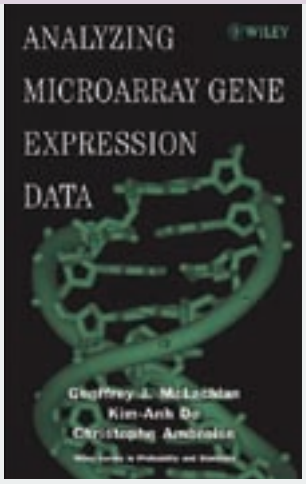
McLachlan, G.J., Do, K-A., and Ambroise, C. (2004). Analysing Microarray Gene Expression Data. Hoboken, New Jersey: Wiley.

McLachlan, G.J., and Khan, N. (2004). On a resampling approach for tests on the number of clusters with mixture model-based clustering of tissue samples. *Journal of Multivariate Analysis* **90**: 90-105.

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

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

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



*Books Geoffrey McLachlan has written or contributed to: (Top) "Analyzing Microarray Gene Expression Data" and (Above) "Methods of Microarray Data Analysis IV".*

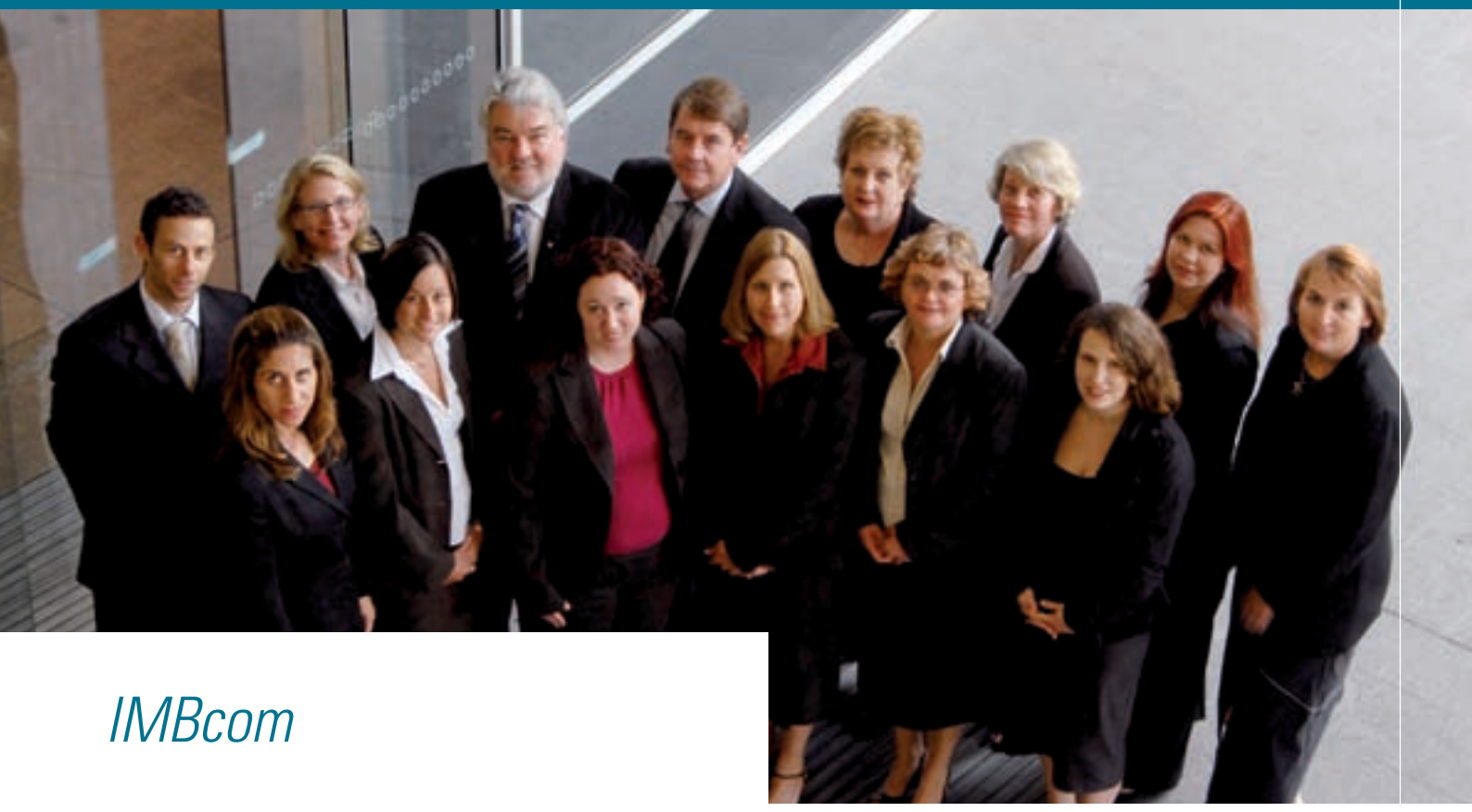
IMBcom Pty Ltd is The University of Queensland's company for commercialisation of the IP arising from the research of the IMB. It is responsible for protection and development of the IMB's intellectual property portfolio. Established in 2000, IMBcom has a skilled, independent Board of Directors and operates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

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

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

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

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



It has been yet another exciting year for the IMB Postgraduate Program, with a record 24 PhD completions (for full list please see page 56). We currently have approximately 120 research higher degree (RHD) students enrolled through the IMB, with the number of new students joining the program each year now almost matching those successfully completing their degree. While some of our graduates have remained within IMB throughout 2006 to complete research projects, many have taken up positions both locally and overseas, in locations such as the University of California, San Francisco, USA (Jennifer Bennetts, David Bryant), Baylor College of Medicine Houston, USA (Grant Challen), Scripps Institution of Oceanography, San Diego, USA (Ben Clark), Max Planck Institute for Brain Research, Frankfurt, Germany (Sebastien Dutertre) and the Karolinska Institute, Stockholm, Sweden (Matthew Kirkham, John Lock). Moreover, both Matthew Kirkham (formerly of the Parton lab) and Sebastien Dutertre (Lewis lab) have recently been awarded prestigious EMBO Fellowships to continue their research in Sweden and Germany respectively. Of those that wished to remain locally based, Lillian Sando has moved to CSIRO –Livestock Industries, Guy Barry to the Queensland Brain Institute and Manuel Plan to the School of Integrative Biology at UQ. Emma McComb (nee Millard), alternatively, is applying her research experience to her new role as Intellectual Property Development Officer with IMBcom. Still others are soon to be on the move, with Nick Meadows heading to a postdoc position at the MRC Harwell, Oxfordshire, UK in early 2007 and Alistair Forrest taking up a position at the RIKEN Genomic Sciences Centre, Yokohama, Japan next April. Alistair was a finalist in the Postgraduate Student Award Section at the Premier's Awards for Medical Research in June this year and at the close of the year was awarded a NHMRC CJ Martin fellowship to further his research overseas.

A number of our other RHD students also received awards/ accolades throughout the year. Jane Lattin from the Hume group received one of only 20 Smart State PhD top-up scholarships, offered for the first time in early 2006. The scholarships, which are designed to attract and retain promising researchers in Queensland, provide a $7000 per annum top-up to the student's current scholarship and a bonus for submission within 3.5 years. David Ireland, of the Craik group, received the Dr Bert L. Schram Award (29th European Peptide Symposium Poster Presentation Award for most outstanding work at the conference-2006) and the Australian Academy of Technological Sciences and Engineering (ATSE) Young Scientist Ambassador Award (2006) which is given in recognition of achievement and designed to promote science to the community. Christian Gruber, also from the Craik laboratory, was the recipient of The Biochemical Journal Young Investigator Award in Plant Science presented by the Australian Society of Plant Scientists. He also received a University of Queensland Graduate School Research Travel Grant (GSRTG) to undertake a field trip to both South America and Tanzania and then a Research Scholarship from the Swedish Institute to undertake a research placement at the University of Uppsala. Other GSRTG recipients included Stephen Bradford from the Koopman lab, who, with the additional support of a grant from the ARC/NHMRC Network in Genes and Environment in Development (NGED), spent 2 months in a research laboratory in Nice, and Mareike Kurz from the Martin lab who left for a research placement in Zurich in late 2006. Mareike was also awarded the Maslen Scholarship for conference travel, from the Society of Crystallographers in Australia and New Zealand (SCANZ). Ranjala Ratnayake from the Capon group was awarded the American Society of Pharmacognosy (ASP) Student Research Award (designed to recognise outstanding research in the general area of natural products) and as part of this award, gave an oral presentation at the ASP meeting in Washington, D.C. in August. Jennifer Fleming from Wayne Hall's group was an invited speaker at the Australian Health and Medical Research Congress in Melbourne and Helene Johanson from the Sturm group was involved in forming the first National Albanism Support Group in Australia, "Albinism Fellowship of Australia Inc." In addition, Helene helped organise the group's first albinism conference, held in Sydney, where A/Prof Sturm & herself made presentations about the genetic basis of the formation of pigment and albinism. Simon Wilkins from the Perkins lab also had a wonderful year, winning the 2006 Keith Dixon Prize (an ANZSCDB Developmental Biology Poster Prize) presented at ComBio and the ANZSCDB 2006 Student Exchange Travel Award. He featured as a finalist in the Roche Award for Postgraduate Career Development and won the Olympus Life Science Research Postgraduate Travel Award, as detailed below.

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

In July, Roche Applied Science proudly supported an inaugural, and now annual, "Roche Award for Postgraduate Career Development" (RAPCD) at the IMB, which recognises the contribution of a postgraduate student to advancing research in their field in new and innovative directions and provides an award of $1 500 to further develop the career of the recipient to enable them to bring their research to the local and international research community. This award was instigated after discussions between Sharen Warren (Roche Diagnostics) and Stephen Bradford (SIMBA) and we thank them both, together with the Roche Executive, for this brilliant initiative. We had a number of wonderful applicants from which our three finalists, David Ireland, Simon Wilkins and Peter van der Heide, were selected to give a verbal presentation of 15 minutes each as part of the Friday Seminar Series. A panel of judges made up of IMB group leaders from all 4 divisions then selected the winner, Peter van der Heide from the Marsh group, with his presentation "Towards a visible cell –reconstructing mammalian cells in 3D at 40-50Å". Pete was presented with his RAPCD by Sharen Warren at the IMB Monday Morning Institute Meeting on 24th July and used the funds to attend the 4th International Congress on Electron Tomography in San Diego, California in November this year. Also in November, Olympus Life Science presented the first Olympus Life Science Research Postgraduate Travel Award to one of our students.

# *POSTGRADUATE RESEARCH*

This award, which grew out of discussions between Professor Jenny Stow (IMB) and Olympus representatives, is open to all IMB postgraduate students and provides travel funds to the value of $1 000, to allow the winning student to present their work at a relevant scientific conference. Submissions could take the form of still images, video or a written abstract depicting or describing part of a life science project, and we received a number of visually as well as scientifically stunning entries. An IMB-based panel narrowed down the field to the four finalists: Natalie Butterfield (Wicking lab), Alex Combes (Koopman lab), Samantha Stehbens (Yap lab) and Simon Wilkins (Perkins lab), before the winner was selected by Ms Violetta Mironova, Mr Kieren McHugh and Mr Paul Pearce from Olympus. The award was won by Simon Wilkins with his entry entitled "Dark side of the moon- visualising the yolk syncytial layer of early stage zebrafish embryos by fluorescence and scanning electron microscopy" and presented at the IMB Monday Morning Institute Meeting of 20th November, by Mr McHugh and Mr Pearce. We are thrilled that this award is also set to become an annual event and greatly appreciate the very generous support of the IMB graduate program, by both Olympus and Roche.

Once again we had a large number of Honours students (31) completing their research projects at IMB during 2006, over 80% of whom obtained the grade of First Class Honours -an amazing result! The Amgen Award, for the most outstanding Honours student at the IMB in 2005, was presented in May by Ms Rebecca Stratford (Clinical Research Associate, Amgen Australia Pty Ltd) to Mr Luke Hammond from Professor Jenny Stow's group. Luke, whose honours project focused on the role of actin microfilaments in trans-Golgi network tubulation and post-Golgi transport, continued his research in the Stow lab as a PhD student in 2006. Amgen Australia has been presenting our Honours students with this award for over a decade and we are thrilled by their continued support of our young researchers.

IMB also continued the Undergraduate Research Scholarship Scheme (URSS) in 2006, giving 22 third-year students the opportunity to work in a laboratory within one of our divisions for eight hours per week during semester. Additionally, 16 third-year students completed mini-research projects as part of the "Introduction to Research" module of their respective degrees, 15 summer students undertook projects in 2006/2007 and several Advanced Studies students completed research projects as part of their program. We also continued our involvement with the Advanced Studies Program lunchtime seminar program (coordinated by Ms Robyn Evans from the BACS Faculty at UQ). Once again, we hosted many (24) international students, primarily from Germany, Sweden and France but also from India, Singapore, Norway and the Netherlands, who joined IMB for several months as occupational trainees, undertaking overseas research placements as part of their degree requirements within their home institution. We also welcomed a number of year 10, 11 and 12 students from schools throughout Queensland to undertake a brief period of work experience within research laboratories.

Our IMB Student Association (SIMBA) also had a very productive year as indicated in the snapshot from the SIMBA Executive, below:

"2006 was a busy year for SIMBA as we endeavoured to provide a vibrant calendar of social events for students to network within the institute as well as encouraging academic excellence from all of our brilliant student members. A highlight this year was the inauguration of the Roche Award for Postgraduate Career Development (RAPCD) won by Peter van der Heide. Various fundraising events, such as the Melbourne Cup Day Fashion Parade, organized by Rehan Villani and Tania Hudspith, were also very successful. The SIMBA AGM saw a passing of power from the impressive executive team of Angela Jeanes (President), Cheong-Xin Chan (Secretary) and Stephen Bradford (Treasurer) to the equally dynamic all-girl team of Stephanie Wood (President), Natalie Butterfield (Secretary) and Josephine Sprenger (Treasurer). Some red-tape and administrative hoop-jumping saw SIMBA undergo constitutional changes to permit non-UQ Union members on the executive (Kate Ewen as President), and also to introduce a new role of Vice President (Stephanie Wood). Control of SIMBA's electronic student bi-monthly publication, SIMBAlize, was also handed from the highly accomplished editor, Simon Wilkins, into the capable hands of Rehan Villani at the AGM. By popular vote Andrew Noske retained his position as SIMBA's webmaster at the AGM and continues to update SIMBA's internal website."

Another highlight of 2006 was the formation of the IMB Early Career Researcher (ECR) Committee, which has had a positive impact on our postgraduate students as well as many other members of the IMB and the wider research community. An ECR is defined as anyone who is not in the position of laboratory head, principally junior and senior postdocs, but also including PhD students. The committee has been formed with the goal of assisting ECRs to identify the necessary elements for building a strong CV, providing advice on specific issues relating to career development, fellowship and grant writing and to facilitate and encourage interactions and collaborations within the Institute. During the past year the ECR committee has run two sessions on academic and alternative career pathways and assisted with the 'Careers in Biotech' session of IMBcom's BioBusiness Day Out. During 2006 the members of the ECR committee were Dr. Dagmar Wilhelm, Dr. Karen McCue, Dr. Tara Roberts, Dr. Allison Pettit, Ms Angela Jeanes (PhD student) and Ms Kate Ewen (PhD student).

In addition to the SIMBA and ECR-run events and information sessions, the Postgraduate Program continued to run its regular set of workshops designed to assist students in overall career development. These included IMBcom's "Introduction to Bio-Business" Workshop for first-year PhD students, which was held as a whole-day event in April and their three-day "BioBusiness Retreat" for the third-years held from 12 July to 14 July at the Grand Pacific, Caloundra. Once again, feedback from the retreat was extremely positive, with students really enjoying the mentoring sessions, the networking opportunities and career advice. In March, Dr. Danielle Clode, from the University of Melbourne, gave a 2.5 hour workshop on scientific writing which was also extremely well received and will be incorporated in some form as a regular feature of the postgraduate program in future years.

Prof. Rob Capon completed his third year as the IMB Postgraduate Coordinator and once again served as the IMB representative on the UQ Postgraduate Committee of the Academic Board throughout the year. He has continued to take an active interest in all aspects of student matters, from individual cases to the monitoring of trends, which may serve as predictors of success in future years. Through his ongoing dedication and vigilance, he is helping to ensure that our program and student body continue to go from strength to strength.

*Mr Alex Foo, BSc Biotech 1st class Hons (2006), " The Three Dimensional Reconstruction of the Thylakoid Membrane by Electron Microscopy", and his supervisor A.Prof Alasdair McDowall.*

## FAST FACTS

**14** Australian Postgraduate Awards/University of Queensland Postgraduate research Scholarships for 2006 (9 accepted)

**7** IMB PhD scholarships offered for 2007

**3** International Postgraduate Research Scholarships for 2007 (3 accepted)

**3** University of Queensland Joint Research Scholarships in 2006

**4** University of Queensland Graduate School Confirmation Scholarships in 2006

**3** Graduate School Research Travel Awards

**2** ANZ Trustees PhD Scholarships in Medical Research

## PhD CONFERRALS FOR 2006

| LAST NAME | FIRST NAME | GROUP | DEGREE | THESIS TITLE |
|---|---|---|---|---|
| Barry | Guy | Hume | PhD | The Biology of Nod2 |
| Bennetts | Jennifer | Wicking | PhD | The Identification and Characterisation of Novel Genes in Development |
| Bryant | David | Stow | PhD | Analysis of Cadherin and Receptor Tyrosine Kinase Interactions: trafficking and function |
| Challen | Grant | Little | PhD | Molecular and Functional Characterisation of Potential Renal Stem Cells |
| Clark | Ben | Capon | PhD | Studies on the Chemistry of Australian Microbes |
| Dutertre | Sebastien | Lewis | PhD | Probing Membrane Protein Structure and Functions Using Conopeptides and Computational Tools |
| Forrest | Alistair | Grimmond | PhD | Functional Genomics of the Protein Kinases and Phosphatases of Mouse |
| Gardiner | Brook | Sturm | PhD | Moleculare Changes Defining the Transition from Radial to Vertical Growth Phase in Melanoma |
| Hoehl | Michael | Ragan | PhD | Is Multiple Sequence Alignment Required for Accurate Inference of Phylogeny? |
| Hopping | Gene | Alewood | PhD | "Synthesis, Structure and Activity of Disulfide-Rich Conus" Peptides |
| Jin | Ai-Hua (Jean) | Alewood | PhD | Cysteine-Rich Bioactive Peptides: A Structural and Biological Characterisation of Toxins and Bioactive Peptides |
| Kerr | Markus | Teasdale | PhD | Redefining the Retromer |
| Kirkham | Matthew | Parton | PhD | The Role of Caveolin in Endocytosis and Caveolae Biogenesis |
| Korsinczky | Michael | Craik | PhD | Structure-activity Studies of Small Cyclic Peptidic Trypsin Inhibitors |
| Lau | Chiyan | Hancock | PhD | A Study of the Membrane Interactions of K-ras |
| Lock | John | Stow | PhD | Dynamic Imaging of Post-Golgi Protein Transport |
| Mc Cue | Karen | Wainwright | PhD | "Identification of Novel Downstream Targets of Sonic, Indian " and Desert Hedgehog |
| Meadows | Nicholas | Hume | PhD | The Role of Microphthalmia transcription Factor (Mitf) in Osteoclast Gene Regulation |
| Millard | Emma | Craik | PhD | Structural and Functional Characterisation of Novel a-Conotoxin GID |
| Plan | Manuel | Craik | PhD | Chemical and Biological Studies of Cyclotides |
| Quimio | Mariel | Craik | PhD | Studies of Molecular Motions in Cyclic Peptides from the Violaceae and Cucurbitaceae Plant Families |
| Ripoll | Vera | Hume | PhD | Functional Characterisation of Macrophage-specific Transcripts |
| Sando | Lillian | Craik | PhD | Structure and Activity Studies of Cyclotides |
| Shepherd | Nicholas | Fairlie | PhD | "The Design, Synthesis and Structure of Small Alpha-Helical" Peptidomimetics |

**The IMB has an intellectual climate where researchers are encouraged to think beyond their own group to a whole of Institute level, and be curious about what their colleagues in related disciplines are achieving.**

Inspiration and information is provided by weekly seminars where a variety of national and international speakers at the leading edge of molecular bioscience present their research.

The IMB Friday Seminar Series is attended by all IMB research staff and students. Thank you to all of our 2006 speakers and sponsors.

### *Friday 3 February*

**Insights into cell compartmentalisation and membrane trafficking using GFP technology**

A Seminar in Molecular Cell Biology

*Dr Jenny Lippincott-Schwartz, National Institutes of Health, USA*

### *Friday 10 February*

**Studies of Argonaute proteins: central mediators of RNA silencing**

A Seminar in Chemical and Structural Biology

*Professor David Barford, Institute of Cancer Research, London*

### *Friday 10 March*

**Human embryonic stem cells: the past, the present and the future**

A Seminar in Molecular Genetics and Development

*Professor Martin Pera, Australian Stem Cell Centre*

### *Friday 17 March*

**Automating the search for lateral genetic transfer**

A Seminar in Genomics and Computational Biology

*Professor Mark Ragan, Institute for Molecular Bioscience*

### *Friday 24 March*

**Protein complexes in hematopoietic and fungal development**

A Seminar in Chemical and Structural Biology

*Dr Joel Mackay, Department of Biochemistry, Sydney University*

### *Friday 31 March*

**Maternally-controlled processes and the BMPs of zebrafish development**

A Seminar in Molecular Genetics and Development

*Associate Professor Mary Mullins, Department of Cell and Developmental Biology, School of Medicine, University of Pennsylvania*

### *Friday 7 April*

**Vacuole fusion needs SNAREs, chaperones, GTPases, phosphoinositides, sterols, diacylglycerol, and actin, all dancing in a ring**

A Seminar in Molecular Cell Biology

*Professor Bill Wickner, Department of Biochemistry, Dartmouth Medical School, Hanover, NH, USA*

### *Friday 21 April*

**Divide and conquer: the complex anatomy of the bacterial cell division site**

A Seminar in Genomics and Computational Biology

*Professor Glenn King, Department of Molecular, Microbial & Structural Biology, University of Connecticut Health Center*

### *Friday 28 April*

**Large-Scale Genomic Variations: Functional Differences between You and Me**

A Seminar in Genomics and Computational Biology

*Professor Chris Ponting, MRC Functional Genetics Unit and University of Oxford, UK*

### *Friday 12 May*

**Axon navigation in the vertebrate brain - lessons from the frogs, fish and mice**

A Seminar in Molecular Genetics and Development

*Professor Brian Key, School of Biomedical Sciences, The University of Queensland*

### *Friday 19 May*

**Genetic disorders of Excess Bone Formation - Some Rare, Some Common**

A Seminar in Molecular Genetics and Development

*Professor Matt Brown, Centre for Immunology and Cancer Research, The University of Queensland*

### *Friday 26 May*

**Being metastable in an extreme environment: structural studies on prokaryote serpins**

A Seminar in Molecular Cell Biology

*Dr James Whisstock, Biochemistry and Molecular Biology, Monash University*

# *VISITING SPEAKERS*

### *Friday 2 June*

**Structural basis of fatty acid synthesis in eukaryotes**

A Seminar in Molecular Cell Biology

*Professor Nenad Ban, Institute for Molecular Biology and Biophysics, Eidgenössische Technische Hochschule Hönggerberg, Zurich, Switzerland*

### *Friday 9 June*

**Epigenetic reprogramming in development**

A Seminar in Molecular Genetics and Development

*Professor Emma Whitelaw, Queensland Institute of Medical Research*

### *Friday 16 June*

**A new anti-inflammatory arsenal in the war on obesity**

A Seminar in Molecular Genetics and Development

*Professor Mark Febbraio, School of Medical Sciences, RMIT University, Bundoora*

### *Friday 23 June*

**Dissecting the apoptotic pathways utilised by pharmacological and biological anti-cancer agents**

A Seminar in Molecular Genetics and Development

*Associate Professor Ricky Johnstone, Peter MacCallum Cancer Research Institute, Melbourne*

### *Friday 30 June*

**e-Research**

A Seminar in Genomics and Computational Biology

*Professor Ah Chung Tsoi, Monash e-Research Centre, Monash University*

### *Friday 7 July*

**How viruses enter animal cells**

A Seminar in Molecular Cell Biology

*Professor Ari Helenius, Institute of Biochemistry, Eidgenössische Technische Hochschule, Zurich, Switzerland*

### *Friday 4 August*

**Life in the pouch: womb with a view**

A Seminar in Molecular Genetics and Development

*Professor Marilyn Renfree, Department of Zoology, University of Melbourne, Victoria*

### *Friday 11 August*

**The hidden layer of non-coding RNA in the evolution and development of complex organisms**

A Seminar in Genomics and Computational Biology

*Professor John Mattick, Institute for Molecular Bioscience*

### *Friday 25 August*

**Copper-containing amine oxidases: ubiquitous enzymes with the ability to create their own quinone factor**

A Seminar in Chemical and Structural Biology

*Professor Mitchell Guss, School of Molecular and Microbial Biosciences, University of Sydney, NSW*

### *Friday 1 September*

**Ten rules for the presentation and interpretation of data in publications**

A Seminar in Molecular Genetics and Development

*Professor David Vaux, Department of Biochemistry, La Trobe University, Victoria*

### *Friday 8 September*

**Phosphoinositides and vesicular exocytosis**

A Seminar in Molecular Cell Biology

*Dr Fred Meunier, School of Biomedical Sciences & Institute for Molecular Bioscience, The University of Queensland*

### *Friday 15 September*

**Odds and ends: strange features of telomere biology**

A Seminar in Molecular Genetics and Development

*Professor Roger Reddel, Children's Medical Research Institute, NSW*

### *Friday 22nd September*

**Understanding CNS immunity: from animal models to MS patients**

A Seminar in Chemical and Structural Biology

*Professor Claude Bernard, Monash Immunology & Stem Cell Laboratory, Monash University, Victoria*

### *Friday 29 September*

**TOR signalling in yeast and mammals**

A Seminar in Molecular Cell Biology

*Professor Michael Hall, University of Basel, Switzerland*

### *Friday 13 October*

**Isolation of mammary stem cells and their potential role in breast cancer**

A Seminar in Molecular Genetics and Development

*Associate Professor Geoff Lindeman, Walter & Eliza Hall Institute*

### *Friday 20 October*

**Computational modelling of immunology and stem cell biology**

A Seminar in Genomics and Computational Biology

*Professor David Winkler, CSIRO Molecular and Health Technologies*

### *Friday 27 October*

**Exploring principles of biological organisation to guide the exploration of chemical diversity**

A Seminar in Chemical and Structural Biology

*Associate Professor Mark Smythe, Institute for Molecular Bioscience*

### *Friday 3 November*

**Molecular mechanisms important in the regulation of energy balance and metabolic disease**

A Seminar in Molecular Genetics and Development

*Professor Greg Cooney, Garvan Institute, NSW*

### *Friday 17 November*

**Commercialising the BioFiniti handheld biosensor: experiences of a Queensland startup**

A Seminar in Commercialisation

*Dr Cedric Robillot, Cleveland Biosensors*

# *COLLABORATIVE RESEARCH PARTNERSHIPS*

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

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

### *ARC Special Research Centre for Functional and Applied Genomics*

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

### *Australian Phenomics Facility*

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

### *ARC Centre of Excellence in Biotechnology and Development*

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

### *ARC Centre in Bioinformatics*

The ARC Centre in Bioinformatics, with headquarters at IMB, brings Australian and overseas researchers together into interdisciplinary programs designed to explore how information in the genome is transformed into structure and function in the mammalian cell. Perspectives and technologies of mathematics, statistics, high-performance computation, information technology, genomics and high-throughput experimental phenomic biology are focused on representing the mammalian cell as a complex system of molecular networks, and building a common modelling

and visualisation environment to simulate its development and behaviour. Although directed in the first instance towards understanding human health and development, the Centre's technologies and output are generally applicable to biotechnology, while building critical mass in advanced bioinformatics is vital to Australia's international competitiveness in bio-based industries.

## CRC for Chronic Inflammatory Diseases

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

## Australasian Invasive Animals CRC

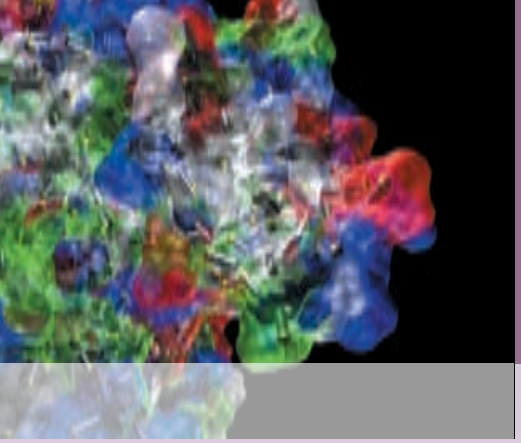
Australasian Invasive Animals CRC is a venture aiming to counteract the impact of invasive animals through the development and application of new technologies and integrating approaches across agencies and jurisdictions. It is the first time that research, industry, environmental, commercial and government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

## Nanostructural Analysis Network Organisation

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

## Australian Stem Cell Centre

The Australian Stem Cell Centre (ASCC) is a national research and funding facility set up by the ARC, The Victorian Department of Industry, Innovation and Regional Development, and the Federal Department of Education, Science and Training through a linked MNRF. The ASCC is primarily based at Monash University, but through the guidance of the Scientific Management Advisory



Committee (SMAC) and a process of due diligence, the ASCC funds research which falls within its core expertise platform areas or its therapeutic focus areas. The IMB has very close links with the ASCC. Professor Melissa Little sits on SMAC as The University of Queensland representative. Associate Professor Andrew Perkins, Dr. Sean Grimmond and Dr. Rohan Teasdale hold a joint grant in the therapeutic platform of "haematological disorders". The aim of this project is to harvest the immense potential of embryonic stem cells to provide a novel supply of haematopoietic stem cells (HSCs) for bone marrow transplantation, as well as other blood products. Dr. Sean Grimmond also holds a joint project grant with Professor Martin Pera of the ASCC in the core platform technology of "embryonic stem cell technology". Dr. Grimmond's international expertise in expression profiling is employed to try to dissect the genetic hierarchies involved in human ES cell differentiation. In addition, the Renal Regeneration Consortium and Nephrogenix, which are both based at two hubs – the IMB and Monash University – have very close links with the ASCC through a research memorandum of understanding. An eventual core aim of the RRC is to employ embryonic and adult stem cell technologies to deliver cells with therapeutic potential to patients with end-stage renal failure. Ongoing links between the IMB and ASCC are likely to strengthen along with the growth of the exciting new area of stem cell research.

## Australian Genome Research Facility

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

## ACRF Dynamic Imaging Facility for Cancer Biology

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

## RIKEN

RIKEN is the Institute for Physical and Chemical Sciences of the Japanese Science and Technology Agency, and a major site of genomics research in Japan. IMB Professors David Hume and John Mattick have visiting scientist appointments at RIKEN. The RIKEN Genome Sciences Centre is based at Yokohama and Wako, in the Tokyo area. In the late 1990s, RIKEN established a program aimed at elucidating the complete transcriptional output of the mouse. More recently, the program has shifted focus towards the elucidation of transcriptional control networks. Both activities have involved the establishment of large international consortia, firstly the FANTOM consortium (Functional Annotation of Mouse), and more recently the Genome Network consortium. In 2006, the consortium published a comprehensive analysis of the human and mouse transcriptomes, resulting in a series of papers in *Nature Genetics, PLoS Genetics, PLoS Computational Biology, Genome Biology* and *Genomics.*

## Queensland Facility for Advanced Bioinformatics (QFAB)

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

### IMB Website www.imb.uq.edu.au

The IMB website is the main source of information about the Institute for the public, with news, details of research programs, upcoming events, student and employment opportunities and more. It is the most popular site in the category of "molecular bioscience" when searched using Google.

### IMBoutput

This is the IMB's quarterly newsletter. It describes the research that has been performed at the IMB, and the grants and awards received by IMB researchers, in plain language that non-scientists can understand. It is sent to researchers, politicians, business and community leaders and members of the public, and is also available on the IMB website, under "About the IMB". To receive IMBoutput, follow the "Subscribe to IMB News" link on the front page of the IMB website.

### IMB Tours

The IMB hosted many tour groups throughout 2006. Visitors have included dignitaries, politicians, researchers and university and school students. Tours of the IMB include a description of the IMB's history, research and commercialisation, as well as viewing of some of the laboratories and equipment.

### Royal Queensland Show ("Ekka")

The IMB was part of the UQ stand at the 2006 Royal Queensland Show, or "the Ekka", as it is more commonly known. In addition to showcasing its research, the IMB also provided an interactive experiment, where school students extracted DNA from strawberries. This was a fun way of engaging children in science, and an effective method of reaching students, with over 1000 participating over the course of the Ekka.

### Science Ambassador

PhD student David Ireland, from Professor David Craik's laboratory, was named as a 2006 Young Science Ambassador by the Australian Academy of Technological Sciences and Engineering. This award aims to encourage talented young researchers to promote science and science education, and are chosen based on scholarly excellence and personal qualities. Mr Ireland visited schools and spoke about science as well as conducting experiments with students, and also attended a Science in Parliament day as part of his role.

### Open Day

IMB participated in UQ's Open Day on August 6, which attracts more than 11 000 people to the St Lucia campus. The Institute was opened up with a poster display about the research of each of the different groups, and tours conducted by PhD students.

# COMMUNITY ENGAGEMENT AND AWARENESS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# FINANCIAL STATEMENTS

## *Statement of Operating Income and Expenditure*
## *Year Ended 31 December 2006*

| INCOME | Note | 2002 | 2003 | 2004 | 2005 | 2006 |
|---|---|---|---|---|---|---|
| University of Queensland (Operating Grant) | 1 | 6,023,929 | 8,122,858 | 6,877,099 | 7,225,765 | 16,470,311 |
| University of Queensland Research Grants | | 269,358 | 277,337 | 228,999 | 334,500 | 252,252 |
| State Government | | 6,000,000 | 8,500,000 | 10,000,000 | 10,425,000 | 10,175,000 |
| SRC Grant (Australian Research Council) | | 1,148,975 | 1,005,151 | 1,117,038 | 1,137,436 | 1,159,047 |
| Australian Research Council | 2 | 1,599,576 | 3,218,103 | 4,261,849 | 4,744,519 | 5,218,279 |
| Arthritis Foundation of Australia | | 0 | 0 | 0 | 14,950 | 0 |
| Australian Cancer Research Foundation | | 0 | 0 | 600,000 | 600,000 | 0 |
| Australian Nuclear Science & Technology Organisation | | 0 | 0 | 0 | 85,355 | 78,757 |
| Australian Stem Cell Centre | | 0 | 0 | 306,219 | 161,691 | 159,780 |
| Cancer Council South Australia | | 0 | 30,500 | 30,500 | 0 | 0 |
| Community Health + Tuberculosis Australia | | 0 | 0 | 0 | 0 | 49,000 |
| CRC for Discovery of Genes for Common Human Diseases | | 122,469 | 48,946 | 0 | 0 | 0 |
| CRC for Chronic Inflammatory Diseases | | 943,401 | 968,800 | 1,261,017 | 1,367,457 | 1,326,058 |
| CRC for Pest Animal Control | | 0 | 0 | 0 | 0 | 122,210 |
| Dairy Australia | | 0 | 0 | 338,779 | 203,765 | 167,644 |
| Department of Primary Industries | | 98,040 | 0 | 0 | 0 | 0 |
| Diabetes Australia Research Trust | | 37,700 | 0 | 0 | 0 | 45,000 |
| Human Frontiers Science Program | | 0 | 146,291 | 138,057 | 0 | 0 |
| Juvenile Diabetes Foundation International | | 77,084 | 0 | 151,732 | 177,814 | 178,634 |
| National Institute of Health (US) | | 1,391,005 | 1,049,548 | 1,475,684 | 1,132,358 | 1,176,642 |
| National Health and Medical Research Council | 2 | 4,306,397 | 6,761,404 | 6,438,350 | 9,819,880 | 7,888,967 |
| National Heart Foundation | | 50,000 | 42,735 | 50,000 | 50,000 | 0 |
| Novartis | | 0 | 641,790 | 0 | 0 | 0 |
| Post Graduate Scholarships | | 38,214 | 73,467 | 91,968 | 140,237 | 261,263 |
| QIMR | | 53,908 | 60,575 | 0 | 0 | 0 |
| Queensland Cancer Fund | | 92,750 | 72,590 | 140,000 | 215,100 | 148,700 |
| Sylvia and Charles Viertel Charitable Foundation | | 165,000 | 0 | 0 | 0 | 0 |
| Wellcome Trust | | 0 | 204,763 | 180,706 | 150,311 | 0 |
| Commercial Income | | 2,127,649 | 1,517,449 | 1,473,905 | 1,856,012 | 2,018,054 |
| Cross-Institutional contributions to LIEF | | 0 | 122,500 | 192,800 | 60,000 | 509,472 |
| University of Newcastle (re ARC Centre) | | 0 | 127,727 | 127,893 | 47,727 | 252,562 |
| QBP recoveries | | 0 | 331,594 | 312,979 | 316,211 | 386,092 |
| Shared Grants | | 0 | 105,845 | 128,764 | 262,062 | 234,685 |
| Conference Income | | 0 | 55,275 | 25,501 | 73,032 | 66,615 |
| QBPStore | | 0 | 0 | 44,021 | 247,890 | 276,819 |
| Wesley Research Institute | | 0 | 0 | 0 | 0 | 20,000 |
| Miscellaneous Income | | 19,593 | 392,822 | 355,652 | 416,707 | 399,887 |
| **TOTAL INCOME** | | 24,565,049 | 33,878,069 | 36,349,512 | 41,265,778 | 49,041,729 |
| Funds brought forward from previous year | 3 | 3,594,479 | 7,545,101 | 6,746,999 | 6,557,150 | 9,050,612 |
| **TOTAL FUNDS AVAILABLE** | | 28,159,528 | 41,423,170 | 43,096,511 | 47,822,929 | 58,092,341 |

## *Statement of Operating Income and Expenditure Year Ended 31 December 2006 continued...*

| EXPENDITURE | Note | 2002 | 2003 | 2004 | 2005 | 2006 |
|---|---|---|---|---|---|---|
| Salaries -Research | | 9,066,745 | 12,238,779 | 16,195,354 | 18,430,158 | 20,110,376 |
| -Administration | | 1,342,520 | 1,365,120 | 1,243,375 | 1,343,782 | 1,205,466 |
| -Infrastructure | | 1,012,400 | 1,735,158 | 2,131,608 | 2,383,622 | 2,673,620 |
| Research Services | | 4,865,433 | 6,938,972 | 7,667,863 | 9,976,365 | 10,995,871 |
| Education Programs | 4 | 500,939 | 484,360 | 418,784 | 375,177 | 358,445 |
| Administration | 5 | 452,021 | 519,046 | 383,224 | 379,317 | 529,612 |
| Corporate Services (UQ) | 1 | 0 | 0 | 0 | 0 | 5,703,000 |
| Infrastructure | 6 | 786,809 | 1,568,251 | 1,772,942 | 1,287,442 | 1,295,139 |
| Capital Equipment | 7 | 1,840,664 | 8,649,700 | 5,521,066 | 3,389,715 | 2,569,801 |
| IMBcom | | 746,896 | 1,176,785 | 1,205,144 | 1,206,738 | 1,209,741 |
| **TOTAL EXPENDITURE** | | 20,614,427 | 34,676,171 | 36,539,360 | 38,772,316 | 46,651,071 |
| **FUNDS CARRIED FORWARD** | 8 | 7,545,101 | 6,746,999 | 6,557,150 | 9,050,612 | 11,441,270 |

## *Explanatory Notes to Statement of Income and Expenditure*

### *1/ a) In-kind Contributions*

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

| | Department | Percentage |
|---|---|---|
| G. McLachlan | Mathematics | 80 |
| A. McDowall | Microscopy & Microanalysis | 80 |
| V. Brusic | NRAVS | 80 |

### *b) Gross Income & Corporate Services Charge*

The University of Queensland has changed the way that income and expenditure is accounted for in its Operating Grant. Income is now the gross amount and a Corporate Services charge is shown seperately under expenditure

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

| | |
|---|---|
| **Australian Research Council** | |
| Projects | 3,002,947 |
| Fellowships | 1,148,156 |
| | **4,151,103** |
| **National Health and Medical Research Council** | |
| Projects | 5,449,990 |
| Fellowships | 2,141,763 |
| | **7,591,752** |

### *3/ Funds carried forward to 2006*

| | |
|---|---|
| University of Queensland Operating Grant | 1,829,209 |
| University of Queensland Research Grants | 120,508 |
| Post Graduate Scholarships | 27,342 |
| State Government | 1,653,694 |
| SRC Grant | 246,214 |
| Fellowships (as approved by funding bodies) | 47,647 |
| Overseas Grants funded mid year | 770,147 |
| Contract Research | 1,119,639 |
| Project Grants (as approved by funding bodies) | 3,236,212 |
| | **9,050,612** |

### *4/ Education Programs*

| | |
|---|---|
| Postgraduate scholarships | 339,113 |
| Postgraduate recruitment & training | 19,332 |
| **Total Education Services** | **358,445** |

### *5/ Administration*

| | |
|---|---|
| Annual Report | 18,074 |
| Marketing | 57,328 |
| Personnel Recruitment and Training | 92,480 |
| Visiting Scientists/Seminars | 27,532 |
| Fees | 130,482 |
| Quinquennial Review | 3,053 |
| Entertaining | 16,114 |
| Photocopying | 73,951 |
| Postage and Freight | 2,160 |
| Printing & stationery | 2,160 |
| Telephone | 59,140 |
| Travel Expenses | 35,657 |
| Board Fees | 11,435 |
| Cost Recovery | 45 |
| **Total Administration** | **529,612** |

### *6/ Infrastructure*

| | |
|---|---|
| Building Maintenance | 43,616 |
| Rental -Storage | 10,488 |
| Safety Equipment | 37,199 |
| Laundry | 3,394 |
| Minor Equipment & Furniture | 47,047 |
| Equipment Maintenance | 282,382 |
| Animals | (67,577) |
| Computer Services | 531,554 |
| Glass washing and replacement | 35,713 |
| Reticulated gases, RO water & dry ice | 100,629 |
| Sundries | 11,516 |
| Stores | 259,177 |
| **Total Infrastructure** | **1,295,139** |

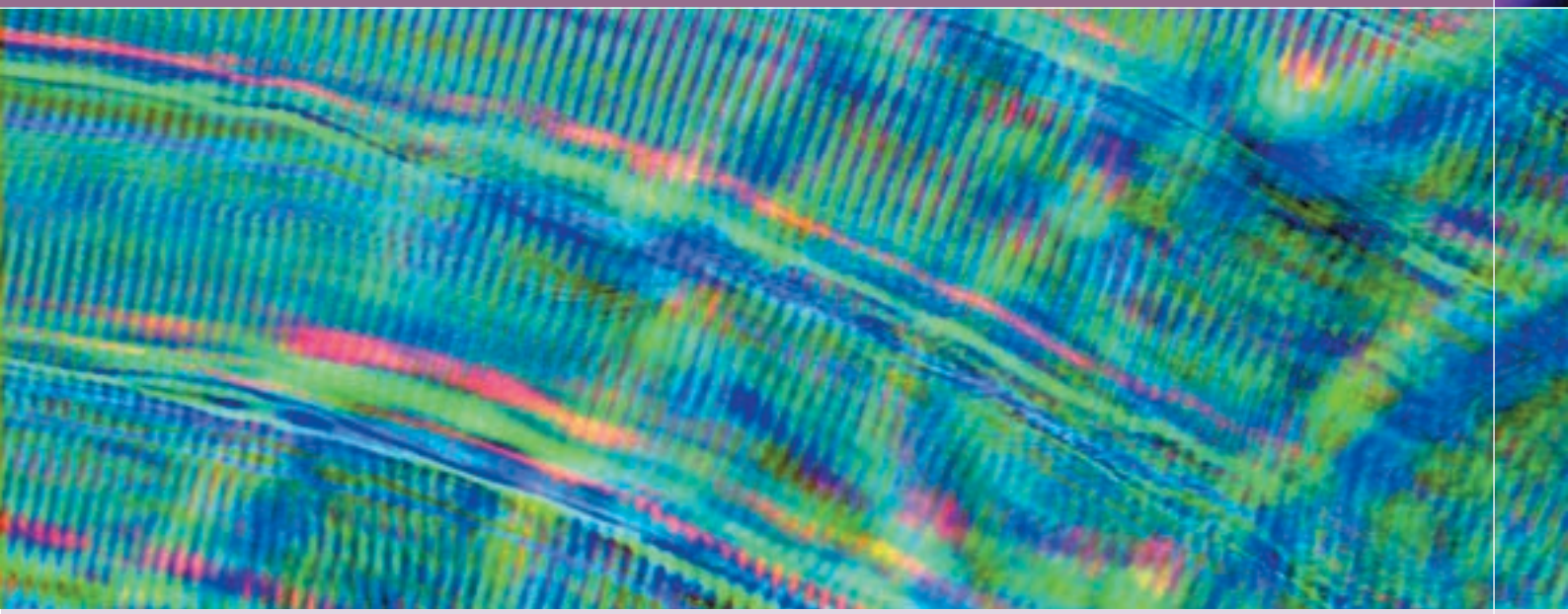
### *7/ Capital Equipment*

| | |
|---|---|
| Scientific Equipment | 1,993,332 |
| Minor Equipment | 576,469 |
| **Total Capital Equipment** | **2,569,801** |

### *8/ Funds carried forward to 2007*

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

#Of this, $1.8m is the carry forward on IMB Group Leader core accounts, $0.5m relates to oustanding 2005 equipment commitments



**Ampipathic** A characteristic where something can have both the property of being hydrophobic (repels water) and the property of being hydrophilic (attracts water).

**Amyloid aggregates** Deposits of protein fragments found in the brains of Alzheimer's Disease sufferers.

**Analogous** Characteristics or structures that evolved separately but share a similar form or function.

**Angiogenesis** Formation of new blood vessels.

**Antibody** A protein that recognises and helps to fight foreign substances in the body.

**Antigen** A foreign substance in an organism that triggers an immune response, i.e. the production of antibodies.

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

**Atherosclerosis** The process where arteries harden and narrow over time.

**Bioassay** A method of determining a substance's concentration by testing it in a living organism.

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

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

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

**Biosynthesis** The production of chemical compounds in living organisms.

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

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

**Chloroplast** The site of photosynthesis in plants.

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

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

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

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

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

**Cytoskeleton** The protein framework of a cell.

# *GLOSSARY OF TERMS*

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

**Dimer** An organic molecule formed by combining two smaller molecules.

**Discrete** Entities that are separate and distinct from one another.

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

**E-cadherin** A protein that acts as a tumour suppressor, and is also involved in adhesion in epithelial cells.

**EGFR** Epidermal growth factor receptor.

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

**Endocytosis** Uptake of material into a cell.

**Endosome** An organelle involved in protein trafficking.

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

**Epithelial** Pertaining to or composed of epithelium, which consists of cells joined by small amounts of cementing substances. Covers internal and external surfaces of the body.

**Epitope** The site on the surface of an antigen that causes the body to produce antibodies, and to which these antibodies bind.

**Erythropoiesis** The development of mature red blood cells.

**Eukaryote** Organisms whose cells have chromosomes organised in a double helix structure, enclosed by a nuclear envelope, with compartmentalisation of functions in distinct cytoplasmic organelles.

**Gene** Considered the basic unit of heredity, a gene is a region of DNA that encodes all of 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** The hereditary genetic makeup of an organism.

**Germ cells** The reproductive cells in multicellular organisms (eg. Sperm and eggs).

**Golgi Apparatus** An organelle that is involved in the processing and export of proteins.

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

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

**Homologous** Characteristics or structures that have a common evolutionary origin, even though they may differ in form or function.

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

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

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

**In vivo** A process occurring within an organism.

**Insulin** A hormone that regulates sugar concentration in the blood.

**Islets of Langherans** Clusters of cells in the pancreas that secrete insulin.

**Junk DNA** DNA that does not appear to code for genes. Makes up more than 90% of the human genome.

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

**Knockout** An organism in which a gene has been inactivated in order to understand the function of the gene.

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

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

**Lysosome** An organelle capable of digesting microorganisms and cellular debris.

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

**Macropinocytosis** The formation of fluid-filled macropinosomes.

**Macropinosomes** Large, heterogeneous, dynamic vesicles formed by membrane ruffling.

**Meiosis** The process by which germ cells divide and eggs and sperm are produced.

**Membrane** A thin layer of tissue.

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

**Mesoderm** The middle layer of cells in the early embryo.

**Microarray** A technique for studying how large numbers of genes interact with each other and how a cell's regulatory networks control vast amounts of genes simultaneously.

**Mitochondria** The organelle in which a cell's energy production and respiration occur.

**Mitosis** The process where a somatic cell divides to become two identical cells.

**Morphogenesis** The process where cells differentiate into different structures.

**Motif** A conserved region of a protein sequence that often correlates with a particular function.

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

**Mycotoxin** Toxic compounds produced by fungi.

**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.

**Nucleic Acid** A molecule consisting of a chain of nucleotides.

**Nucleotide** Organic molecules that are sequenced with one another to create genetic information. They consist of a five-carbon sugar, a phosphate and an organic base.

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

**Oncogenesis** The initiation and formation of a tumour in an organism.

**Organelle** A discrete subcellular structure with a specialised function.

**Organogenesis** The development of organs.

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

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

**Pancreas** A glandular organ that secretes insulin and digestive fluid.

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

**Pathogen** A disease-causing organism.

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

**Peptide** A compound of two or more amino acids.

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

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

**Photosynthesis** The process by which plants convert water and carbon dioxide into carbohydrates and oxygen.

**Polymer** A large organic molecule formed by linking many smaller molecules in a regular pattern.

**Prion** An infectious protein molecule that does not contain nucleic acid.

**Prokaryote** Organisms (bacteria and cyanobacteria) characterised by the possession of a simple naked DNA chromosome, occasionally two, without a nuclear membrane and with a very small amount of organelles.

**Pronuclear injection** An injection of DNA into the nucleus of an unfertilised egg.

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

**Protein** A large molecule composed of one or more chains of amino acids in a specific order; 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 and antibodies.

**Proteinase** Any enzyme that catalyses the splitting of proteins into peptides and amino acids.

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

**Proteosome** A macromolecular assembly that disassembles proteins into peptide fragments.

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

**Retrovirus** A type of RNA virus that produces an enzyme that uses an RNA template to make a DNA copy of its genetic information, in direct contrast to the usual process in cells. HIV is a type of retrovirus.

**Ribosome** The organelle in which proteins are made.

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

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

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

**Spliceosome** A complex of RNA and proteins that removes non-coding introns from unprocessed messenger RNA.

**Stem cells** Relatively unspecialised cells of the same family type that retain the ability to divide and cycle throughout postnatal life to provide cells that can become specialised and replace those that die or are lost.

**Stochastic** A process that is governed by random chance.

**T-cell** A type of white blood cell that attacks foreign and infected cells, and also produces chemicals that regulate the immune response.

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

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

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

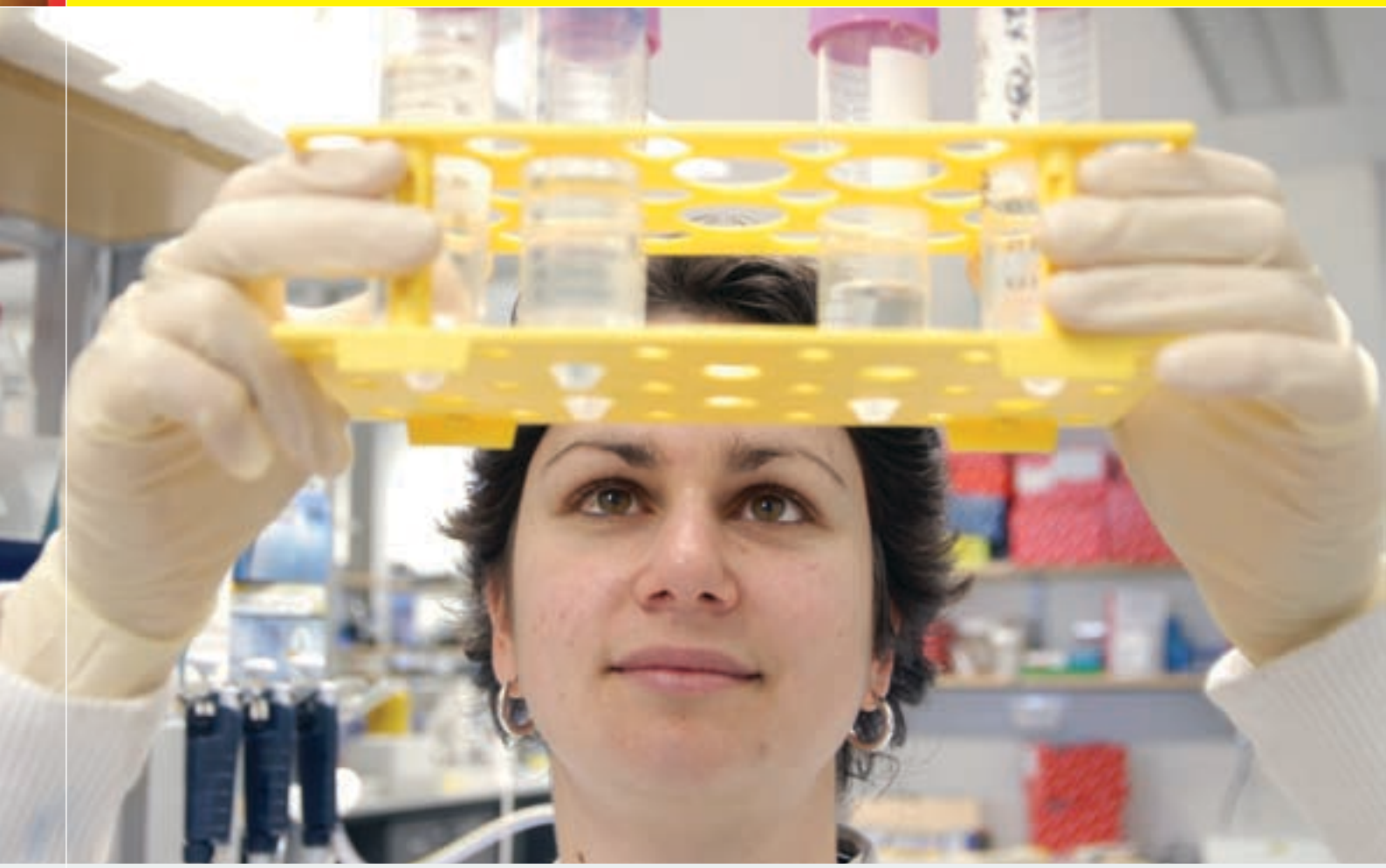
**Transcription** The formation of RNA from a DNA template.

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

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

**Vesicle** A closed membrane shell.

**WT** Wild-type. Refers to the genotype or phenotype that is most commonly found in nature.



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