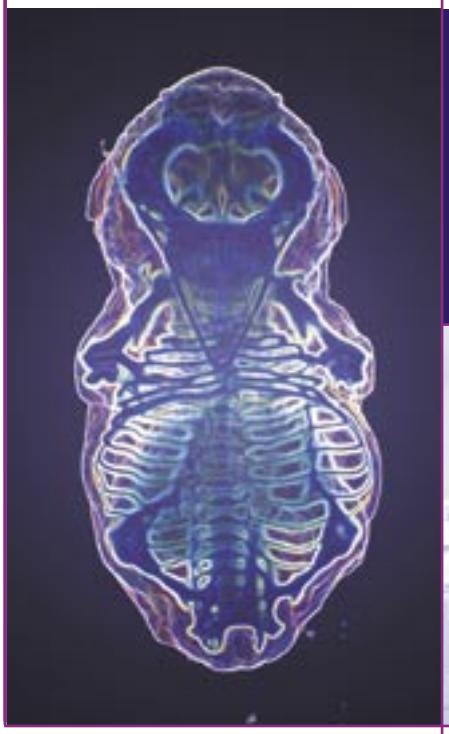


Contents

Professors John Mattick and Peter Andrews, Co-Directors of the Institute for Molecular Bioscience, talk with Peter McCutcheon

Why is Queensland, which has traditionally relied on mining, agricultural and tourism industries, developing an advanced research centre for molecular bioscience?

Professor Mattick: It is clear that we are in the midst of one of the greatest periods of discovery in history – the genetic and molecular basis of life and its diversity. The genome projects are laying out the genetic blueprints of different species, from microorganisms to humans, and functional studies are leading us to understand how these components work together to produce complex outcomes. And the flip-side of this is to understand disease. Sooner or later this knowledge and its applications will transform all of the biologically-based industries, which occupy perhaps half the world economy, and lead to entirely new industries based on understanding genetic programming and biological chemistry. So this is clearly a fundamental knowledge revolution that has huge potential and will have huge ramifications.

Why Queensland ? – I think that Queensland is emerging as the California of Australia. It not only has great natural resources and primary industries but has great capacity to develop new high technology industries, and this is already underway. It is well positioned in the Asia-Pacific region. Queensland is also a state with great dynamism and we are very fortunate to have a government that understands the importance of developing an advanced, knowledge-based economy.

Professor Andrews: The world's most rapidly growing economies are all knowledge-based industries, and the focus of those industries is increasingly on biotechnology. In fact, recent advances in genetic engineering techniques and the sequencing of the human genome have extended the applications of biotechnology from common foodstuffs into most aspects of our lives, including medicine, energy and the environment. For me, the question is not why would you do it in Queensland, it's why wouldn't you!

The Queensland Government has made a significant investment in the Institute. Are there other funding arrangements in place for the IMB, and is it enough?

Professor Mattick: The Queensland Government has been generous to the IMB, and has vested a great deal of faith in us, which we will work hard to justify and repay. We have also been fortunate to have raised funding from the Federal Government through the Federation Fund, and from a private donor, to construct the Institute. And we're delighted to have the CSIRO now joining us in the construction of the Institute complex, a joint venture that will create a very large and vibrant centre for advanced research in molecular biology and biotechnology.

The IMB also obtains substantial funding for its research projects and programs from the Australian Research Council, the National Health and Medical Research Council, the Cooperative Research Centres scheme, and many others, including industry. The IMB hosts the ARC Special Research Centre for Functional and Applied Genomics and is a core partner in the Cooperative Research Centre for the Discovery of Genes for Common Human Diseases, as well as being the host (along with the Walter & Eliza Hall Institute of Medical Research) of a major national research facility, the Australian Genome Research Facility. So we do have a good balanced portfolio of research funding.

In terms of whether we've got enough, no we don't. Research funding in Australia remains low by international standards, and our ability to attack big problems and create new opportunities is limited by the relatively restricted resources available to us. Our funding is still well below that of comparable Institutes in other parts of the world including Asia. We need more funds to mount strategic genomics projects, to build the computing infrastructure for bioinformatics, to enable the next generation of structural analysis in cell biology, and to develop new chemical libraries, to mention a few. Although we are doing the best we can, and will do well with what we have.

My view, shared by many others, is that there is insufficient attention paid in our society to investing in the future, which is what research is. It's a bit like a home budget – you have to pay the bills, buy the food, maintain the house. But the amount of money you can save and invest for the future determines your future prosperity and quality of life. It's the same for the nation as it is for a household. So I'd like to see more emphasis on this aspect of national development, and an acknowledgment that as much of our natural resources as possible be invested on everyone's behalf to create better futures, especially in the areas of education, R & D and strategic industry development. Other countries in our region have been doing this for the past 20 years, and the benefits are very obvious.

"Queensland is a state with great dynamism and we are very fortunate to have a government that understands the importance of developing an advanced, knowledge-based economy."

The IMB depends on private as well as public funding. Although the Australian private sector doesn't have a strong track record on R & D investment, is there any sign of a change in investment culture?

Professor Andrews: There's a real breath of fresh air emerging in the Australian venture capital community, and a lot of them are looking to the IMB as a source of new investments. We've had three venture capital firms invest in spin-off companies from the IMB in the past year, and we're currently in negotiation with several firms interested in IMB technology platforms that may form the basis for further spin-offs in 2001.

New industries by definition can be unpredictable. The NASDAQ index dropped 35 percent in the US in 2000. Is biotechnology really becoming a credible investment item for the Australian business community?

Professor Mattick: I think it is. You've got to see the stock exchange as partly a reflection of commercial and industrial reality, and partly a reflection of people making considered bets on future industrial development. In the short-term the latter is unpredictable; in the longer term there is no doubt that, in relation to biotechnology, the direction is up, and the figures bear that out, although market confidence waxes and wanes. I'll give you one example of the economic value of this sector. Two pharmaceuticals which are widely used in medicine – and interestingly there's very little public concern about these products – are genetically engineered insulin and erythropoietin (EPO). The market for these products last year was roughly US$9 billion - greater than the entire Australian grains crop.

The IMB is unusual in that it comprises both basic research facilities and spin-off companies. It has been described as a "pipeline" from genomics to pharmaceuticals. Why is it set up that way?

Professor Mattick: Because we would like the IMB to fulfil two objectives. First and foremost, we want to earn a reputation as being a very fine research institute, capable of winning Nobel prizes. New knowledge is not only important to understanding our world, it is also the basis for economic development, as the history of the past two centuries shows. Secondly, therefore, we also want to fulfil our responsibility to those that invest in us, by earning a reputation as being well connected with industry, and having a very pro-active stance in terms of taking our discoveries, technologies and expertise into practical applications. This in turn will feed back into support for further research.

"New knowledge is not only important to understanding our world, it is also the basis for economic development, as the history of the past two centuries shows."

Queensland's is one of two state governments which has announced heavy investment in biotechnology, the other state of course is Victoria. How will Victoria's initiative affect the IMB?

Professor Mattick: We are very supportive of the Victorian initiative. Victoria has traditionally been the strongest centre of biomedical research in this country. It is also now clear that Brisbane has emerged as a major centre in its own right, and will additionally become a major centre for advanced biological research and biotechnology. This is important for Australia. We have many partnerships with Victorian research institutions in areas such as the Australian Genome Research Facility. So we see ourselves as friendly rivals but above all as partners. We are Australians first and we have to work together, we do work together, to make the most of our resources and research strengths.

Although the IMB is large by Australian standards, it is modest by international standards, especially compared to developments in the United States. Can the IMB be a serious player in global science and biotechnology?

Professor Andrews: The by-product of pharma industry mergers is a vast increase in the extent to which the industry outsources its R&D to research organisations and biotechnology companies. And that's where we have a huge opportunity to be very serious players.

One fascinating example is a molecule discovered by IMB researchers in the venom of a marine cone snail from the Great Barrier Reef which has been licensed to Australian pharmaceutical company Amrad for clinical trials as a pain therapeutic. This and several other lead molecules with novel pharmacological activities are currently progressing through the pipeline of an IMB spin-off company, Xenome Ltd.

Another example is our work in designing molecules mimicking growth hormones and other cytokines. These are proteins that send signals from one cell to another by interacting very selectively with other proteins on the cell surface. These and other protein-protein interactions represent one of the biggest classes of potential therapeutic targets, but no one has been able to develop generic ways of attacking them. Dr Mark Smythe's group, working with Glaxo Wellcome and the National Health and Medical Research Council (NHMRC), has solved that problem, and that gives us a very serious edge in a major aspect of drug development.

These examples are interesting – Xenome because it utilises Australia's natural resource strengths as well as our science, and the cytokine project because it illustrates that a bunch of scientists sitting in an Institute like this a long way from the main game can nevertheless be the best in the world.

What do you see as the strength of the IMB in an international context?

Professor Mattick: One strength is that, being somewhat separated from the rest of the world, we can be more creative because we are not necessarily being swept along with current fashions. I think that's always been something of a hallmark of Australian science. Being out of the mainstream has had its down-side, but its up-side is that Australian scientists tend to be a bit more creative and think about things more laterally.

"Australian scientists tend to be a bit more creative and think about things more laterally."

A particular strength of the IMB is our integration of genomics with chemistry and our heavy emphasis on the emerging fields of bioinformatics and computational biology. Biology is becoming an information science in its own right, with an increasing intersection with information technology. We are positioning the Institute to be an international centre of excellence in this, and we have developed close relationships with some of the key players internationally.

Also now with the Internet and improved communications and travel, Australia is much better connected with the rest of the world. So it doesn't matter so much whether something is in Brisbane or Tokyo or Paris, and in fact we collaborate with laboratories all around the world. We're part of a network and part of the feature of the establishment and growth of this Institute is the development of partnerships internally and externally.

Professor Andrews, there has also been some public debate over the patenting and selling of genetic information, particularly in relation to the actions of the US company, Celera. What is your view on the commercial use of research findings?

Professor Andrews: The reality is that while it costs so much to create a new drug, companies need the protection that a patent gives them to effectively develop and market them. But if you ask "Should Celera be able to patent the human genome?" – that's a lot more difficult to answer. I find it difficult to handle the concept of patenting gene sequences. The next stage on, when we can say "Now we have the sequence of this gene and we know its function", is a much more defensible basis for patenting, and when it comes to developing a new product based on our knowledge of the gene and its function, patents are absolutely essential.

The IMB is accommodating a wide variety of personnel from basic science researchers, spin-off company employees through to patent lawyers. Will this lead to major changes in research culture?

Professor Andrews: Well it is already leading to a change in culture. I think scientists throughout the IMB are increasingly recognising that if they are to see something valuable, in a public good sense, emerge from their research, they also need to be thinking about how to develop it. So there's a lot more interest in intellectual property, and how to protect it, as well as working with industry.

The other big cultural change is in the way our scientists think about their career options. In the past, postgraduate students and postdoctoral fellows in research institutions had little option but to pursue limited career opportunities in universities or other public research organisations. Now, a good percentage of our graduates and postdocs are finding great career prospects in start-ups and spin-offs associated with IMB.

Professor Mattick, you mentioned earlier there has been very little public concern about genetically modified medicines. They are widely used. However in parts of Europe the debate over genetically modified foods has extended to pharmaceuticals as well.

"A bunch of scientists sitting in an institute like this a long way from the main game can nevertheless be the best in the world."

How do you see the debate playing out in Australia?

Professor Mattick: In the end, any applications of modern biotechnology are only going to be taken up in the marketplace if they are perceived as being useful and safe by the people who use them – that's the public. By and large there has been wide acceptance of medicines produced from biotechnology because the people who need those medicines know that they are useful, safe and well-tested.

The benefits of genetically modified food are not so obvious yet to the consumer, although they are more obvious to producers because they lower insecticide loads, increase yields and will eventually allow more innovative and higher quality food products. But in the end it's not a matter of saying you should or shouldn't buy this. People will decide for themselves depending on what they see as the benefits to them, and I am quite confident that good outcomes will occur, despite some overstated claims by the proponents and fear mongering by the ideological opponents of biotechnology.

Every time that there is a major technological change, there is a section of society who are inclined to point out some of the problems, real or imagined, which may arise from the technology. My personal view is that you keep a level head. You also have to progress. It is interesting for scientists to learn about how life works, to understand ourselves, the natural world and the basis of disease. Out of that will come some sensible applications and the public will respond according to their own priorities and needs.

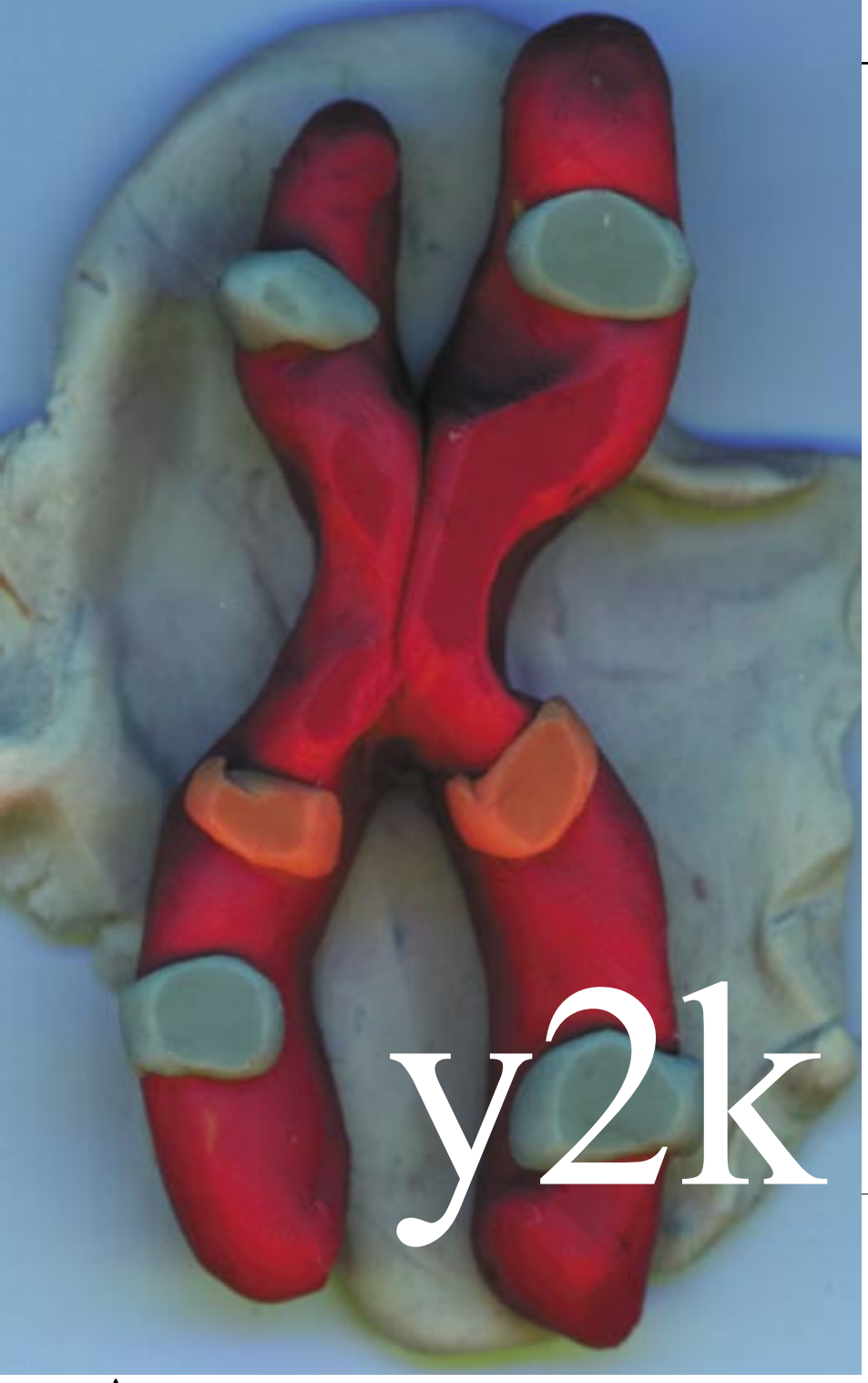
It's unusual for an Institute like this to be run by two Co-directors. How is it working out?

Professor Mattick: It is working out very well. Peter and I have worked closely together for some years now to develop the concept of the IMB and to bring it to fruition. We freely agreed to amalgamate our two research centres (the Centre for Molecular and Cellular Biology, and the Centre for Drug Design and Development) to form the core of the IMB. I enjoy Peter's company, both professionally and personally, and appreciate his advice and wisdom. We work extremely well together and have complementary skills and experience, which I think adds another dimension to the Institute's potential.

Professor Andrews: Of course, the ultimate relationship is still evolving. Over the past year we've played dual roles as ex-directors of our original research Centres and as Co-directors of the Institute. In the latter role, John is increasingly picking up research responsibility across the entire spectrum of our activities, and I am taking on much more of the commercialisation activities. The bottom line is – we're having fun!

Professor Mattick: I would also add that we have both enjoyed the support and involvement of other key players in the development of the Institute, such as Professor Kevin Burrage who is the Director of the Advanced Computational Modelling Centre and is helping to develop our bioinformatics capabilities, as well as the Deans and other colleagues in the Faculties of Biological & Chemical Sciences, Health Sciences, Engineering, Physical Sciences & Architecture, and Business, Economics & Law, and other organisations such as CSIRO, the Queensland Department of Primary Industries, and the Queensland Institute of Medical Research, who are collaborating closely with us through joint appointments and through the development of joint research programs and facilities. The strong support of the Vice-Chancellor, Professor John Hay, the Deputy Vice-Chancellor Research, Professor Paul Greenfield, and other senior colleagues at the University of Queensland has been essential throughout and is much appreciated.

Peter McCutcheon is the Assistant Director of the University's Office of Marketing and Communications. He has worked for the ABC in Sydney, Darwin, Melbourne and most recently in Tokyo as the ABC's North Asia Correspondent.



y2k high

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Ångstrom Art is a new initiative for the IMB and is the brainchild of a group passionate about visual art and committed to raising the awareness of science in the community. Their idea is to use stunning images sourced from current research and to link these images to a website providing background information about the science behind the image.

Ångstrom Art was awarded a 2000 Science and Technology Awareness Program grant of $50,000, to fund the distribution of a series of science image postcards throughout Australia. Keep an eye out for these Ångstrom Art postcards, coming to a café near you in 2001.

In November, Ångstrom Art hosted the “Art in Science” competition that attracted over 30 entries from within IMB. Images were judged by a panel that included UQ dignitaries and a Brisbane artist. One of the winning entries, a cellular Christmas tree by Kylie Georgas, was chosen for the IMB Christmas card. Other winners were “Fluoro Macrophage Dragon” by Wenda Shurety and Darren Brown and “Chromosome” by Alisa Poh (illustrated). An image by Michael Dooley of a molecular Christmas wreath was subsequently selected for the University of Queensland Christmas card.

Ångstrom Art is looking to expand its activities and include scientific art from outside IMB. Further details can be found on the Ångstrom Art website at www.angstrom-art.com.

Cardiovascular breakthrough >

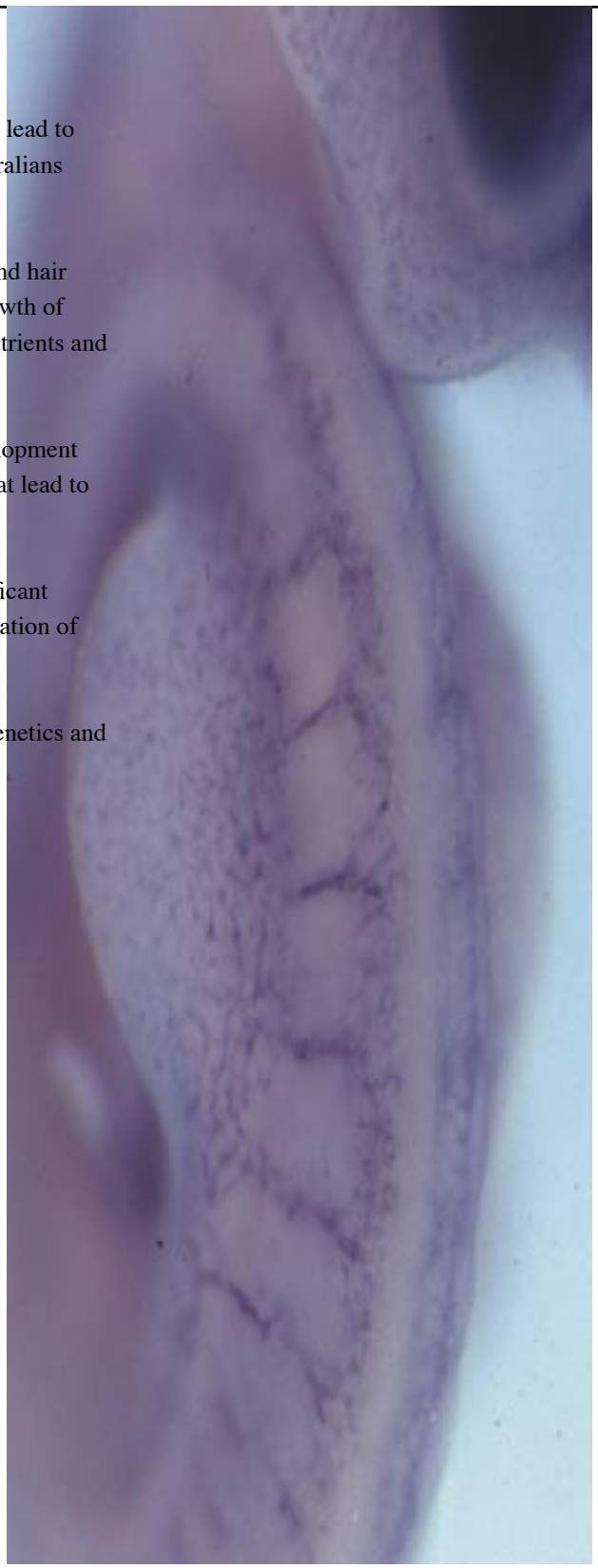
Drs Peter Koopman and George Muscat discovered a gene that could lead to breakthrough treatment for many of the cancers that kill 34,000 Australians yearly.

Sox18 is the gene responsible for the development of blood vessels and hair follicles, and this gene has the potential to significantly effect the growth of tumour cells by restricting the growth of blood vessels that supply nutrients and oxygen, effectively starving a tumour.

Sox18 could also have applications in speeding up blood vessel development to help heal wounds faster and treat circulation problems common that lead to amputation in diseases like diabetes.

Actual treatments could still be several years away but this is a significant discovery in the understanding of human development and the application of this understanding to human health care.

This work was published in the prestigious science journal Nature Genetics and is the product of six years work.



lights

Frontier women

In September The Courier Mail published a feature article highlighting the achievements of IMB Group Leaders (L-R) Jenny Martin, Judy Halliday, Melissa Little, Carol Wicking and Jenny Stow . The story dealt with issues such as the speed of scientific advancement, returning to Australia to do scientific research and how science can become a lifestyle rather than just a career.

y2k highlights...

Skin cancer test

IMB Group Leader Dr Rick Sturm and his research team, in collaboration with Professor Nick Martin from The Queensland Institute of Medical Research, have developed a genetic test that could help identify an individual's susceptibility to skin cancer.

The procedure, published in the *American Journal of Human Genetics*, identifies any variations of the gene called *Melanocortin-1 Receptor* or *MC1R*. This gene confers red hair colour and the ability to tan.

With excessive exposure to the sun every person can develop skin cancer, however the danger is higher for people with a variant of the *MC1R* gene. The new test, in conjunction with appropriate counselling, could drastically reduce the incidence of skin cancers in Australia.

Sixty percent of Queenslanders have sunspots or lesions removed in their lifetime and 250 people in Queensland die from skin cancer each year.

Cash instalment

The first allocation of $3.75 million for the IMB was handed over to the University as part of the State Government's ten year, $77.5 million commitment to partly fund the operational costs of the Institute.

IMB Co-director Professor Peter Andrews said the funding allocation is an important step towards building a vibrant new knowledge based economy.

"The IMB brings together Research and Development, commercialisation, Queensland government funding commitments and spin-off companies that will herald the beginning of an exciting new era in Queensland development," said Professor Andrews.

Asian network

The IMB has been elected as the 9th Centre of Excellence in the Asia-Pacific International Molecular Biology Network (IMBN), which is being established as a regional organization for research co-operation and training in molecular biology, similar to the European Molecular Biology Organization (EMBO). This places the IMB alongside other prestigious Institutes from the region, including the Weizmann Institute of Science; IMCB, Singapore; Institute of Medical Science, University of Tokyo; the Walter and Eliza Hall Institute, Melbourne; and the Institute of Biological Chemistry, Academia Sinica, Taiwan.

Boost for Queensland crystallographers

Biotechnology in Queensland was given a major boost with the announcement of substantial funding for a world class protein crystallography facility.

The Australian Research Council awarded the University of Queensland $1.1 million for the facility. This grant is the largest individual national grant in the ARC's Research Infrastructure Equipment and Facilities (RIEF) round.

IMB Associate Professor Jenny Martin, until recently head of the only protein crystallography research group in Queensland, said the relocation of several key scientists to Queensland and the rate of growth of biotechnology initiatives in this state provided the impetus for this grant's success.

The facility will allow the visualisation of the largest and most complex biological molecules and this information will be critical in the design of novel and improved therapeutics.

in brief

Top-down approach

The IMB was visited in September by the Hon. Kim Beazley, Leader of the Federal Opposition.

Mr Beazley was interested in the impact biotechnology will have in the coming years and where the IMB fits into these coming developments.

Achievement Award

John Mattick was presented with The Eppendorf Achievement Award, recognising his scientific research contributions and his promotion of molecular biology throughout Australia.

IMB researchers recognised

Several IMB senior scientists were successful in the 2000 round of promotions. Peter Koopman was promoted to Professorial Research Fellow, while Melissa Little and Mark Smythe were both promoted to Principal Research Fellows. George Muscat became a Principal Research Fellow of the NHMRC.

Four new research groups in IMB

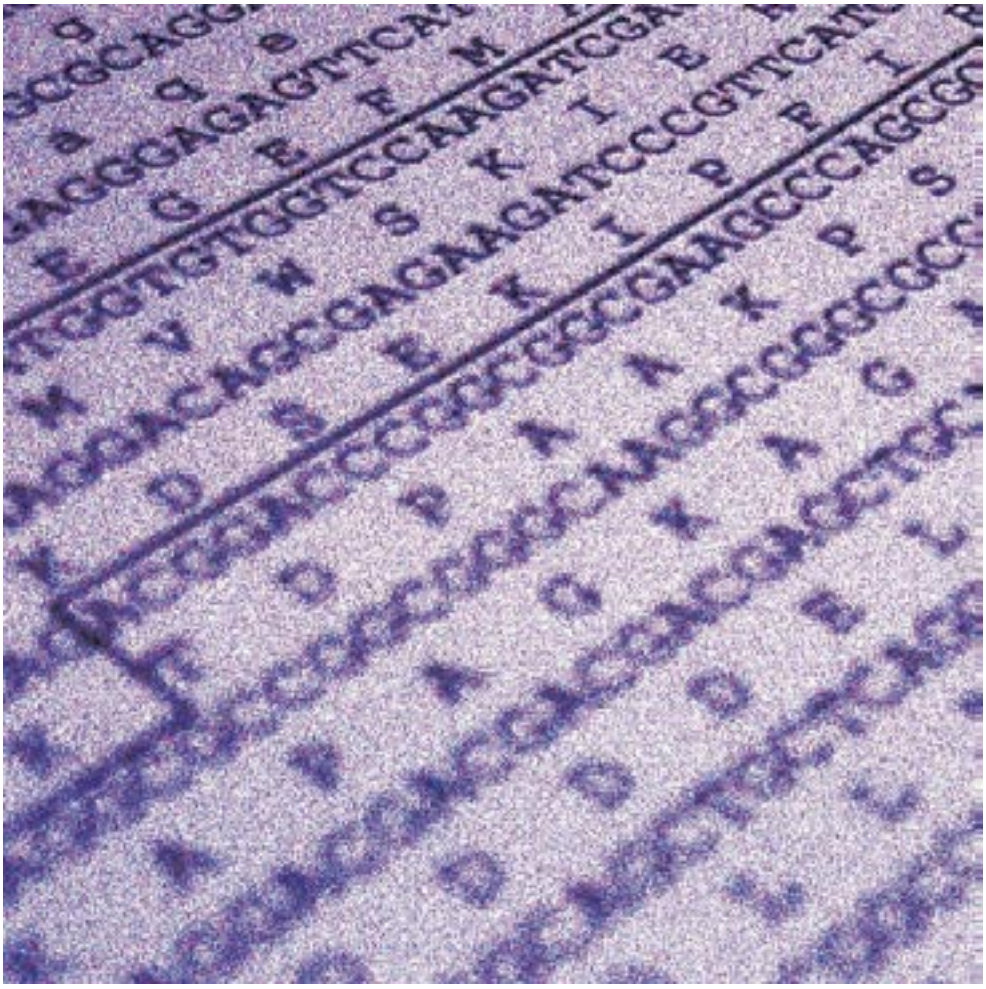
The year 2000 saw the establishment of four new research groups in the IMB. Rohan Teasdale, Mark Ragan, Jennifer Hallinan and Sean Grimmond bring their extensive experience in bioinformatics, genomics, computational biology and microarray analysis.

Olympic torch bearer

IMB group leader Judy Halliday had the honour of participating in the Olympic torch relay on June 14.

AMP nominated Judy as a result of her work with the Australian Society for Medical Research and AMP, in promoting the AMP-QLD Biomedical Research Awards.

Genomics & Bioinformatics



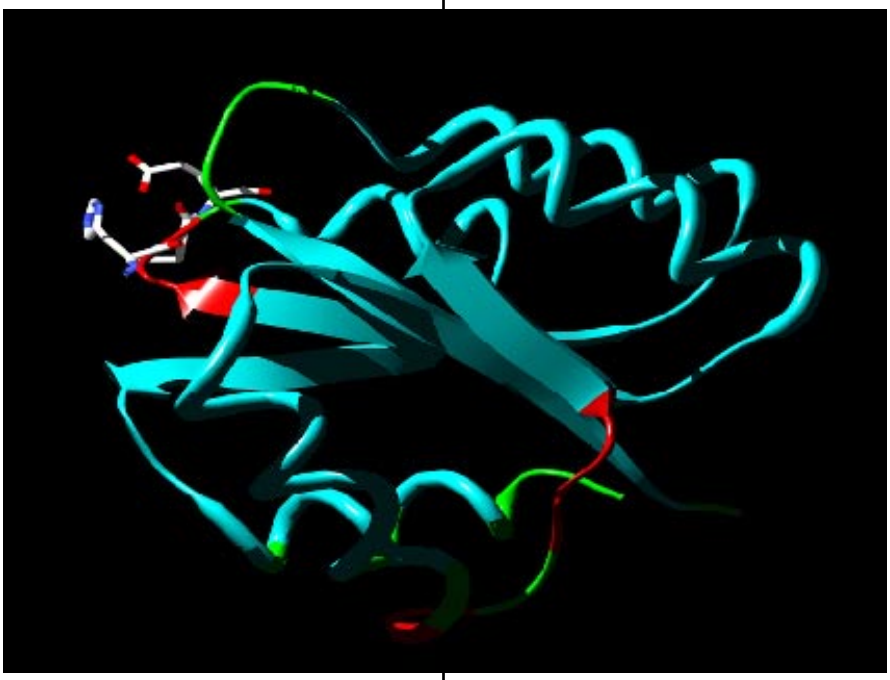
The interface between biology and computer science promises a more quantitative understanding of the complexities of living organisms, and new models for advanced computation. We apply computer-based methods to problems in molecular biology, and develop new approaches and software to investigate complex biochemical and biophysical processes.

Pseudomonas aeruginosa genomics and

Pseudomonas aeruginosa infection poses a serious threat to immuno-compromised patients, burns victims and cystic fibrosis sufferers. This bacterium produces many virulence factors which are used to colonize host tissues. We are identifying the important genes and proteins involved in infection, and the regulatory pathways controlling their expression, using a combination of genetic, genomic and biochemical approaches.

Analysis of the P. aeruginosa genome

The complete sequence of the genome of *P. aeruginosa*, the largest bacterial genome sequenced to date (6.2 Mb), was published in 2000. Our group was involved in the annotation of this genome [see Nature 406, 959-64 (2000)] as well as in more detailed analyses which revealed a large number of unexpected genes encoding, among others, four complete chemosensory systems, three type II protein secretion pathways, a number of surface haemaglutinin-like adhesins, three types of type I fimbriae, and a new global physiological regulation / signal transduction system based on cyclic di-GMP, all of which are likely to play important roles in pathogenesis



Genes encoding type IV fimbriae

Type IV fimbriae are long filaments which emanate from the pole of the bacterial cell and which impart a form of surface translocation called twitching motility. We have completed a high density transposon mutagenesis analysis of the P. aeruginosa genome and identified over 40 genes involved in the biogenesis, function and regulation of these structures. Many of these genes are homologous to genes involved in type II protein secretion and DNA

pathogenesis

Group leader • John Mattick

Assistant group leader • Cynthia Whitchurch

Postdoctoral staff • Ben Huang

Research assistants • Jacqueline Emery, Jen Sargent

Students • Scott Beatson, Larry Croft, Andrew Leech, Michael Young

uptake, revealing that each of these is an evolutionarily and structurally related subset of a supersystem which places multimeric complexes on the cell surface.

Regulation of virulence factors

We have identified a number of signal transduction systems which regulate the expression and function of type IV fimbriae, including PILSR, FimS/AlgR, Vfr (virulence factor regulator) and a complex chemosensory system whose central component ChpA is the most sophisticated signal transduction protein yet described in nature. The last three of these systems also control other virulence factors, such as secreted proteases, toxins, pyocyanine and lactones, and appear to be components of a global regulatory system that intersects via phosphotransfer cascades and connects environmental signals with molecular motors and gene expression.

The human genome contains around 30,000 genes, but the vast majority of the output of the genome is non-protein-coding RNAs. We are examining the hypothesis that noncoding RNAs are not junk, but comprise a higher order parallel processing system underlying sophisticated genetic programming in the higher organisms.

RNA regulation

Group leader • John Mattick

Assistant group leader • Derek Kennedy

Students • Larry Croft, Budi Utama, Andrea Verhagen, Juliet French, Katherine Irvine, Emily McGhie

Research assistant • Kelin Ru

The role of introns and other noncoding RNAs

Introns and other noncoding RNAs comprise the vast majority of genomic output in the higher eukaryotes. Where studied these transcripts have been found to be developmentally regulated and to have genetic function. Analysis of complex genetic phenomena, including co-suppression, transgene silencing, RNA interference, imprinting, and transvection, indicates a far wider role for RNA in gene control than has been previously recognized. We are exploring the possibility that RNA may have evolved to function as a higher order parallel control system for the integration and multitasking of gene networks in the higher organisms, analogous to internal control codes in computer programming and efference signals that underlie motor coordination and cognition in neurobiology.

Nrap, a new nucleolar protein

Nucleoli are membraneless nuclear organelles that are essential for the transcription and processing of ribosomal RNA. We have identified a previously unknown nucleolar protein (Nrap, nucleolar RNA associated protein) that is highly conserved from yeast (*Saccharomyces cerevisiae*) to human, with homologues in mouse, *Drosophila melanogaster, Caenorhabditis elegans, Arabidopsis thaliana, Schizosaccharomyces pombe,* and other species. Nrap is an essential protein and a core component of eukaryotic cell biology which appears to interact directly or indirectly with the 45S rRNA.

G3BP, a new signal transduction protein

We have discovered a new signal transduction protein G3BP which is conserved in animals and links RNA processing to the GAP120 signal transduction pathway. In mammals there are two forms of this protein, and a number of splice variants which appear to be developmentally regulated. The protein has a number of functional domains, including an RNA recognition motif and nuclear import signals. We are investigating the role of this protein in normal cell biology and in cancer (where its expression is disturbed) and attempting to identify its RNA and protein interactions using a range of biochemical and genetic approaches.

DNA microarray technology and yeast two-hybrid protein-protein interaction assays generate large amounts of complex biomolecular data. Our group is interested in using such datasets to build computational models of cells as networks of information flow.

Modeling of cell networks

Dynamics of cellular networks

Naturally occurring networks that are large and complex tend to have a high degree of connectivity arranged so that the number of steps between individual points is vastly smaller than the size of the network. These are called small world networks, as in the "six degrees of separation" phenomenon. Such networks contain a few highly connected nodes, and many less highly connected nodes. Small world networks have characteristic dynamics, being exceptionally resistant to fragmentation by random node deletion, but vulnerable to targeted attack. Several metabolic networks have been identified as small world networks.

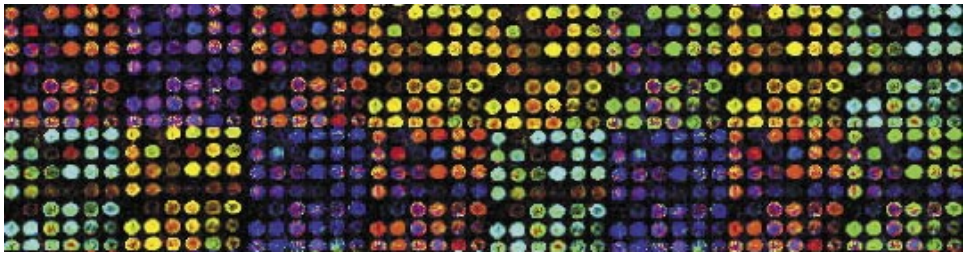
We have demonstrated that the network of protein-protein interactions in *Saccharomyces cerevisiae* forms a small world network, and exhibits the expected response to damage. However, metabolic networks are better modeled as directed graphs, and little is known about the implications of directed links between nodes for the behaviour of a small world network. We are currently building a more comprehensive model of protein-protein interactions in *S. cerevisiae*, incorporating data such as protein subcellular location. This model will be used to test theories of the evolution and dynamics of directed networks which we are developing using simulated idealized small world networks.

Group leader • Jennifer Hallinan

Students • James Tsai, Anthony Percival

GeNexus microarray database

In conjunction with Sean Grimmond's group we are designing and implementing



a relational database to hold the data generated by the IMB Microarray Facility. Once the database is completed we will be incorporating data mining and machine learning algorithms into the system to facilitate the identification of potentially interesting trends and patterns in the data.

Bioinformatic discovery of endosomal

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

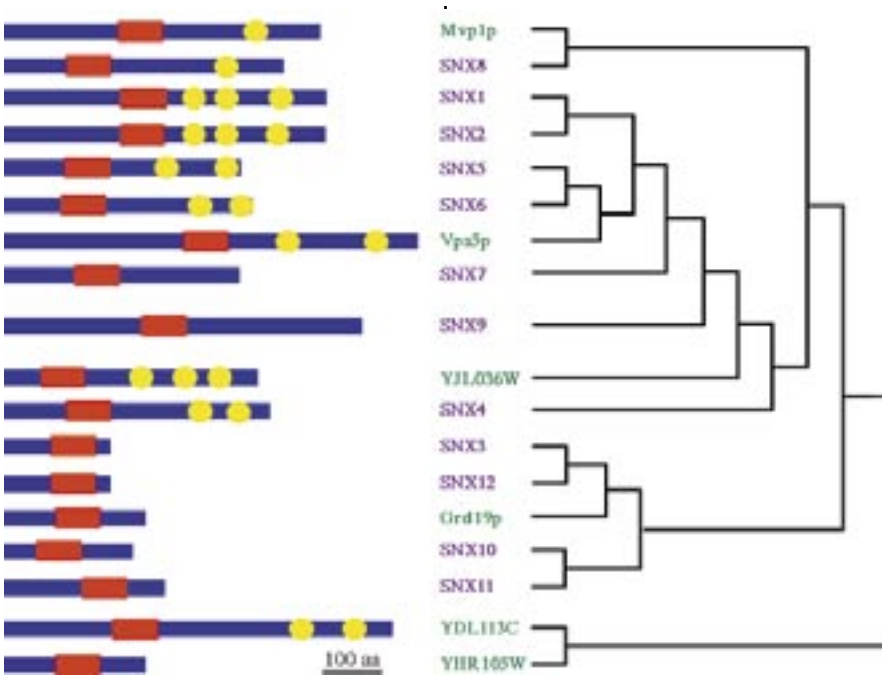
Dissecting the endosomal system through bioinformatics

The endosomal/lysosomal system of mammalian cells is a highly dynamic trafficking pathway that includes membrane transport from the late Golgi and the plasma membrane. The primary function of endosomes is the sorting and segregation of receptors and ligands, a process that is necessary for many cellular operations. The molecular details of protein trafficking and biogenesis of the numerous subcompartments of the mammalian endosomal/lysosomal system are poorly defined. One strategy to identify proteins involved in trafficking within these organelles, is to characterise human homologues of proteins that have been implicated in endosomal function in other organisms, predominantly yeast. This analysis has identified over thirty novel human proteins likely to function in the endosomal system. Specifically we have focused on the sorting nexin family of proteins and the retromer subunits Vps26p, Vps29p and Vps35p.

Protein trafficking in parasites

The Trypanosomatidae comprise a large group of parasitic protozoa,

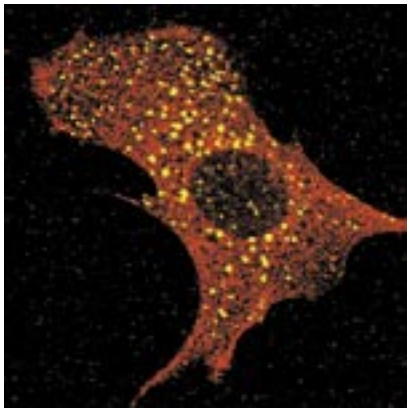
Sorting Nexins



proteins

Group leader • Rohan Teasdale

Students • Kevin Miranda, Rachael Shaw



some of which cause important diseases in humans. These include *Trypanosoma brucei* (the causative agent of African sleeping sickness), *T. cruzi* (the causative agent of Chagas disease in Central and South America) and *Leishmania*. Parasite survival requires the surface expression of specific molecules that form protective surface coats, mediate specific host-parasite interactions and allow the parasite to take up essential nutrients. The biosynthesis, processing and surface transport of these molecules within the intracellular organelles of the parasite secretory pathway are poorly understood. A recent effort to sequence the genomes of these parasites provides us with an opportunity to identify parasite homologues of proteins that function in membrane trafficking. A collaboration with Dr. Malcolm McConville (University of Melbourne) has been established to characterise these numerous proteins.

Intracellular localisation signals

A major issue in cell biology is how distinct intracellular regions of the cell maintain their unique composition of proteins and lipids. For the organelles to maintain their functional integrity, specific resident proteins must be retained while non-resident proteins are allowed passage through them. Individual proteins have "signals" that are responsible for their intracellular localisation. We are currently identifying such signals on several different proteins. In addition, we are identifying novel sequences within the human genome that contain these localisation signals. We have recently characterised a family of proteins with a Golgi Localisation Domain (GLD) and identified the signal responsible for the correct targeting of E-cadherin to the basolateral membrane.

We use advanced computer methods to investigate how genomes (and the proteins they encode) are similar to or different from each other, and to make quantitative inferences about how genomes have come to have their observed contents, arrangements and sequences of genes.

Comparative and computational genomics

Group leader • Mark Ragan

The genealogical history of a gene (or protein) can be inferred from its nucleotide (or amino acid) sequence. Although histories (phylogenetic trees) inferred from different types of genes are often identical, sometimes they are not, even with methods that are robust against methodological artifact. This incongruence suggests that within a single organism (ie within one genome), different genes have different genealogical histories. Many of these conflicts are difficult to explain unless we hypothesize lateral (horizontal) gene transfer: that is, that the gene has entered that genome not by "vertical" transmission from one generation to the next, but by jumping, as it were, from one branch of the phylogenetic tree to another.

Some analyses now suggest that lateral transfer may be very common. If so, this could be of both fundamental and practical importance. The rapid spread of antibiotic resistance between populations of bacteria, resulting in the emergence of drug-resistant "superbugs", makes it clear that some genes do move laterally. If, however, this is only the tip of the iceberg, consequences could be immense throughout environmental science, biotechnology, agriculture and medicine.

In collaboration with Robert Charlebois (NeuroGadgets Inc.), I continue to explore rapid computational methods for identifying atypical genes in microbial genomes. Some of these atypical genes may be the products of lateral transfer. However, other evidence suggests that all "atypical" genes can be of lateral origin.

Thus I have begun to construct an automated computer-based system to infer and analyse phylogenetic trees from complete sets of genomic sequence data. Since arriving at IMB in mid-August, two UQ students and I have implemented some basic modules of this system. We are now refining many of its features. Although phylogenetic inference per se is a major goal of this fundamental research, very similar approaches can and will be implemented to generate databases optimised for mining and recovery of data useful in applied areas of biosciences, including drug design and metabolic engineering.

Research staff and students are currently being recruited for this core project, and to develop in-depth projects in structure-based alignment, analysis of unique genes, and other related topics.

Genetics & Developmental Biology

These are exciting times in biology. The availability of the genome sequences of humans and other organisms is revealing the genetic nuts and bolts of our makeup. Our research is providing spectacular insights into the functions of these genes, how they control our development and life, and how genetic malfunctions result in inherited disease.

Molecular genetics of

organ devel

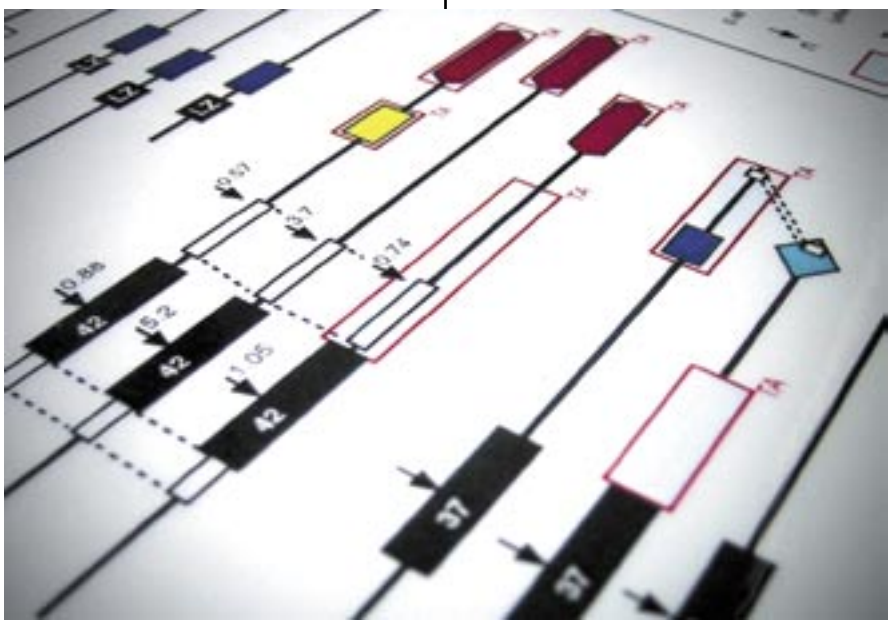
The development of complex organs in the embryo relies on the co-ordinated formation, migration, communication and function of large numbers of cells of many different types. We are identifying genes involved in the development of the gonads, skeleton, blood vessels and other organs. Studying how these genes function and interact provides a basis for understanding the complexities of embryonic development and how birth defects can arise.

Genetic control of sex determination

A major focus of our group is sex determination, the genetically controlled "decision" between male and female pathways of development, that manifests in the embryo as a choice between testis and ovary formation. We are studying several genes involved in testis determination, such as *Sry* and *Sox9*, and continue to make significant progress in understanding the structure and regulation of these key genes. Using microarray technology we have now discovered a large number of other genes active during testis or ovary development. Our goal is to piece together the molecular events that orchestrate the formation of testes and ovaries, organs critical for sexual identity and reproductive ability.

Sox gene function in mouse embryo development

Study of the Y-linked testis-determining gene *Sry* has led us to discover a number of related genes known as *Sox* genes. These are involved in a broad range of processes such as skeletal, cardiovascular, and neural development. *Sox* genes encode transcription factors (regulators of gene activity) that specify the identity of a number of different cell types, and are thus key players in directing organ development. Several of these genes are being studied in this laboratory from a functional standpoint. In addition, we have



opment

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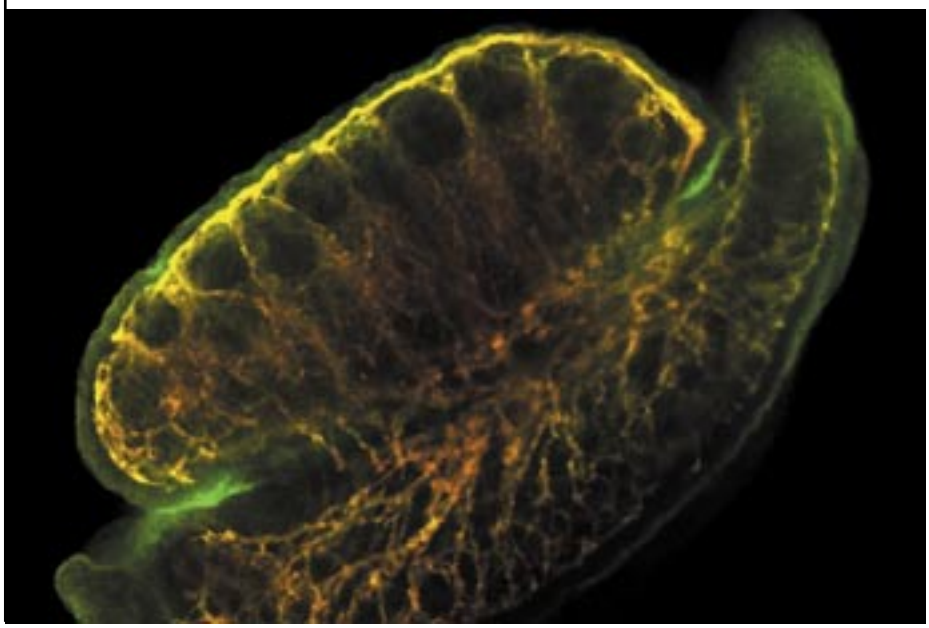
played a leading role in nomenclature and classification of these genes, and studying their evolution and functional relationships.

Sox18: A critical gene in cardiovascular development

In collaboration with George Muscat's group, we have shown that one Sox gene, *Sox18*, is active during the development of the blood vessel system and hair follicles in the embryo. The structure and expression of *Sox18* is conserved among mice, humans and chickens. We found that mutations in *Sox18* underlie a naturally-occurring mouse mutant that has defects in coat and vascular development, further emphasising the importance of this gene. Vascular development is clearly essential for survival of the embryo, and is also required for the growth of tumours. We are currently studying whether vascular development can be accelerated (eg. in wound healing), or slowed (eg. in tumours) through manipulating *Sox18* activity.

Sox8: A novel gene involved in embryo development

We have discovered a novel gene, *Sox8*, in humans and mice. *Sox8* is extremely similar to *Sox9*, and, is expressed in Sertoli cells of the mouse fetal testis around the time of sex determination. We propose that *Sox8* plays a role in male sexual development. *Sox8* is also expressed in the developing brain and spinal cord in mouse embryos, in addition to branchial arches and nascent facial structures. We mapped human *SOX8* close to the telomere of chromosome 16, in a region associated with the facial malformation, mental retardation and genital anomaly syndrome ATR-16. *SOX8* is therefore a strong candidate for contributing to the features of ATR-16.

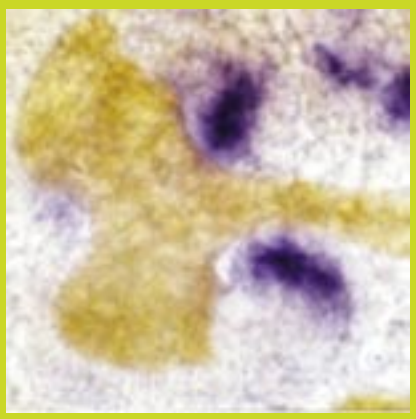


Kidney **development**

Kidneys arise via molecular dialogue between two simple tissues during development. These create highly specialised filtration units and a plumbing system which filter blood to produce urine, control blood pressure and red blood cell number. We are examining what genes control this process to generate a normal and functional kidney. The corollary of this is understanding what goes wrong in kidney disease with a view to diagnosis, treatment and ultimately organ regeneration.

Genetic basis of kidney development

The kidney is a complex and vital organ. If kidneys fail, treatment involves long term dialysis or organ



transplantation, both of which have considerable side effects. The projects under way in this laboratory all focus around the molecular basis of kidney formation: from novel gene isolation, to expression pattern, protein localisation, mode of action and function within the kidney. Our aim is to ultimately impact on renal disease by first understanding the normal process of kidney development.

Mechanism of action of the WT1 protein

The *WT1* gene was isolated as a tumour-suppressor gene mutated in a type of childhood kidney cancer, Wilms' tumour. We have verified that while mutated in sporadic Wilms' tumours, *WT1* is not mutated in all such tumours. *WT1* has subsequently been shown to be critical for normal kidney development and ongoing function and is mutated in a rare renal failure condition called Denys Drash syndrome. The *WT1* gene encodes many related proteins which must interact to regulate both DNA and RNA within the cell. We are investigating how this regulatory protein works to create a kidney and keep it functioning by examining what genes it regulates and what proteins and nucleic acids it interacts with and for to what end.

The Slit genes in kidney development

We recently isolated members of the *Slit* gene family from developing kidney. These genes are related to a fruitfly gene which regulates nervous system and excretory system development. There are three members of this gene family in vertebrates and each has a specific pattern of expression during kidney development suggesting roles in

& disease

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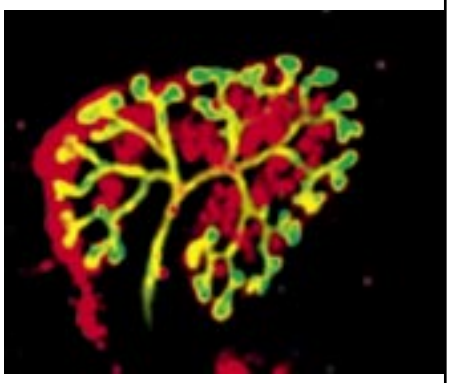
mesoderm migration and nephron formation. We have established a kidney organ culture system to test the role of these gene products in kidney morphogenesis. We are also



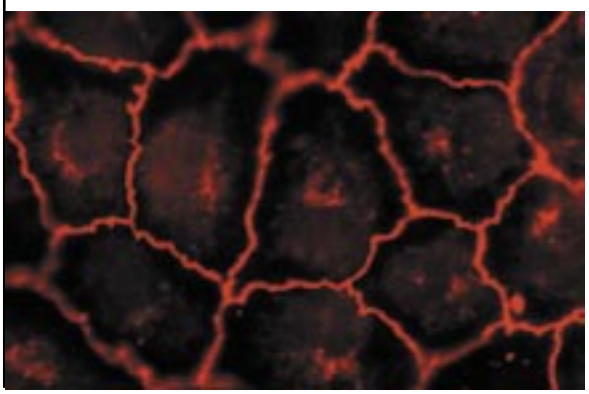
investigating the expression pattern and function of slit receptor proteins, the 'roundabout' proteins.

Crim1: A novel gene involved in organogenesis

Crim1 is another novel gene that we isolated from developing kidney. This gene encodes a large membrane protein with characteristic cysteine-rich motifs likely to interact with a known family of growth factors, the TGFbeta superfamily, to control, not only, kidney development but also lens, spinal cord, brain and tooth. *Crim1* is also expressed strongly in the testis, but not the ovary, suggesting a role in male differentiation. We are biochemically characterising the ability of *Crim1* to interact with growth factors and establishing bioassays to assess its therapeutic potential in kidney, lens and CNS disorders.

Screening for novel genes involved in nephron formation

End stage renal failure (ESRF) is a major health burden worldwide with 250,000 new patients in the US annually. ESRF amongst indigenous populations worldwide is also climbing dramatically for unknown reasons. An understanding of what genes are required to make a nephron provides fundamental information for the early diagnosis of those likely to suffer ESRF later in life and ultimately will enable us to regenerate functional kidneys for the treatment of ESRF patients. To more rapidly isolate important genes in kidney development, we are embarking upon microarray-based high throughput expression analysis. Novel genes isolated from such screens can then be assessed for their importance in kidney development using the organ culture assays we have now established.

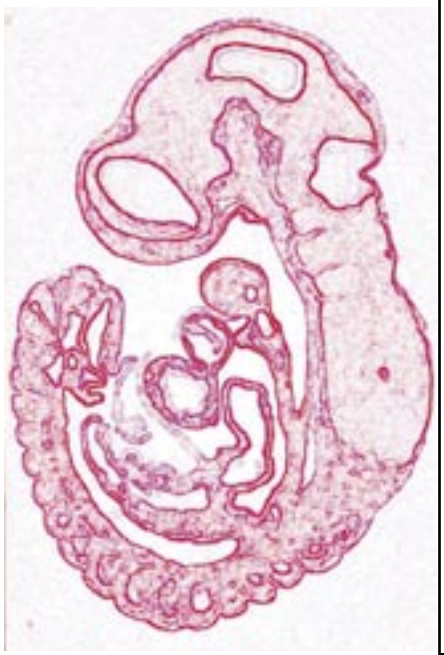


Molecular analysis of **cutaneous**

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

Skin and hair follicle development

A major focus of our group is identifying the signals and messages involved in specifying the formation of the integument. We are studying several genes and their protein



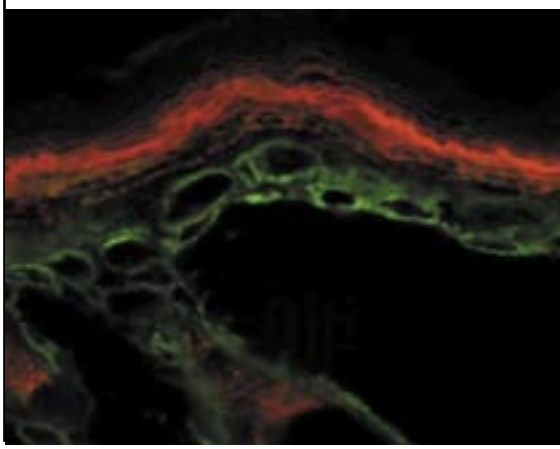
products including, *Smoothened, Frizzled3* and *Gli1*. In collaboration with Brandon Wainwright's group we have made transgenic mice that overexpress *Smoothened* and *Gli1* in order to determine the contribution of these genes to the development of basal cell carcinoma. We have also undertaken a systemic analysis of *Frizzled* gene expression during skin development in collaboration with Graham Cam (CSIRO-Prospect).

Keratinocyte differentiation and formation of the epidermal barrier

Primary functions of the epidermis are to protect us from environmental assault and prevent desiccation. A key protein involved in both these functions is profilaggrin. This large and abundant protein is expressed late in epidermal differentiation and is thought to regulate skin water content, have innate anti-microbial activity, modulate the skin's response to UV damage and act as a calcium sink. We have cloned the mouse Profilaggrin gene and other related genes.

Determination of the roles of the non-helical domains of intermediate filament proteins

Intermediate filament proteins consist of a highly conserved central alpha-helical domain flanked by non-helical domains of varying size and composition. While the function of the helical domain has been known



systems

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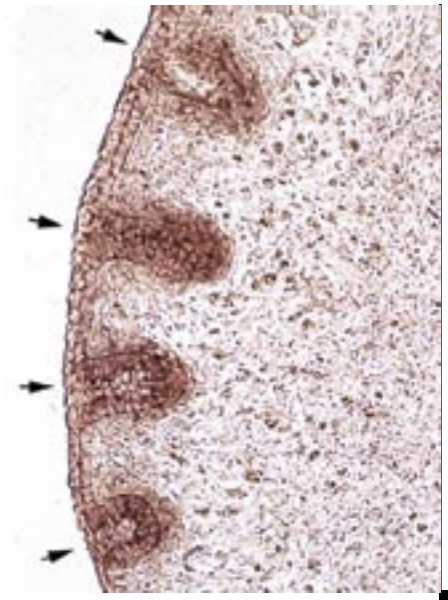
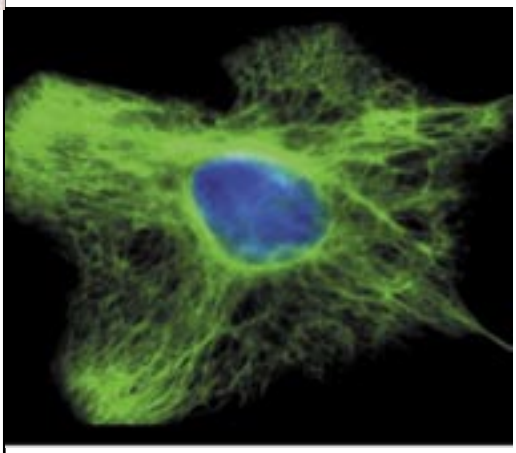


we have examined the promoter of mouse KRT6a in transgenic mice. We found that deletions into the promoter resulted in constitutive expression of the transgene but did not alter cell type specificity. We have localized the *cis*-elements that mediate inducibilty to region 1.5kb upstream of the transcription initiation site.



for several years, the role of the end domains has yet to be fully elucidated. We have used fluorescent tags to determine that a subset of these end domains contain motifs that specify cytoplasmic localization through interactions with microtubule filaments. This knowledge has helped explain several in vitro observations and data from knockout mice.

KRT6a: an inducible epidermal keratin

The *KRT6a* gene encodes keratin K6a, which is normally expressed in the companion layer of the hair follicle but is induced in outer root sheath and epidermal keratinocytes in response to wounding. Because of the utility of an inducible promoter for applications such as gene therapy

Molecular genetics of **pigment**

The physical traits of skin, hair and eye colour are important factors determining an individuals risk of solar UV-induced skin cancer. We are investigating the human genes that are involved in directing pigmentation phenotype and help define a person's skin cancer risk. The group has isolated and characterised several human gene homologues of mouse genes regulating coat colour to use them as tools to investigate the molecular genetics of human pigmentation.

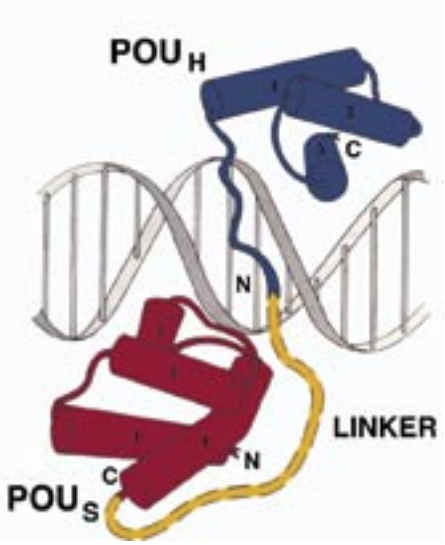
MC1R alleles in normal variation of human pigmentation and skin cancer risk

Classical genetic studies of pigmentation patterns between and within human population groups have so far revealed little as to its molecular basis, although it

is clear that environmental factors may also play a substantial role on sun-exposed skin. Despite this polygenetic inheritance there is likely to be only a few major genes that will exert a dominant influence on pigmentation phenotype with others playing modifying roles. We have studied *MC1R* coding region variation associations with hair and skin colour in humans by genotyping members of a large collection of adolescent caucasian twins from South-East Queensland. Twelve amino substitutions have been found at 11 different sites. Three alleles were linked to red hair with one variant most frequent in fair, blonde and light brown hair colours. These three red hair variants were found to be overrepresented in a population-based sample of 460 familial and sporadic melanoma cases compared to 399 control individuals; each of these alleles doubled melanoma risk and increased risk fourfold if two variants were carried.

Establishment of immortal human melanocyte cell lines of different MC1R genotype

Sensitivity to sunburn and poor tanning ability are well recognised risk factors for both melanoma and non-melanoma skin cancer. We intend to study the functional consequences of these changes on the physiology of the melanocyte which produces the protective pigmentation induced by sun exposure. Melanocyte cell strains will be established from



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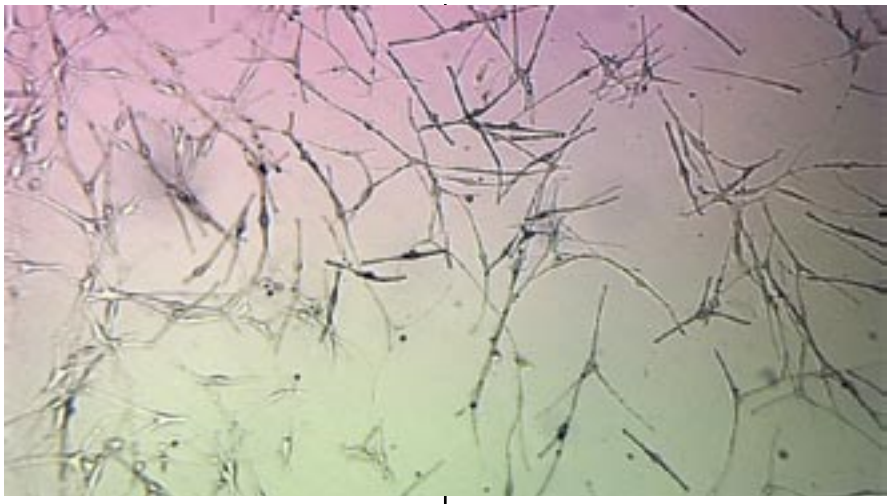


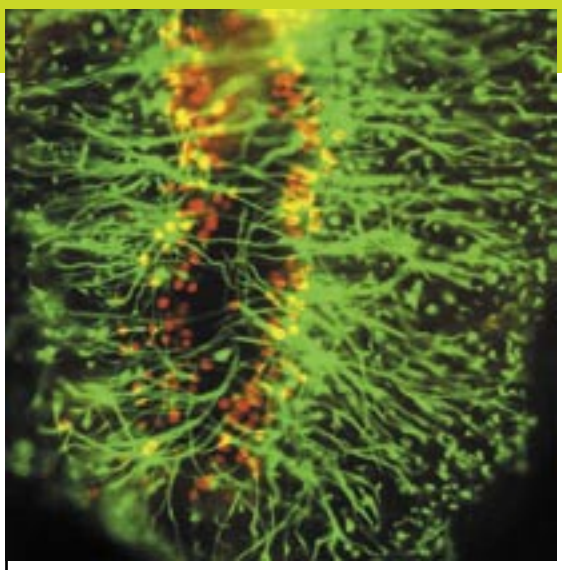
individuals of different *MC1R* genotype and will be immortalised using the catalytic subunit of human telomerase (hTERT). These cells will provide a resource to investigate the role of different *MC1R* alleles in directing different gene expression patterns, UV-sensitivities, and establish the variables in the ability to respond to sun-exposure of cells in culture.

The Brn-2 gene regulates the melanocytic phenotype

A number of Oct-proteins that interact with the control sequence ATGCAAAT and belong to the POU-class of transcription factors have been described. The study of Oct-transcription factors expressed in melanocytic cells has identified the Brn-2 POU domain transcription factor which may act in a similar role as other cell specific Oct-family members in directing melanocytic cell fate and gene expression. An antisense RNA strategy was used to phenotypically knockout *Brn-2* expression in melanoma. This loss of expression was associated with a change in cell morphology and led to the loss of a number of differentiation markers, including the *TYR*, *TRP-1* and *TRP-2* pigmentation genes. The Brn-2 protein has been shown to homodimerise *in vivo* with high affinity, with dimer formation dependent on the presence of both the homeodomain and linker regions of the POU-domain by using Brn-2 deletion expression constructs. We have also studied Brn-2 protein interactions with the basal transcription complex, the transcriptional coactivator p300 and with the Sox10 and Pax3 transcription factors that are known to play an important role in melanocyte formation.

Molecular genetics of **neural devel**

The nervous system is the most complex organ in the body and its formation requires intricate cascades of gene regulation during embryonic and postnatal development. We are investigating the molecular and genetic mechanisms that control the development of the nervous system in vertebrates. Discovering how genes and molecules function and interact during normal development will provide a fundamental understanding of how the functioning brain is generated and maintained, and possible underlying causes of neurological diseases.

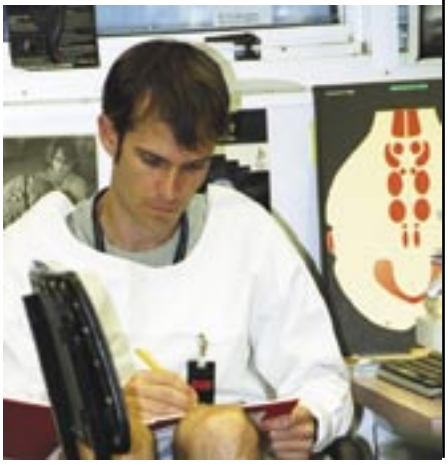


Molecular genetics of neural development in vertebrates

Our laboratory is interested in the molecular genetics of neural development in the vertebrate embryo. During normal development, an embryo has to produce thousands of functionally and morphologically different types of neurons and glial cells at correct positions within the nervous system and interconnected precisely with other neurons or target cells. We are studying how these processes are controlled at molecular and genetic levels during embryonic development. Projects include the control of neural cell patterning and cell-type specification by growth factors, and gene expression in developing brain and spinal cord.

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

The diversity of neuron types in the developing spinal cord is thought to be determined by a gradient of secreted signalling protein, Sonic hedgehog, but the exact details of how this protein works are unknown. This project investigates the roles of Sonic hedgehog and its downstream signalling pathways in neuronal precursors in the developing spinal cord.



Cell-type specification by transcription factors

In response to differentiation signals such as *Sonic hedgehog*, neuronal precursors and young neurons begin to express a variety of transcription factors which act as a "genetic switch" for cell-type specification. In this project, we focus on several transcription factors including *Sox14*, a member of the Sox transcription factor family, whose expression defines unique classes of ventral interneurons in the developing spinal

opment

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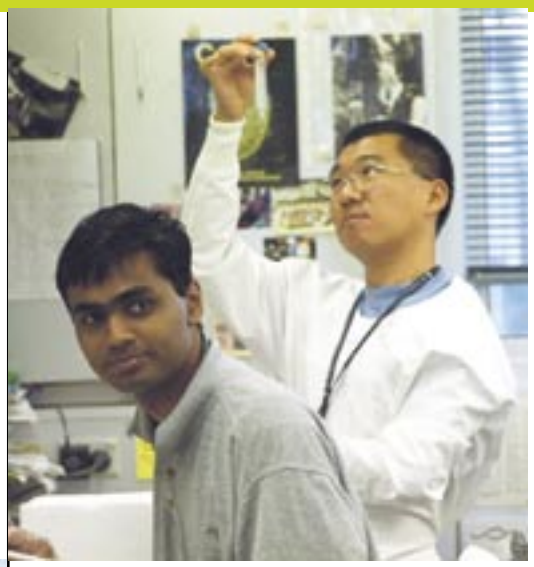
cord. To identify the exact function of this gene, we are currently making a *Sox14* gene knockout mouse model.

Functional analysis of vertebrate Slit genes in developing CNS

The formation of functional neuronal circuits is controlled by complex cell interactions mediated by a variety of secreted signals. We investigate this process by studying the function of vertebrate *Slit* homologues which are expressed in the floor plate and notochord, which are known to be critical in the control of cell



patterning and axon guidance in the CNS, and in developing motor neurons.

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

Crim1 is a newly discovered gene expressed in the floor plate, notochord and developing motor neuron in the spinal cord. The protein product of *Crim1* is thought to regulate the functions of other growth factors in the developing CNS, in particular Bone Morphogenetic Proteins and members of the TGF-beta superfamily, through its highly conserved cysteine-rich repeats. We are studying the functions of *Crim1* in the context of neuronal cell differentiation, cell migration and/or survival in the spinal cord.

Molecular genetics of **human**

As part of our studies into a common cancer, basal cell carcinoma, we isolated the gene responsible and showed that it was also involved in other cancers. We are now looking at the role of this gene and related molecules in both cancer and normal development of the embryo. For our gene therapy studies we use as our model the common inherited disorder cystic fibrosis. This work concentrates on how the gene defect results in the many symptoms of the disease, and how it might be possible to correct it.

Function of the patched tumour suppressor gene

We discovered that the *patched* gene was mutated in basal cell carcinoma of the skin and in the common human brain cancer, medulloblastoma. In order to further define the function of *patched*, we have modelled many of the missense

mutations *in vitro* and examined their localisation and binding to the ligand, Sonic hedgehog (Shh). In collaboration with Dr Michael Fietz, some novel mutants have been over-expressed in *Drosophila* and as a result we have identified a region of patched which appears to be responsible for binding the Shh ligand and the region responsible for transmitting the signal to the nucleus via the G-protein coupled receptor, Smoothened.

Downstream targets of patched signalling

Whilst the patched forms a hetero-trimeric complex on the cell surface (with Smoothened and its ligand Shh) the downstream targets of signalling events are largely unknown. In order to address this issue we have established an *in vitro* model system for patched/hedgehog signalling where we can add the Shh ligand and activate the pathway. We have performed microarray experiments with our collaborators, Drs Sean Grimmond, Carol Wicking, and Lindsay Fowles, and have identified several novel targets of patched/hedgehog signalling which are currently under analysis to define their role in cancer, differentiation and development.

The cellular origin of basal cell carcinoma

Transgenic animal studies from several laboratories have indicated that patched mutant mice develop basal cell carcinoma-(BCC) like lesions. Despite this, it is still not clear which cells of the skin give rise to BCCs. In order to address this issue, we have generated a number of transgenic animals that express Cre recombinase in specific skin

disease

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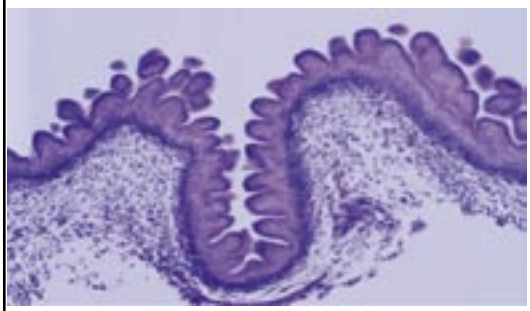
compartments. Gene-targeted mice have been developed which excise the patched gene in the presence of Cre recombinase and current breeding programs are designed to remove patched function from specific skin compartments.

Origin of the cystic fibrosis inflammatory response

Data from a number of laboratories including our own has now indicated that in addition to the known biochemical properties of the CF gene (*CFTR*), CF individuals have a *CFTR*-mediated inflammatory defect such that they respond massively to inflammatory stimuli. Given the cytokine profile of the infected CF lung and existing in vitro data, it appears that both epithelial and inflammatory cells may express cell autonomous *CFTR*-mediated defects in the inflammatory response. In order to address this question we have generated a number of transgenic mice expressing human *CFTR* under the control of a macrophage-specific promoter, and animals expressing human CFTR under the control of an epithelium-specific element. These lines have been crossed to our CF mice, and as a result it appears that the epithelial cells are the source of the inflammatory defect.

Genes controlled by CFTR

Epithelial cells lacking CFTR have a dysregulated inflammatory response after challenge both *in vitro* and *in vivo*. The mechanism of the interaction between CFTR activity and the inflammatory cascade is unknown, and so we have approached this issue using cDNA microarrays. Using a 20 K human cDNA chip we have profiled the genetic response of human airway epithelial cells to *Pseudomonas aeruginosa* in the presence and absence of CFTR. In this way we have identified a number of genes regulated by PA and/or CFTR. Some of these genes/pathways are potential novel targets for therapeutic intervention into cystic fibrosis.



Developmental genes in human

Birth defects arising from abnormal development of the embryo are a major cause of infant mortality and childhood disabilities. Our work involves the identification of novel genes involved in embryonic development as well as investigation of the role of several known genes in the processes of embryogenesis and human disease.

The identification of genes involved in mammalian craniofacial development

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

Subcellular localisation of members of the hedgehog signalling pathway

The hedgehog signalling cascade plays a pivotal role in embryonic development and tumour formation. In collaboration with Rob Parton and Brandon Wainwright we have

disease

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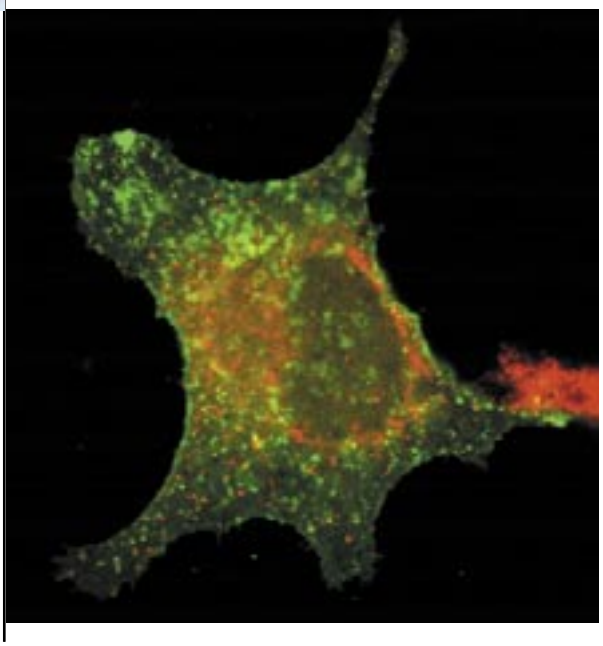
Proteins which interact with the Gli transcription factors

The Gli family of transcription factors are involved in mediating transcription of genes important in the hedgehog signalling pathway. There are three members of this family in vertebrates, at least two of which are involved in human disease. Using a yeast two hybrid approach, we are investigating the nature of the proteins which interact with each of these molecules. This will give us further insight into the role of the Gli proteins in development and disease.

been investigating the subcellular localisation of members of the hedgehog pathway, in particular the hedgehog receptor molecule patched. Employing both immunofluoresence analysis and electron microscopy studies, we have localised patched to endocytic vesicles within the cell. We are extending these studies to other members of the hedgehog pathway in an attempt to understand the processes involved in regulating reception of the hedgehog signal. Because cholesterol is known to play an important role in this pathway we are also investigating its possible involvement in protein localisation and trafficking.



Microarray expression profiling is a rapidly developing technology that combines robotics, molecular biology and bio-informatics to study expression of tens of thousands of genes at once in a single experiment. In this way we can identify and study genes involved in normal biological processes and those whose expression are altered in disease states.

Microarray expression profiling

Group leader • Sean Grimmond

Research assistant • Alistair Forrest

Expression profiling of melanoma

We are using expression profiling with cDNA and tissue microarrays to define the genes involved in development and progression of melanoma tumorigenesis, define transcription patterns associated with the presence of key oncogenic and tumour suppressor gene mutations commonly associated with melanoma (P53, P16, PTEN, N-RAS, B-Catenin), and analyse melanoma patient samples to find those genes whose expression patterns correlate with pathology, prognosis and therapeutic response. This work is being done in collaboration with Drs Nick Hayward, Sandrah Pavey and David Whiteman at QIMR, and Drs Jeff Trent and Mike Bittner at NHGRI, NIH.

Studying tumour suppressor function of e-cadherin

This project aims to identify genes regulated by the invasion suppressor gene, E-cadherin. Cadherins are a family of cell-cell adhesion molecules that control tissue and cell patterning in most tissues of the body. In collaboration with Dr Alpha Yap (IMB), global gene expression profiling is being used to study the action of human E-cadherin in a series of E-cadherin inducible human colon and breast cancer cell lines with differing metastatic potential.

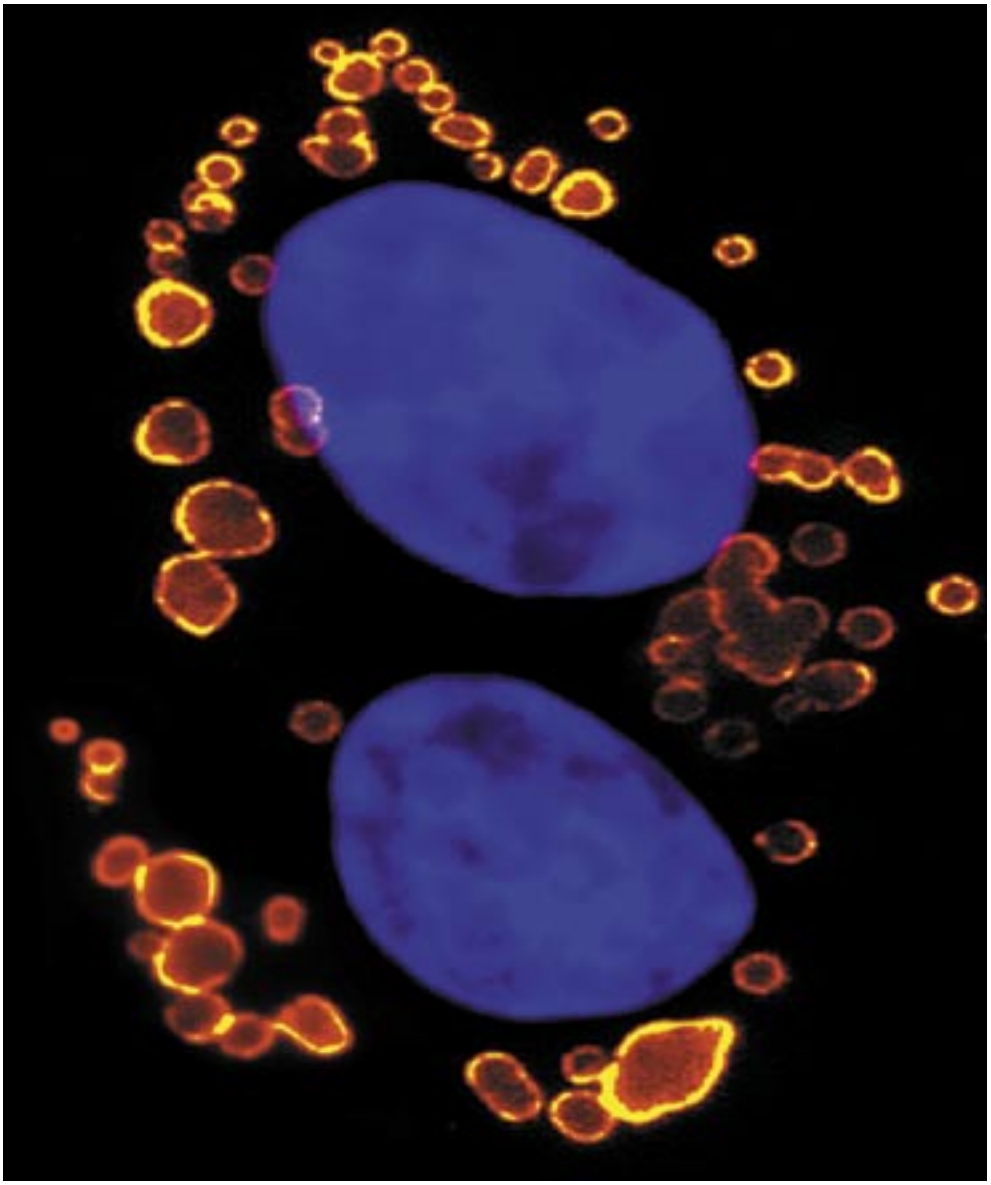
Redefining endothelial cell biology by expression profiling

Angiogenesis, or the development of a vascular network, is a complex process governed by cellular interactions, changes in environment and signalling by soluble factors. Perturbation of this process leads to a variety of pathologies. An ever-expanding list of agonists/antagonists of angiogenesis have been defined. Many of these agents act directly on endothelial cells, key cells involved in generation of new vessels. We are defining the transcriptional responses of endothelial cells to endogenous and exogenous modulators with the aim to better define the processes of migration, proliferation and differentiation.

Genomic and proteomic dissection of the molecular basis of kidney development

This work is being performed in collaboration with Dr Melissa Little (IMB) and aims to improve our understanding of mouse kidney development. The temporal gene expression pattern of the developing kidney and the process of mesenchyme-to-epithelial transition is to be monitored by expression profiling.

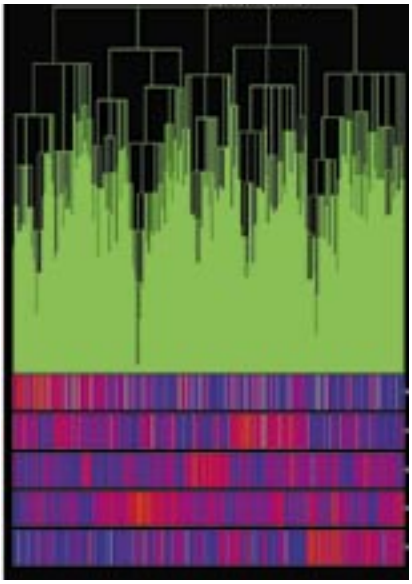
Cell Biology



The cell is the fundamental unit of life. Cell biologists strive to understand the complex molecular mechanisms that act together to make up complex organisms such as man. Our understanding of these processes is vital to our fight against disease.

Macrophages *and* osteo

Macrophages are large white blood cells that form a front line defence against infectious disease and contribute to normal tissue turnover in development and wound repair. Osteoclasts are related cells in bone that control the release of calcium. By understanding how these cells function, we hope to bolster normal immunity and restrict their activities in diseases like arthritis, osteoporosis and atherosclerosis where they are responsible for much of the pathology.



Actions of microbial DNA

Mammalian macrophages are able to recognize danger signals that are generic to wide classes of microorganisms, such as the cell wall component lipopolysaccharide (LPS), and respond by amplifying innate defences and releasing regulators that prime the acquired immune response. One of these "pathogen-associated molecular patterns" is bacterial DNA, which contains unmethylated CG dinucleotide sequences that are suppressed or methylated in the mammalian genome. We have found that replication protein A, a protein involved in DNA damage recognition and normal DNA replication, has a selective ability to bind macrophage-activating DNA sequences. The mechanisms linking this recognition to signalling in macrophages are currently being elucidated.

Control of the c-fms and TRAP genes

Like all cell types, macrophages and osteoclasts express a wide range off lineage-specific genes that are required for specific functions. We have an ongoing program aimed at identifying the key elements of the *c-fms* and *TRAP* genes required for expression in macrophages and osteoclasts respectively. The *c-fms* gene contains a key element in the first intron that is highly-conserved in mouse and human. This element has been shown to be in open chromatin only in macrophages. We have found that the fms intronic regulatory element (FIRE) is both an enhancer required for macrophage-specific transcription and an inducible repressor that controls the level of expression. We have succeeded in identifying the minimal elements required for tissue-specific expression of fms, and created

clasts

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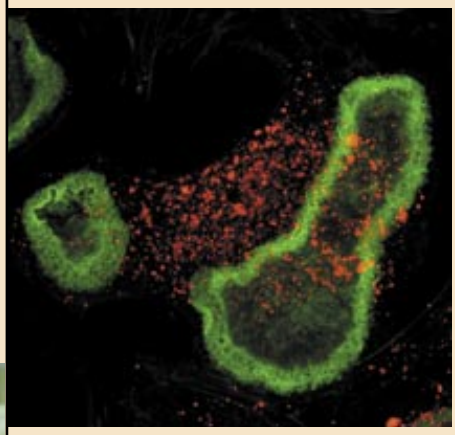
transgenic mice in which the fms promoter drives expression of the green fluorescent protein to cells of the macrophage lineage. Studies of the *TRAP* gene, which encodes a key protein required for bone resorption, have focussed on the regulatory importance of transcription factors of the microphthalmia gene family. We have also identified a novel TATA-element that is utilised only in osteoclasts. The study of osteoclast differentiation has been expedited by the identification of a subclone of a macrophage cell line (RAW264) that can express osteoclast-specific genes when stimulated with osteoclast-differentiation factor.

cDNA microarrays

Traditional studies of gene regulation focus on one gene at a time. The availability of large numbers of sequenced cDNAs, and technology to be array them in grids of thousands on glass slides, permits a more global analysis. We have obtained arrays of macrophage-expressed genes and begun to analyse inducible gene expression in macrophages. Completed studies provide insight into the remarkable plasticity of gene expression in macrophages. Subclones of the macrophage cell line RAW264 display widely divergent spectra of expression of macrophage-specific genes either in the basal state, or particularly when stimulated with LPS. Clustering algorithms reveal families of genes



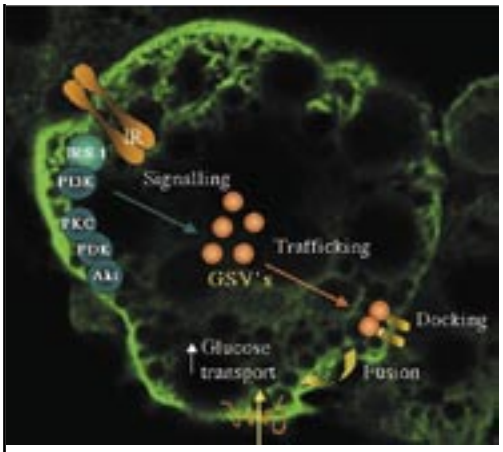
that tend to be coregulated. In another study, we have used arrays to analyse the effect of a mutation of the putative receptor for LPS, TLR4. Mice with this mutation (C3H/HeJ) fail to induce a set of inflammatory genes in response to LPS, but array analysis reveals sets of genes that retain LPS responsiveness. The results suggest that either the mutation is only a partial loss of function, or there is another receptor.

Cell biology of **diabetes**

We are deciphering the molecular basis of Type II diabetes, a disease affecting as many as 1.5 million Australians. Insulin is secreted in response to increased blood sugar to enhance glucose uptake into muscle and adipocytes. This is mediated by a complex series of molecular reactions that somehow go awry in Type II diabetes.

Insulin signal transduction

A major question is how different growth factors achieve biological specificity given the tremendous overlap in downstream signalling pathways. The insulin receptor (IR), like many growth factors, stimulates phosphatidylinositol 3' kinase and a serine threonine kinase (Akt) in muscle and fat cells as an essential part of the metabolic program. However, metabolic regulation is highly specific to IR. We are currently exploring the molecular basis for this specificity by focussing on the intracellular location of these signalling events in adipocytes, because location combined with strength and duration of signalling are essential parameters in defining specificity. In addition, we are using a proteomics approach involving mass spectrometry to discover new targets that are downstream of insulin-stimulated Akt in adipocytes.



Regulated exocytosis of GLUT4

GLUT4 is the major glucose transporter in muscle and adipocytes. Insulin stimulates the exocytosis of this molecule from intracellular vesicles called GSVs to the plasma membrane of the cell. We have identified a targeting motif in the cytosolic tail of GLUT4 that controls early endosomal sorting. This motif is also found in a number of other proteins including an insulin responsive amino peptidase, a protein convertase and certain Syntaxins. We have recently devised a strategy for

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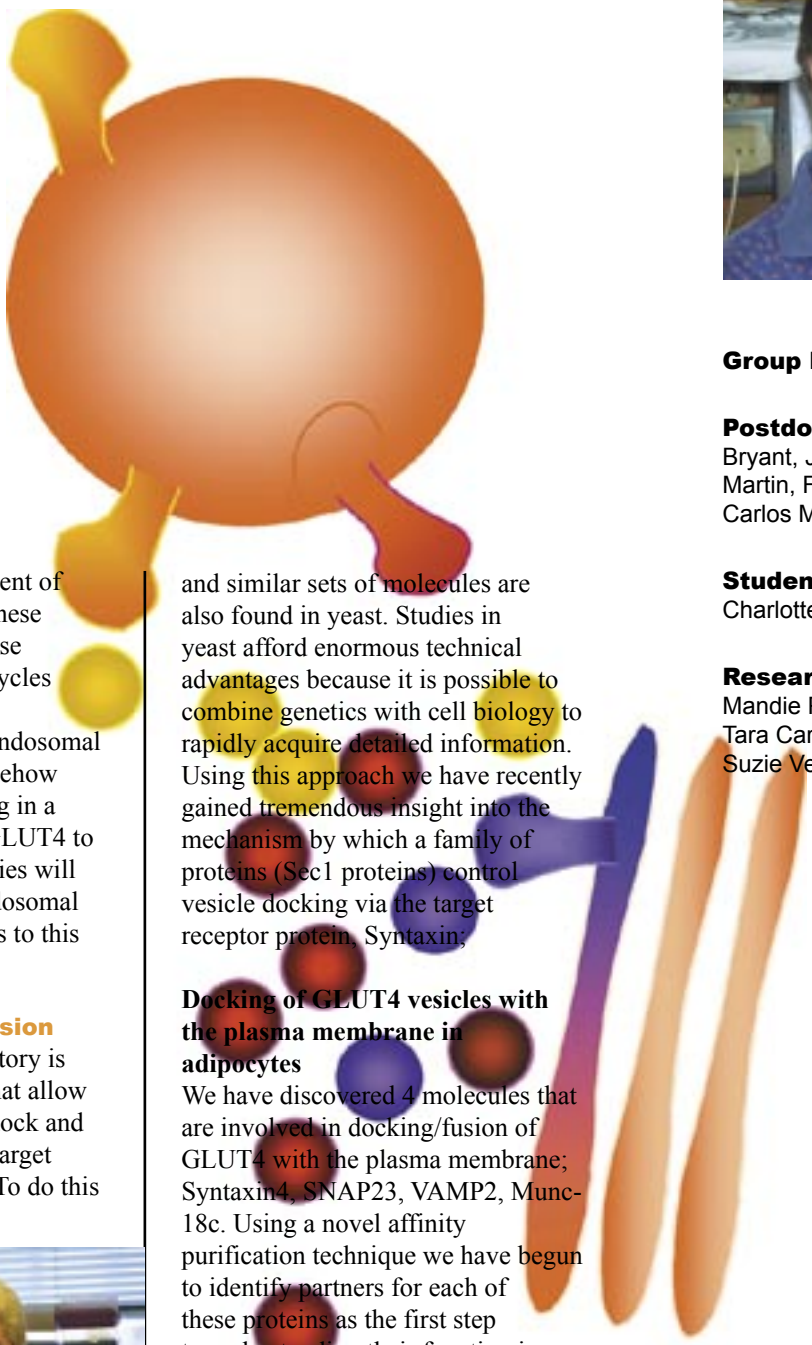


studying the kinetic movement of GLUT4 in adipocytes and these studies have led us to propose a model in which GLUT4 cycles between the Golgi and the endosomes via the unique endosomal targeting motif. Insulin somehow overrides this cycle resulting in a shift in the distribution of GLUT4 to the cell surface. Future studies will focus on identifying the endosomal sorting machinery that binds to this new class of sorting motif.

Vesicle docking and fusion

A major focus of our laboratory is to define the mechanisms that allow discrete vesicle carriers to dock and fuse with their appropriate target membranes inside the cell. To do this we focus on 3 areas:

Vesicle transport in *Saccharomyces cerevisiae*

Many of the molecules that regulate vesicle docking/fusion in mammalian cells are conserved through evolution and similar sets of molecules are also found in yeast. Studies in yeast afford enormous technical advantages because it is possible to combine genetics with cell biology to rapidly acquire detailed information. Using this approach we have recently gained tremendous insight into the mechanism by which a family of proteins (Sec1 proteins) control vesicle docking via the target receptor protein, Syntaxin;

Docking of GLUT4 vesicles with the plasma membrane in adipocytes

We have discovered 4 molecules that are involved in docking/fusion of GLUT4 with the plasma membrane; Syntaxin4, SNAP23, VAMP2, Munc-18c. Using a novel affinity purification technique we have begun to identify partners for each of these proteins as the first step to understanding their function in insulin action;

Melanogenesis

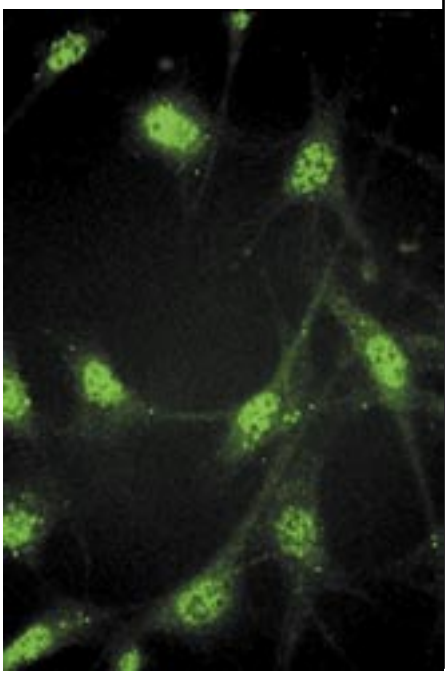
We have recently discovered that Syntaxin7 is involved in late endosomal transport and is substantially upregulated in B16 melanocytes. Taking advantage of this observation we have immunopurified Syntaxin7 complexes from these cells and have identified several new Syntaxin7 binding partners including VAMP8, mVti1b, alpha SNAP and a myosin phosphatase regulatory subunit.

Muscle and nuclear hormone

Age and injury-induced muscle wasting, cachexia, muscle tumours and hypertrophy reflect a malfunction in the balance between muscle growth and wasting. These processes are adaptive responses to exercise, injury and pathological stimuli. Our group focuses on investigating the role of nuclear hormone receptors and associated cofactors in muscle development as a critical step toward elucidating the function of these proteins in muscle disease.

Nuclear receptor cofactor function in skeletal myogenesis

Nuclear hormone receptor mediated activation of transcription is associated with cofactors collectively denoted as the steroid receptor coactivators (SRCs). SRCs interact with p300/CBP and recruit PCAF to a complex that synergistically activates transcription. PCAF and p300 have also been shown to function as critical coactivators for the myogenic transcription factors, MyoD, myogenin, and MEF-2 during differentiation. We examined the role of one SRC, GRIP-1, in muscle differentiation, an ideal paradigm for the analysis of the events that govern the cell's decision to divide or differentiate. Ectopic expression studies with GRIP-1 in muscle cells demonstrated that this SRC is necessary for contractile protein gene expression and differentiation. Furthermore, we demonstrate that, GRIP-1, coactivates myogenin- and MEF-2C-mediated transcription. The mechanism involves direct protein-protein interactions between MEF-2C, myogenin and GRIP-1. This work demonstrates that the steroid receptor coactivator, GRIP-1, potentiates skeletal myogenesis.



Cofactor sub-cellular localisation in muscle and rhabdomyosarcoma cells

GRIP-1 is necessary for skeletal myogenesis, and functions as a cofactor for the transcription factor MEF2. We localised GRIP-1 in the nucleus of proliferating myoblasts, however, notable expression was observed in the cytoplasm. Differentiation induces a predominant localisation of GRIP-1 to the nucleus. MEF2 is primarily expressed in the nucleus, although we observed a mosaic or variegated expression pattern in myoblasts. However, all nuclei in myotubes express MEF2. Rhabdomyosarcoma (RMS) cells derived from malignant skeletal muscle tumors express GRIP-1 in a diffuse nucleo-cytoplasmic staining pattern. MEF2 and the other SRC cofactors, SRC-1 and SRC-3 are abundantly expressed in RMS cells, however, the staining is not localised to the nucleus, and

receptors

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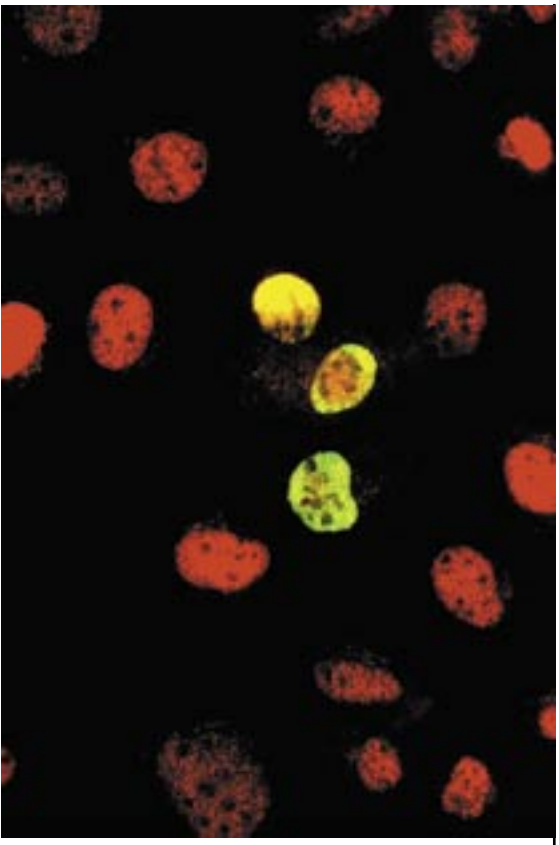
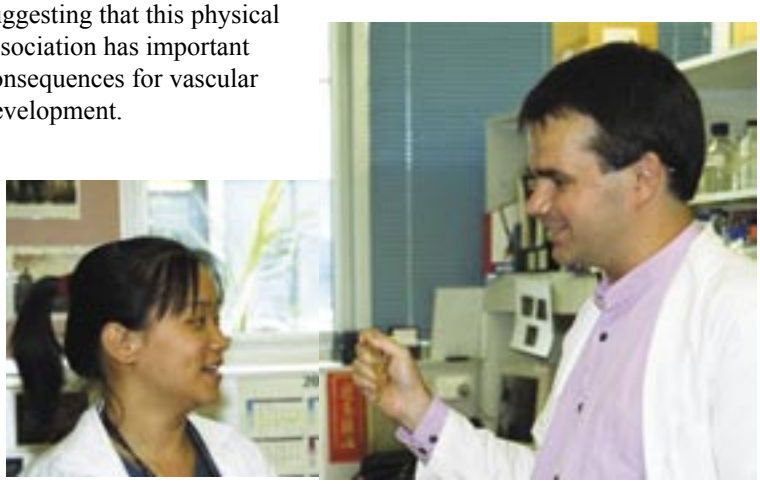


predominantly accumulates in the cytoplasm. This suggests trafficking of transcription factors and steroid receptor coactivators is a critical event during myogenesis. More importantly, the breakdown in SRC trafficking in rhabdomyosarcoma cells suggests this process has a critical function in differentiation and the onset of tumorigenesis.

Sox18, and the regulation of endothelial gene expression

In collaboration with Peter Koopman's laboratory we demonstrated that mutations in the Sry-related HMG box gene *Sox18* underlie cardiovascular and hair follicle defects in the mouse mutant ragged (*Ra*) and the allelic mutant *RaJ*. MEF2C is expressed in developing endothelial cells. Deletion of the *Mef2c* gene in mice results in vascular abnormalities with some similarity to the Ra defects. We show direct interaction between the MEF2C and SOX18 proteins which results in synergistic trans-activation. This interaction is mediated by the MADS domain of MEF2C, and by two regions of the SOX18 protein, the HMG domain, and a carboxy terminal region that includes the activation domain. In situ hybridization and immuno-fluorescence established that MEF2C and SOX18 are expressed and colocalised in endothelial cell nuclei. The *Ra* and the *RaJ* mutant SOX18 proteins fail to interact with MEF2C suggesting that this physical association has important consequences for vascular development.



Cell biology of the plasma

Animal cells are enclosed by a membrane, termed the plasma membrane. This membrane acts as a barrier to stop invasion by pathogens while allowing communication between the outside environment and the interior of the cell. We are studying how the plasma membrane functions in healthy cells, how toxic agents such as viruses have managed to overcome the cell's defences, and how the normal functions of the plasma membrane are disrupted in diseases such as muscular dystrophy and cancer.

Structure and function of caveolae

Caveolae are a characteristic and abundant feature of the plasma membrane of many mammalian cells. These 60-80nm uncoated flask-shaped pits have been implicated in many different cellular processes but their exact function remains unclear. The major membrane proteins of caveolae are integral membrane proteins termed caveolins. Caveolins have been linked to a number of disease conditions, including tumorigenesis, Alzheimer's disease, Niemann-Pick type C, and limb-girdle muscular dystrophy. A major focus of our group is to understand the role of caveolae and caveolins in cellular function.

Entry of viruses into animal cells

We have shown that the tumour virus, SV40, hijacks caveolae as a means to gain entry into the cell and ultimately to reach the cell nucleus where it replicates. We are now characterising the trafficking pathway. We have also examined the role of caveolins in SV40 entry by generating mutant caveolin proteins and assaying their effects on the infectious entry pathway. In this way we were able to generate dominant negative inhibitory mutants of caveolin which inhibited viral infection.

Functional studies of caveolins

Dominant inhibitory mutants of caveolin identified with the SV40 screen were tested for their effect on specific signalling pathways (in collaboration with Prof. John Hancock). A caveolin mutant specifically inhibited signalling by one Ras isoform, H-ras, but not by a different isoform of Ras, K-ras. Unexpectedly, the mutant caveolin protein was shown to be acting through an effect on cholesterol transport and, as a consequence, inhibited signalling events occurring in cholesterol-rich cell surface domains. This study provided the first evidence that H-ras signalling occurs in specialised domains of the cell surface termed 'lipid-raft' domains. We are currently studying how caveolin regulates lipid transport, an area of intense interest at the present time.

Muscle development and muscular dystrophy

Muscular dystrophy is characterised by increased membrane fragility and disorganisation of surface domains in muscle cells. We discovered a major component of muscle caveolae, now called caveolin-3. Two recent studies suggested that specific mutations in caveolin-3 occur in patients with a type of limb girdle muscular dystrophy. In mature muscle caveolin-3 is an abundant protein of the muscle plasma membrane where it may play a role in the functional organization of the muscle fibre surface. We analysed the effects of dystrophy-associated mutations

membrane

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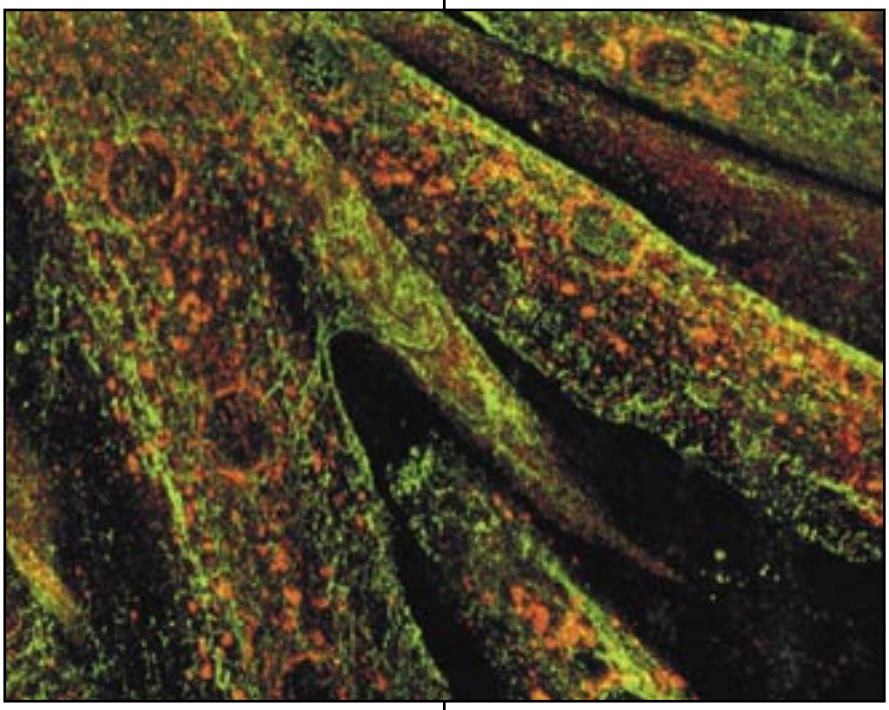
on the localisation of the caveolin protein and on caveolar function. Caveolin-3 trafficking is blocked in cells expressing one of the mutant proteins. Using the Ras signalling assay we also showed that a second mutant might perturb lipid raft domains and so disrupt specific signalling pathways.

developed. We are using a number of novel tools for examination of lipid distribution at the electron microscopic level. Combined with on-section labelling techniques, these agents are giving the first insights into the distribution of lysobisphosphatidic acid, an antigen associated with an autoimmune



Electron microscopic localisation of lipids

Specialised domains of lipids, such as lipid rafts, have been shown to be of crucial importance for many important physiological processes. However, the tools and techniques for lipid localisation are not well

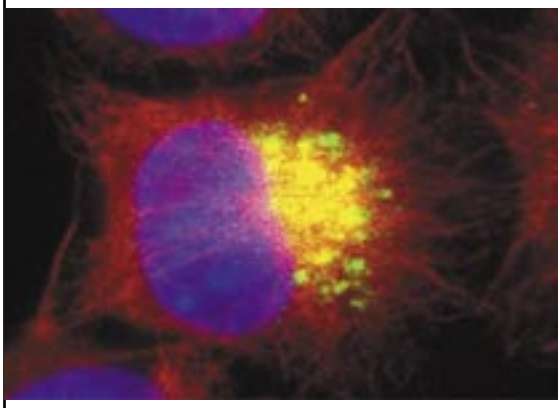
disease, phosphatidylinositol-3-phosphate, which regulates membrane traffic, and sphingomyelin, a marker of lipid raft domains.

Protein trafficking

All cells of the body have complex trafficking pathways for moving and regulating proteins. We are studying protein trafficking in epithelial cells, in organs such as the kidney and gut, and in macrophages. Our studies aim to identify molecules that regulate normal trafficking and can be developed as drug targets for the treatment of cancer and inflammation.

Regulation of protein trafficking

A major focus of our work is to define the functions of some of the genes that regulate protein trafficking in cells. This work involves determining the location and function of selected proteins using a combination of biochemical and microscopy techniques. We have now mapped extensive sets of signal transduction, cytoskeletal, structural and lipid modifying proteins found on different transport. In particular we have shown how G proteins and regulators of G protein signalling (RGS) proteins associate with specific membrane domains and transport vesicles, providing insights into how these protein families might interact. Several new RGS proteins that have the potential to link cell growth and trafficking are also being studied. With Paul Gleeson (Monash University) we have defined the specific membrane domain of a Golgi localisation domain that targets proteins to specific vesicles. Using gene expression and imaging of live cells we are following protein transport in 'real time', and further characterising the transport carriers and the roles of specific vesicle-associated proteins. Our goal is to develop a molecular map of the secretory pathway and determine how movement of proteins to the cell surface is regulated.



Cadherins and cancer

Our work in epithelial cells led us to study how vital cell adhesion proteins- cadherins- are trafficked.

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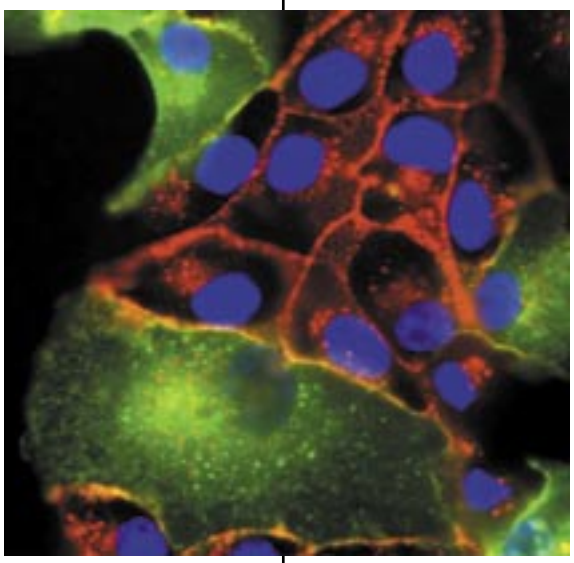
E-cadherin has important roles during early development and in the function of many organs. The loss of E-cadherin is an early event in metastasis of breast, colon, prostate and many other cancers indicating it is also a potent tumour suppressor. In work with Alpha Yap (IMB) we have identified a new pathway for endocytosis of E-cadherin and have shown how its uptake and function can be regulated by signalling pathways. We are also studying E-cadherin trafficking and expression in breast cancer cells with the ultimate aim of developing new manipulations or strategies for tumour suppression. More recently with Rohan Teasdale (IMB) we have begun to characterise targeting signals in cadherins, using bioinformatic and mutagenesis approaches, with the first identification of a signal in cadherins for polarised trafficking to the cell surface.



Cytokine secretion in macrophages

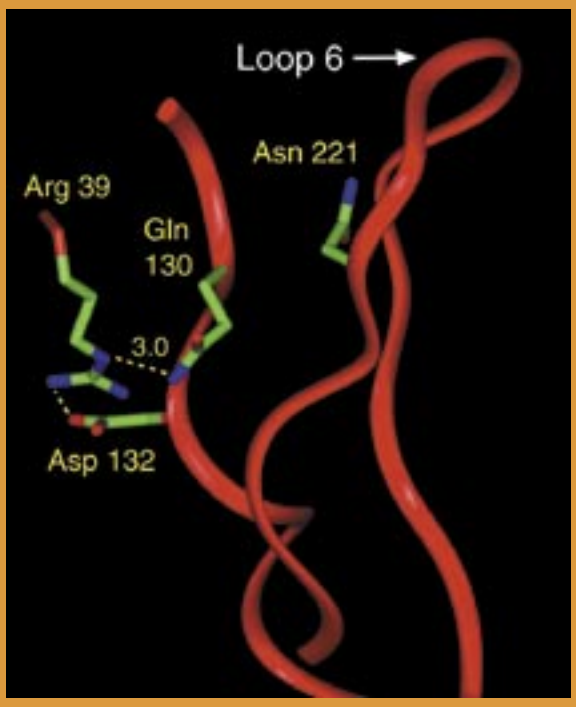
Secretion of cytokines such as tumour necrosis factor (TNF) is a critical part of the host defence against bacterial invasion and the growth of tumour cells. Our group is characterising the pathway and molecules that regulate TNF secretion in macrophages. These studies first described the pathways for exocytic and endocytic trafficking of cleaved, biological active TNF, and we have now also described the disparate trafficking of uncleaved forms of TNF. This latter study has provided new insights into current clinical strategies focussed on using proteinase inhibitors for controlling excess TNF. In current work we are studying gene expression in the secretory pathway of macrophages with the aim of finding strategic, pathway-specific regulators.

Molecular physiology of **growth**

Growth hormone and related cytokine hormones regulate many important physiological processes such as postnatal growth, metabolism, reproduction, lactation and immune function. We study the molecular basis for this regulation at all levels, from the cell surface receptors to the genetic programs used. Research outcomes have implications in the fields of livestock production, clinical treatments for short stature and giantism, diabetic kidney disease and blindness, periodontal disease, and for several aspects of ageing.

Receptor signalling mechanisms

Since cloning the growth hormone (GH) receptor collaboratively, we have have studied the mechanics of its signalling extensively through



mutagenesis of hormone and receptor, through the use of monoclonal antibodies specific to the receptor, and through model peptide systems. We have evidence that a specific conformational change in the extracellular domain of the receptor can differentially affect cellular signalling pathways. We have characterised the epitope and binding characteristics of the monoclonal antibody to receptor able to stimulate growth. We have also created a constitutively active receptor by substituting the external domain with a fos-jun zipper. The latter two findings have potential in livestock production.

Genetic programs regulated by GH

Our group was the first to publish on the use of gene arrays in GH action, identifying a number of important hepatic targets of acute GH action. Using suppression subtractive hybridisation we have studied gene expression during the earliest phase of differentiation from fibroblasts to adipocytes as initiated by growth. This has identified several GH targets intimately involved in differentiation, and supports our view that GH is involved in this process during embryogenesis. Aspects of this are being studied with the use and creation of specific GH receptor knockout mouse models.

Direct nuclear actions of GH receptor

We have shown that the extracellular domain of the GH receptor can be nuclear localized, and that targeting the receptor to the nucleus can sensitize the cell to GH action. We have shown the GH receptor

hormone

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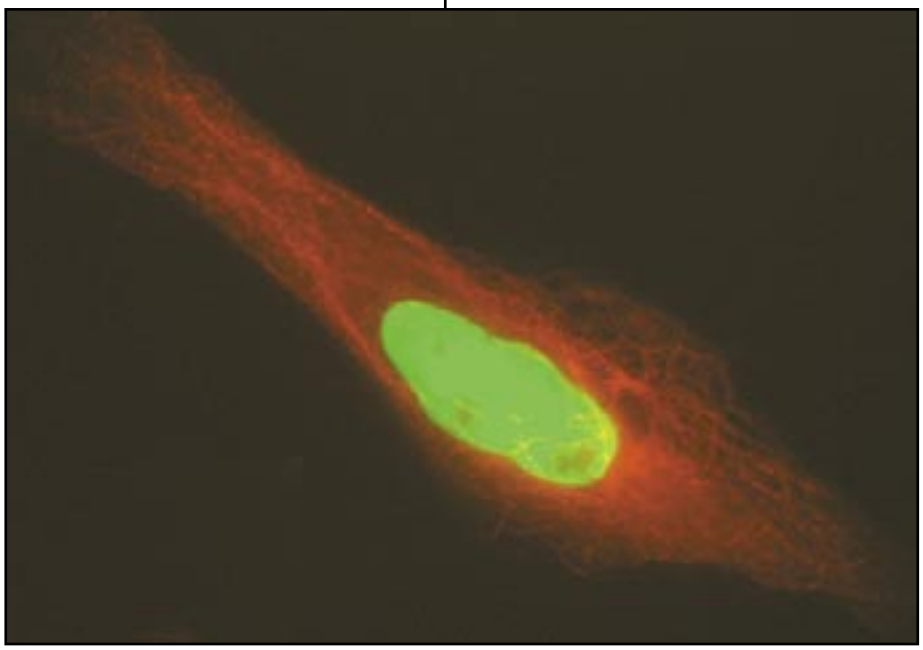
extracellular domain can act as a gene transactivator, and have identified putative interacting nuclear proteins using proteomics approaches. We believe that nuclear GH receptor (extracellular domain, cleaved from the receptor) serves to reinforce the signal coming from the cell surface receptor in response to GH binding.

Role of suppressors of Cytokine Signalling (SOCS) in breast cancer and lactation

SOCS genes are rapidly induced by GH and the closely related hormone of lactation, prolactin. They induce resistance to further hormone stimulation in a feedback mechanism. If induced by other factors, they can result in tissue resistance to the anabolic actions of cytokine hormones, such as occurs in inflammation. We have evidence *SOCS* genes are used to shut down lactation when the gland fills, and that they may control hypothalamic feedback sensitivity to prolactin. We also find expression of *SOCS* genes are elevated in breast cancer, and one *SOCS* is constitutively activated in all breast cancer lines examined. This may be important in preventing immune cytokine-mediated attack on breast cancer cells.



Cell adhesion and

morpho

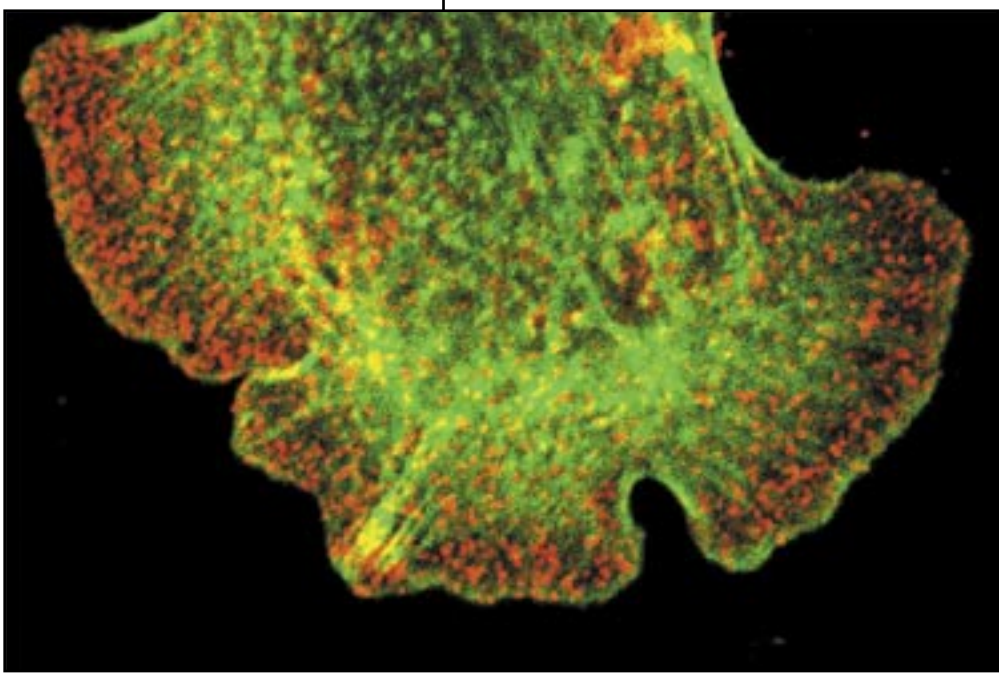
The organization of different tissues in the body depends upon the ability of cells to recognise and adhere to one another. Our research aims to understand how adhesion molecules mediate cellular recognition and tissue patterning. We focus on E-cadherin, which is essential for epithelial organization and acts to retard tumour progression. Elucidating how E-cadherin controls cell recognition and morphogenetic movements will provide a basis for understanding tissue patterning in health and disease.

Coordination of cadherin activity and the actin cytoskeleton

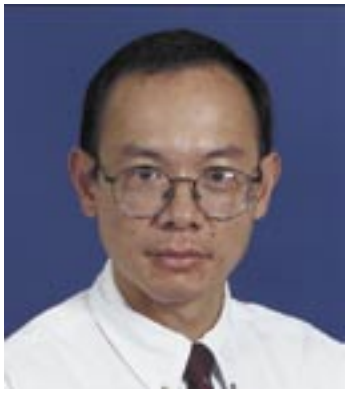
It is becoming increasingly clear that early adhesive recognition between cells entails the close coordination between cadherin activity and the actin cytoskeleton. We have developed assays that allow us to analyse the relationship between cadherin presentation and the organization of the actin cytoskeleton. We have found that E-cadherin associates with two quite distinct states of the actin cytoskeleton. In the earliest contacts, E-cadherin co-localizes with actin filaments that are actively polymerizing, but later associates with more stable actin bundles. This implies that there is dynamic interplay between cadherin adhesive binding and the organization of the actin cytoskeleton, which is likely to be critical to cell patterning and recognition. We are now studying the molecular mechanisms which may mediate the interplay between E-cadherin and actin dynamics.

Role of Rho family GTPases in cadherin function

A major goal of our work is to understand how the morphogenetic effects of E-cadherin are controlled at the cellular level. We have identified a critical role for the Rac GTPase in controlling early cadherin adhesive



genesis



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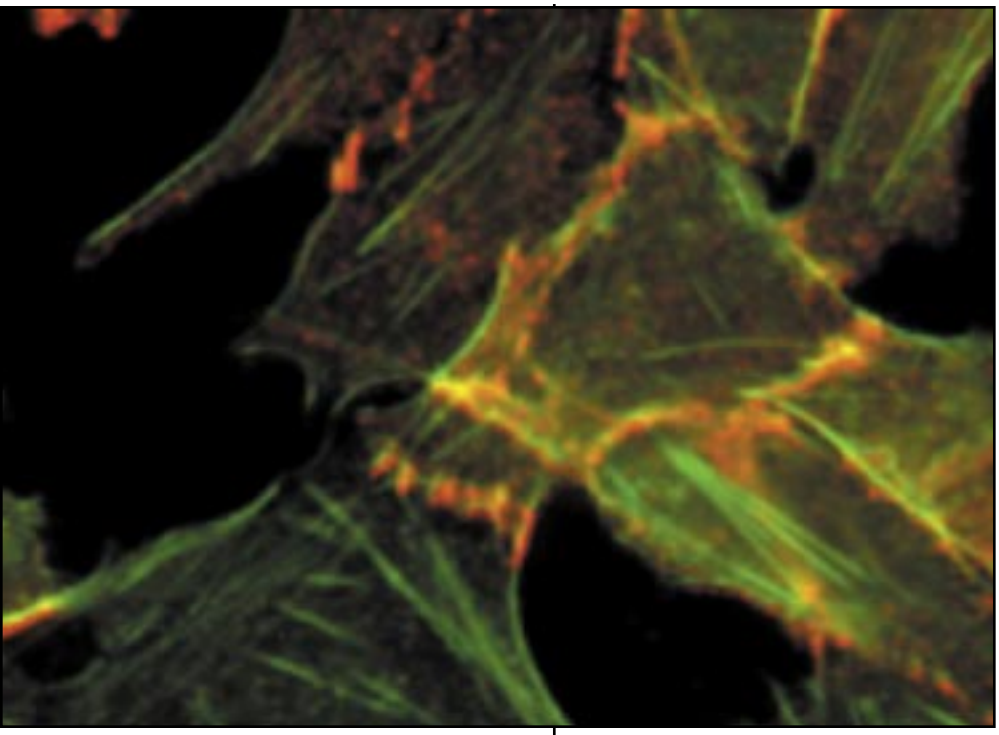
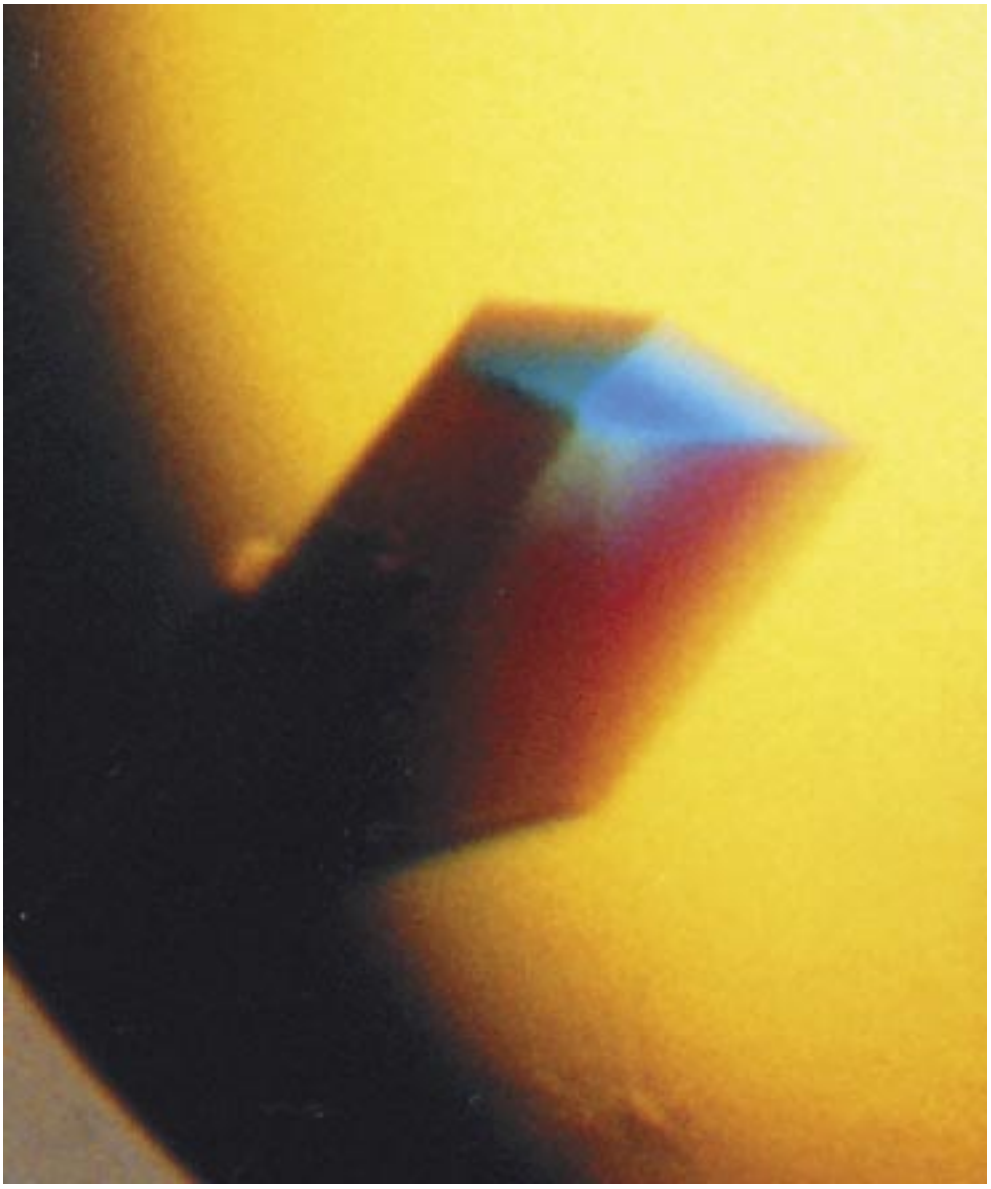


events. Rac activity is essential to coordinate cadherin presentation and actin polymerization necessary for cells to make their first adhesive contacts. Furthermore, the formation of cadherin-based contacts may mark the sites for rac signaling to occur. We are currently testing the notion that E-cadherin determines the site for activation of downstream signals that link Rac activity to the actin cytoskeleton.

Role of the membrane lipid environment in cadherin regulation

The lipids that surround membrane proteins such as cadherins, play a critical but ill-understood role in their biological activity. We recently demonstrated that the lipid kinase PI3-kinase, is necessary for cadherin activity, implicating membrane lipids in cadherin function for the first time. The transient association between PI3-kinase and E-cadherin may be essential for cells to make contacts with one another, marking sites for stabilization of adhesion and reorganization of the actin cytoskeleton.

Structural Biology



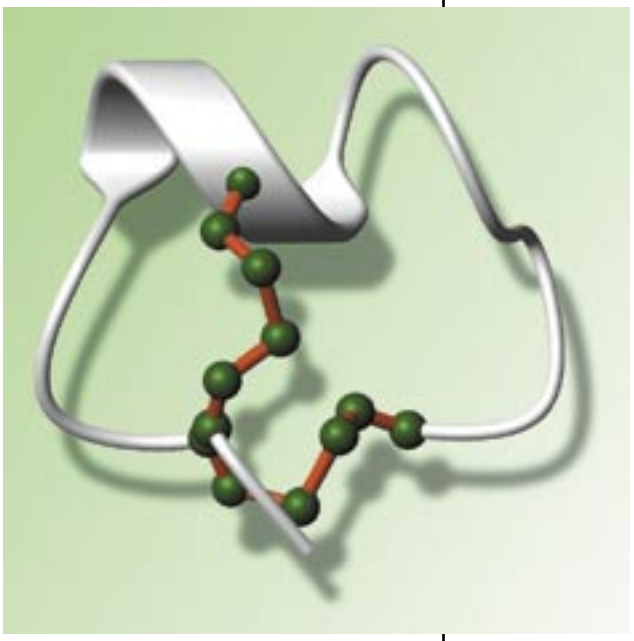
We are determining the three-dimensional structures of proteins implicated in a variety of physiological functions and disease states. An understanding of protein architecture provides the foundations for a range of drug design programs.

NMR in drug design

The function of a protein depends on its three-dimensional shape. We use Nuclear Magnetic Resonance (NMR) spectroscopy to determine the structures of key proteins implicated in disease states. Knowledge of protein structures allows us to understand their function and to design drugs that may moderate that function to block disease. Reports from native medicine applications often provide us with leads for interesting proteins from plants and animals, and we mix our lab work with field trips to discover new natural products.

NMR as a tool in drug design

A major focus of our group is the use of small disulphide-rich proteins as leads in drug design. Such proteins often have potent biological activities and, because of their cross-linking disulphide bonds, usually have well



defined three-dimensional structures that can be determined using NMR spectroscopy. The proteins we study come from animal and plant sources, as well as "designer" proteins we produce in the lab. In particular we have been exploring the bioengineering of circular proteins. By cyclising proteins and creating embedded knots within the structures using disulphide bonds, we are able to significantly enhance the stability of proteins. Our goal is to overcome current limitations on the use of conventional proteins as drugs, i.e., their poor bioavailability and susceptibility to degradation in vivo. In addition to core programs in protein structure determination we use NMR to study protein folding, protein dynamics, and ligand binding interactions.

Anti-microbial peptides and proteins

There is an urgent need for the development of new antibiotics, given the widespread development of microbial resistance to existing drugs. We are exploring the potential of peptide-based molecules as therapeutics. To this end, we have recently determined the three-dimensional structures of MiAMP1, an antifungal protein from macadamia nuts, RK1, an antibacterial molecule from rabbit kidney, and drosocin, an antibacterial peptide from the haemolymph of fruit flies. These studies involve collaborations within the university (MiAMP1, CRC for Tropical Plant Protection), nationally (RK1, Howard Florey Institute, Melbourne) and internationally (Wistar Institute, USA).

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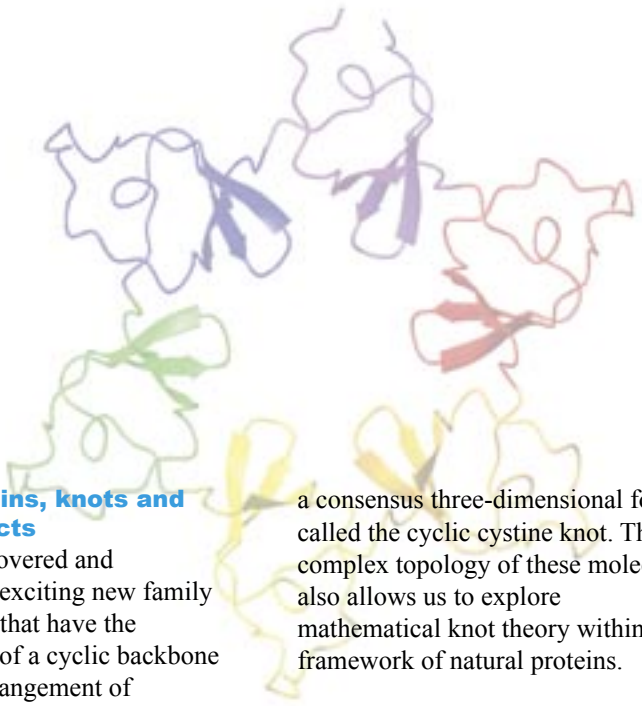

Circular proteins, knots and natural products

We recently discovered and characterized an exciting new family of plant proteins that have the unusual features of a cyclic backbone and a knotted arrangement of disulphide bonds. A major program based on this discovery involves fieldwork in Cape York, protein isolation and sequencing, protein structure determination and protein bioengineering. We have named this novel family of proteins the plant cyclotides and are exploiting the exceptional stability of these molecules as frameworks for the delivery of peptide based therapeutics. We have now determined the structures of several family members and have determined a consensus three-dimensional fold, called the cyclic cystine knot. The complex topology of these molecules also allows us to explore mathematical knot theory within the framework of natural proteins.

Structures of protein-based venom components and plant toxins

Many animal venoms and plant toxins contain disulphide-rich proteins that are valuable leads in drug design. Our group uses NMR to determine the structures of these molecules, with recent examples including conotoxins from marine cone snails, spider toxins from the Australian funnel web spider and Mexican red-knee tarantula, a protease inhibitor from the skin secretions of the frog Bombina bombina, and a newly-discovered protein from the venom of Australian taipan snakes. Our goal is to understand structure-function relationships of these toxin molecules to design new drug leads. In related studies in collaboration with Dr Marilyn Anderson of La Trobe University, we are determining the structures of a series of plant-derived protease inhibitors that have potential applications as insecticidal agents.

Structural basis of protein

The formation of interactions between macromolecules is a crucial part signal transduction, apoptosis, transcription, cell-to-cell communication and protein folding. We are interested in understanding the mechanisms underlying such interactions, through employing a combination of structural, biophysical and molecular biology techniques. Our studies will lead to a detailed understanding of cellular processes, and uncover new ways to design therapeutic agents that manipulate these processes in disease.

Intrasteric (active site-directed) regulation

Regulation of protein function is vital for the control of cellular processes. Allosteric regulation is a well established mechanism of protein regulation, describing effectors that bind to regulatory sites distinct from the active sites and alter protein function. We have been studying a number of proteins including protein kinases, metabolic enzymes (phenylalanine hydroxylase) and receptors (nuclear transport factor importin-alpha) which are instead regulated through intrasteric, active-site directed mechanisms, representing the counterpart of allosteric control.

The available data suggest that intrasteric regulation is emerging as an increasingly important regulatory mechanism in most cellular processes.

Phenylalanine hydroxylase

Phenylalanine hydroxylase (PAH) is a metabolic enzyme, the defects in which cause the disease phenylketonuria, one of the first characterized genetic diseases that can lead to mental retardation and death. PAH is therefore tightly regulated *in vivo*. We used X-ray crystallography, nuclear magnetic resonance and mutagenesis to understand the structural basis of its complex regulation, which we show includes intrasteric control.

interactions

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Importin-alpha and nuclear import

In eukaryotic cells, proteins need to be imported into the nucleus. Such transport is directed by special signals termed the nuclear localization sequences (NLSs). Importin-alpha is the nuclear import receptor that recognizes these NLSs. To obtain a complete overview of interactions formed by importin-alpha during the essential process of nuclear import, we determined the three-dimensional structures of importin-alpha and its complexes with NLSs, and kinetically and thermodynamically characterized the interactions. The process of nuclear import is shown to be regulated through an intrasteric mechanism, and coordinated through an intricate set of interactions with varying affinities.

Retroviral envelope proteins

Enveloped viruses fuse their membranes with host cell membranes to enable the transfer of their genome into the host cell. To understand the molecular basis of retroviral membrane fusion and explore novel strategies for therapeutic design, we studied the envelope protein from HTLV-1 (human T cell leukemia virus type 1), the virus associated with adult T-cell leukemia and tropical spastic paraparesis. The combination of crystal structure analysis and site-directed mutagenesis revealed the fusion mechanism, whereby a signal is transmitted from the receptor binding subunit to induce the fusion-activated conformation of the transmembrane subunit. The structure of the protein is now being exploited to develop new therapeutics using structure-based drug design.

Solenoid proteins

Structural biology hopes to uncover the relationships between amino acid sequences, three-dimensional (3D) structures and protein functions. Solenoid proteins, containing a superhelical arrangement of repeating structural units, convey the least complicated relationship between a sequence and the corresponding 3D structure. These proteins have particularly useful characteristics for forming protein-protein interactions, as exemplified by the nuclear import factor importin-alpha, a protein built from armadillo repeats. The repetitive structure also facilitates 3D structure prediction, which can illuminate protein function, as we show in the example of Leishmania surface protein containing leucine-rich repeats, proteophosphoglycan.

Protein structure and **drug**

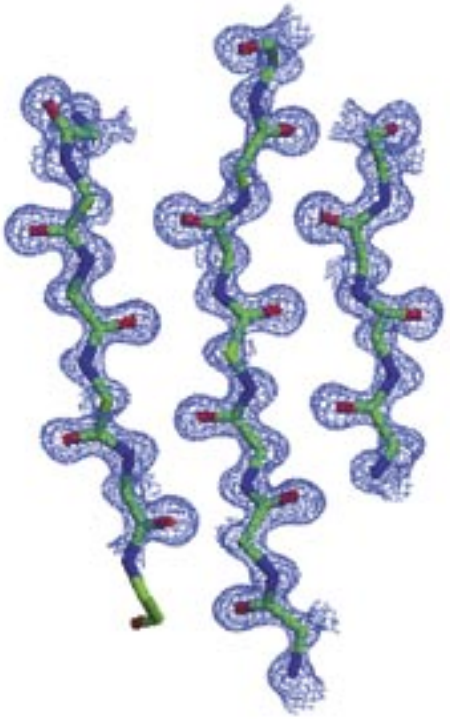
The ability to see what a protein looks like at atomic resolution allows us to understand how a protein functions in the normal state, and malfunctions in a disease state. Most importantly, each newly derived structure of a protein represents a quantum leap in our ability to develop novel drugs by structure-based design technologies. Current research centres on the areas of diabetes, hypertension, drug metabolism and antimicrobials.

Bacterial disulphide proteins

A long standing aspect of our research is the study of bacterial disulphide catalysts that help to fold secreted proteins. Many of these Dsb proteins have been found to be important in the production of bacterial toxins and virulence factors, and so may represent therapeutic targets for antivirulence drugs. In collaboration with Dr Linda Thony-Meyer (ETH Switzerland) we have determined the structure of DsbE, a protein disulphide reductant, at 1.2 Å resolution. This will be used in a structural comparison of proteins that incorporate a thioredoxin fold to investigate protein evolution and to form the basis of structure-based antivirulence drug design.

Adrenaline synthesis

In collaboration with Professor Gary Grunewald (University of Kansas) and Dr Michael McLeish (University of Michigan) we have determined the crystal structure of the adrenaline synthesising enzyme, PNMT, and



are currently using this structure to design potent and selective inhibitors.

Sulphonating enzymes

In collaboration with Mick McManus (Physiology UQ) we are investigating the structures of several human sulfotransferase enzymes that metabolise xenobiotics. Two of these proteins have been purified to homogeneity and initial crystallisation trials have yielded promising results.

design

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In collaboration with Paul Young (Microbiology UQ) and David Fairlie (IMB) we are investigating the structure of the Dengue virus protease, a target for the design of antivirals. During this year we have successfully overexpressed and purified the protease and developed in vitro assays to identify suitable inhibitors. Crystallisation studies are currently underway.

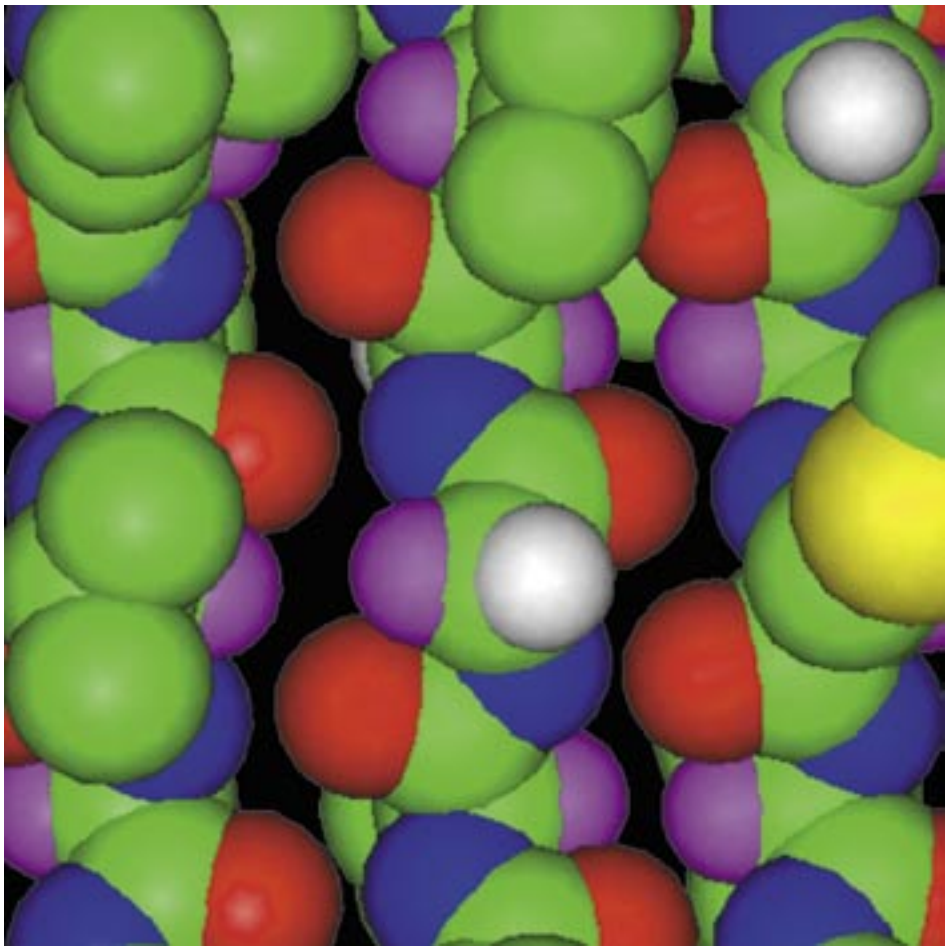
HIV Virus

Over the past few years we have determined the structures of several complexes of HIV-1 protease with designed inhibitors. This year we have determined the high resolution structures of substrate-bound and product-bound forms of the HIV-1 protease enzyme. The work is a collaboration with David Fairlie and Paul Alewood (IMB), and the structures were determined by Len Pattenden, a PhD student in David Fairlie's group. The three-dimensional information could yield vital information on how to combat the HIV virus, particularly with respect to viral resistance.

SNARE proteins involved in glucose transport

In collaboration with David James and Judy Halliday (IMB) we are studying SNARE proteins that regulate the trafficking of the insulin-regulated GLUT4 glucose transporter to the plasma membranes of adipocytes. We have produced two of the proteins involved in the regulation of GLUT4 trafficking, in quantities sufficient for crystallisation trials, and we have begun to investigate their intermolecular association using biosensor technology.

Biological Chemistry



Metabolic functions essential for life in a complex organism involve a multitude of chemical reactions. We exploit the diverse chemistries of living systems in the pursuit of a better understanding of how the organism works. This understanding will allow us to design and produce new and better drugs.

Bioactive peptides *and*

A major focus in my laboratory is the use of synthetic chemistry to determine the roles that proteins and peptides play in living cells. Solid phase technologies and chemistry are continually being developed to give ready access to milligram quantities of protein domains, bioactive peptides and structurally-constrained toxins. Such molecules typically interact with receptors, ion channels and enzymes and provide tools, reagents and possibly drug leads for our research programs in cancer, pain and inflammation.

Discovery, synthesis and structure-function relationships of Australian toxins

Small disulphide-rich proteins have a variety of diverse functions in both plants and animals, but are commonly found in animal venoms. These venoms are often used in prey capture or defense and comprise the vast majority of toxins from Conus species, snakes, ants, stone-fish, platypus, scorpions and spiders. These small proteins range from approximately 10-120 amino acids and typically contain 2-8 disulphide bonds, which play a key role in stabilising and shaping the proteins. They bind to their receptors with high affinity and specificity, and the binding residues are situated on well-defined surface loops and other secondary structures. Because they have such well defined structures they are excellent candidates for protein engineering, and in suitable cases may be used as templates for drug design. Current projects focus on toxins which target ion channels, G-proteins and transporters.

Chemical synthesis of proteins

Large biotechnology-based initiatives, like the human genome project and other major sequencing projects, are rapidly providing an increasing array of new protein sequences. An outcome will be an explosion in the number of gene-encoded proteins that are considered novel or important drug or agricultural targets. We are addressing one of the first requirements for the study of these new targets, namely the reliable and rapid access to the proteins of interest in micro- to multi-milligram quantities. The total chemical synthesis of proteins provides a rapid

proteins

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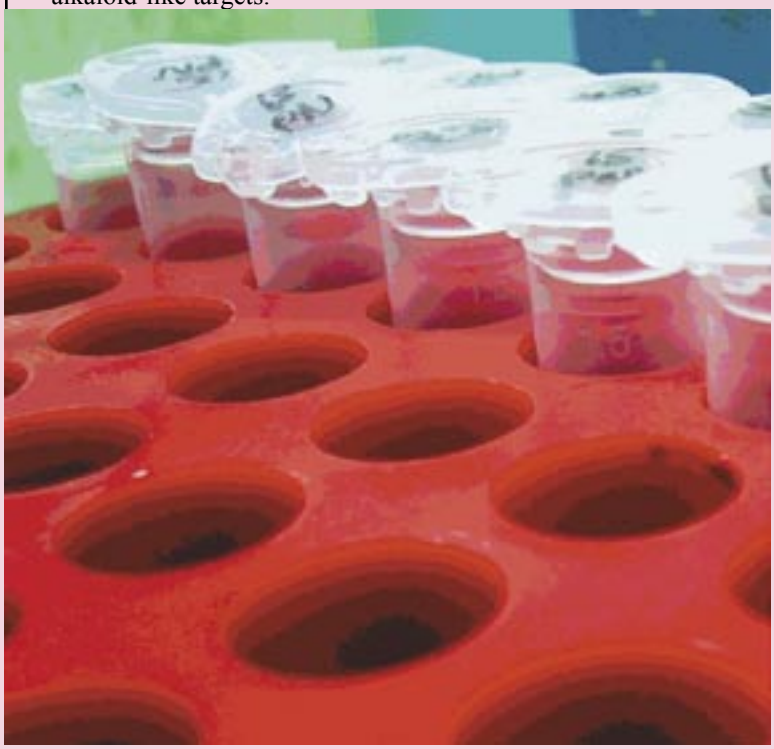
and effective route for the production of homogenous proteins free of biological contaminants, while at the same time offering flexibility through the incorporation of unnatural amino acids or other chemical modifications that improve protein efficacy. Furthermore, chemical synthesis allows for facile introduction of biochemical and biophysical probes that cannot be made by biological methods. Analysis of sequence data from the genome projects indicate that the average protein protein is approximately 300 residues, while functional folding domains usually consist of about 150 amino acid residues making them a viable target for chemists.

Solid phase combinatorial chemistry

Chemical drug lead discovery and optimisation have traditionally been achieved in a linear fashion using solution phase chemistry, where analogues are synthesised one by one, and then screened in a relevant bioassay. Different analogues generally have wide-ranging physical properties due to the nature of the different substituents. Consequently, synthetic procedures often require modification for the successful synthesis of each analogue (or corresponding intermediate), especially with regard to the work up procedures and solvents used in the synthesis. This lack of uniformity between analogues usually prohibits simultaneous and rapid solution phase analogue synthesis. Solid supported chemistry (where starting materials are reversibly bound to an insoluble polymer), with its distinctive operating principles, can achieve such uniformity of synthesis and work up procedures.

The proficiency of solid phase chemistry in library synthesis is well demonstrated in peptide chemistry where millions of oligopeptides (peptide libraries) can be assembled in a few weeks. We have recently developed methods that apply novel combi-chemistry to a range of bioactive toxins and small molecule alkaloid-like targets.

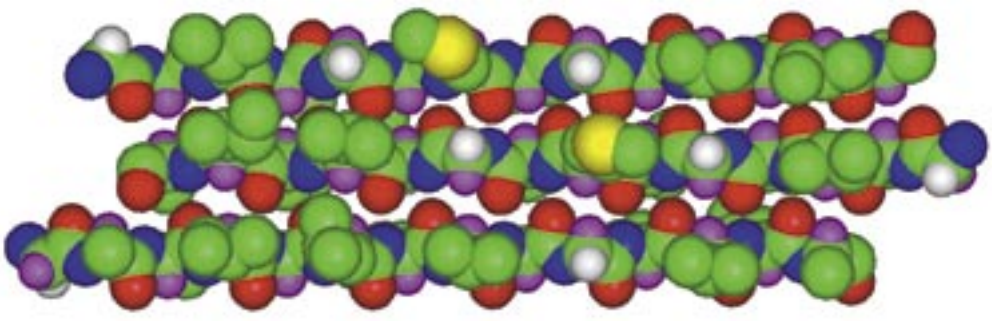


Chemistry *and* human thera

Chemistry underpins every facet of the molecular biosciences. Understanding how molecules interact, how structure influences reactivity, and how chemical reactions work, enables design and synthesis of reactive and bioactive compounds, and a better understanding of the molecular basis for biological processes, disease development, and drug action. We invent new molecules and develop them into potent enzyme inhibitors and receptor antagonists, as potential drugs for cancer, viral and parasitic infections, inflammation, and Alzheimer's disease.

Chemical synthesis, structure and mechanism

Our principal thrust is the design of new molecules, the development of new methods to make them, the determination and analysis of their structures, mechanistic investigations of their reactivities, the use of small molecules to probe biological processes, and to elucidate relationships between chemical structure and disease regulation. In 2000 we used a range of solution and solid phase organic synthesis methodologies to synthesise bioactive molecules (e.g. *de novo* designed drugs, natural product analogues, and peptidomimetics), reactive intermediates, highly functionalised molecular templates, structural constraints, and artificial receptors. We also synthesised metal complexes as folding templates, as catalysts for organic reactions, and as models of metalloproteins. We are engaged in design and structural analysis, determination of chemical structures by NMR spectroscopy and X-ray crystallography, spectroscopic investigations of chemical and biological reactions, enzyme kinetics, cell biology, and molecular pharmacology in vitro and in vivo.



Protein surface mimics

A key strategic objective has been to mimic small bioactive protein surfaces that are recognized by other proteins, DNA or RNA during disease processes. We have identified peptide conformations that are common recognition elements for protease enzymes, for classes of G protein-coupled receptors, and for transcriptional receptors. One of our synthetic chemistry programs has been aimed at developing generic technologies for creating small organic molecules to mimic

peutics

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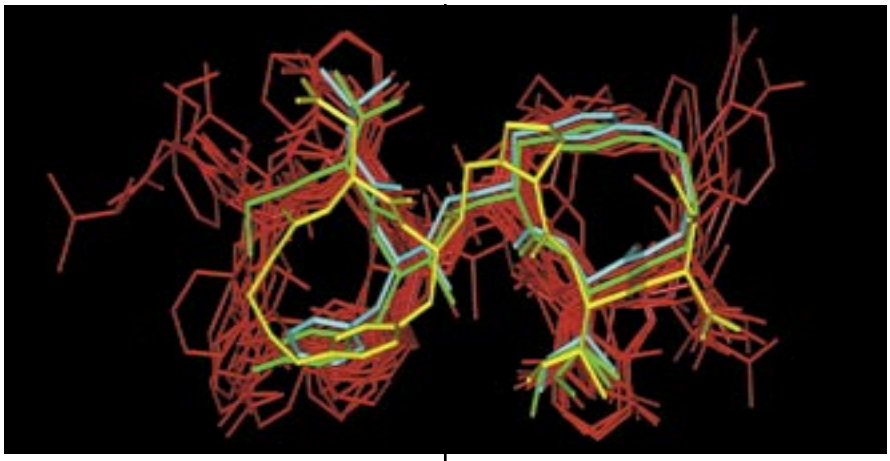

elements of protein structure, such as beta-strands, beta and gamma turns, beta-sheets, alpha-helices, helix bundles, and multi-loop bundles. This effort has resulted in numerous small organic molecules that we have demonstrated to be both structural and functional mimics of bioactive protein surfaces.

Drug design and development

The generic technologies that we have developed to date have already led us to successfully design potent and selective inhibitors of aspartic, serine, metallo and cysteine proteases, as well as potent and selective antagonists and agonists of G protein-coupled receptors that protrude from human cellular membranes and mediate cell signalling. Multiple classes of small orally active organic molecules developed in our labs have been shown to possess antitumour, antiparasitic (against malaria, giardia, and schistosomal proteases), antiinflammatory, antiviral (low resistance inhibitors of HIV and Dengue proteins), and anti-Alzheimer's activities. These compounds are all in various stages of pharmacological development in animal models of human diseases.

Glycobiology

We are studying the metabolic pathways necessary for the addition of carbohydrates to cellular proteins and lipids. These glycosylation events are important for a number of cellular functions including: cell to cell communication; binding of ligands to receptors; normal cell growth and differentiation; interactions between cells and invading pathogens. Unusual glycosylation patterns in cells are associated with inflammation and diseases such as cancer.

Development of a technology platform for the production of sialic acid-containing oligosaccharides

We have an established collaboration with Alchemia Pty Ltd, a Brisbane based biotechnology company whose core business is the chemical synthesis of oligosaccharide- (or carbohydrate-) based molecules have not been fully exploited as potential drugs, mainly because they are difficult and expensive to produce using synthetic methods and to extract from their natural sources. The collaborative project between the IMB and Alchemia is aimed at developing technology that will combine chemical synthesis with parts of the naturally occurring biological synthesis machinery. This technology will open up opportunities for the cost effective production of carbohydrate-based molecules. A successful outcome from this R&D project will have many long term benefits including the development of new drugs and other products, which will in turn help to build the biotechnology industry in Australia.

Structural studies on SNARE proteins involved in insulin action

This project aims to understand the structure and function relationships between the SNARE proteins that are involved in the transportation of the GLUT4 molecule to the cell surface in response to stimulation by insulin. This pathway is important in maintaining correct blood glucose levels. Novel treatments for diabetes could be developed from this work. [Collaborative project with Prof. David

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James, (IMB), Dr Jennifer Martin, IMB, Dr Ulrika Rova, (IMB) and Dr Scott Rowlinson, (IMB)]

Novel proteases involved in natural product biosynthesis

This project involves the characterisation of the specific proteases present in the venom ducts of cone snails that are important for the production of the bioactive molecules found in the venom. [Collaborative project with Trudy Bond (IMB), Prof Paul Alewood (IMB), Dr Jenny Martin (IMB) and Dr Terry Walsh (QUT)].

Marine glues

These studies are focused on the specialised glue proteins that some marine parasites use to attach to their hosts. These specialised proteins have many interesting physicochemical properties and could potentially form the basis for the design of specialised glues for use in industry and medicine [Collaborative project with Dr Ian Whittington (Microbiology and Parasitology) and Dr Bronwen Cribb (Centre for Microscopy and Microanalysis), Tamarind Hanwood (IMB and Microbiology and Parasitology)].

Venom peptides to drugs

Mini-proteins in the venoms of Australian cone snails (conopeptides) are a rich source of new molecular probes. Our group isolates conopeptides with interesting features, which are then synthesised and their precise mode of action and structure determined. Some of the conopeptides we have discovered have the necessay characterisitics to be developed as drugs or drug leads. Some of these leads have been used to establish the spin-out Biotechnology company Xenome.

Neuronal inhibitors for the control of pain

The supply of pharmaceuticals for pain relief is a multi-billion dollar industry. The narrow therapeutic basis of action of existing drugs means that the treatment of many forms of chronic pain is poor. We recognise this situation as an excellent opportunity to develop new treatments for pain management. The end product from the research will be a conopetide that selectively inhibits sensory nerves and can be used for the treatment of chronic and neuropathic pain. Such a drug could be given to patients who no longer, or have failed to, respond to morphine and other painkillers.

Omega-conotoxin probes of N-type calcium channel subtypes

Voltage-sensitive calcium channels (VSCCs) play an important role in regulating the excitability of neurones and in triggering neurotransmitter release. The N-type VSCC has emerged as an exciting new target for pain following the successful treatment of morphine-resistant and post-operative pain with omega-conotoxin MVIIA (Ziconitide). We have recently discovered a new series of potent omega-conotoxins from Australian cone snails. One member of this series, CVID (AM336), has been identified as the most N-type vs P/Q-type selective peptide known (provisional patent PP8419/99). We have found that CVID has a widened therapeutic window between side effects and antinociception. Importantly, this difference does not arise from greater N-type vs P/Q-type selectivity, but likely stems from differences in the ability of these omega-conotoxins to inhibit different N-type VSCC splice variants. The broad goals of our research are to develop improved omega-conotoxins for better pain and stroke management based on an understanding of the precise site(s) and mode(s) of action of CVID.

Alpha-conotoxin probes of the nicotinic acetylcholine receptor

New alpha-conotoxins have been discovered in the venom of Australian cone shells which have the unique potential to distinguish among the nicotinic acetylcholine receptor (nAChR) subtypes expressed in neurones. We are now determining the potency and selectivity of native and mutant alpha-conotoxins using voltage clamp techniques in Xenopus oocytes expressing different neuronal nAChR subunit combinations. Alpha-conotoxins that differentiate among these nAChR subunits will be used to characterise the native nAChRs expressed in parasympathetic neurones using whole cell patch clamp techniques. This study provides a basis for understanding the structural features which confer alpha-conotoxin selectivity.

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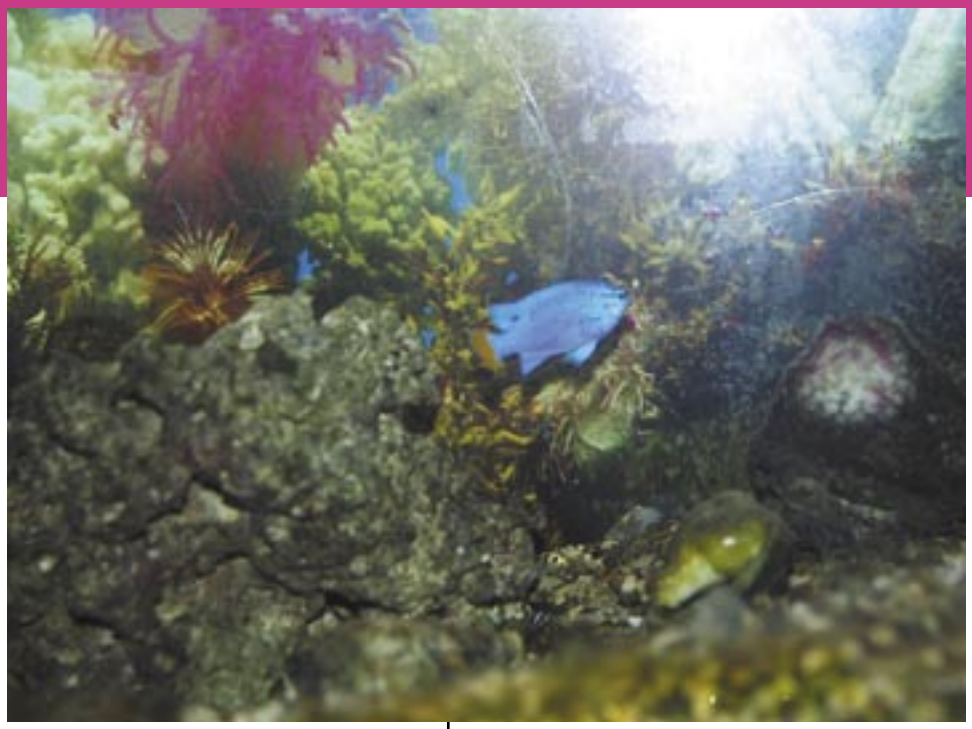


Delivery of alpha-conotoxins to the central nervous system

Nicotinic acetylcholine receptors are important members of the ligand-gated ion channel superfamily that are intimately involved in signal transmission. The goal of our research is to develop alpha-conotoxins that can act centrally as subtype-selective inhibitors of nAChRs. Our approach is to design, synthesise and evaluate a CNS delivery system for alpha-conotoxins conjugated to carrier molecules.

Conantokin probes of the human NMDA receptor

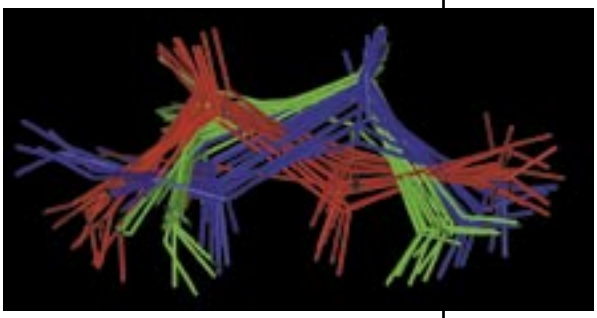
The NMDA-glutamate ion channel is an abundant excitatory amino acid receptor in the brain. Recent results from our group have identified conantokin-G analogues which differentiate between NMDA receptors found in different regions of normal and Alzheimer human brain. The aim of this project is to understand the molecular basis for this selectivity, with the view to better understanding and perhaps treating Alzheimer's disease.

Combinatorial ch *and* molecular

We are developing methods to discover small molecule protein mimetics, by studying the chemical and conformational diversity of protein surfaces. This information, together with chemoinformatics and the development of new linkers and cyclisation auxiliaries, allows the synthesis of arrays of molecules that mimic protein surface shapes. Our work is aimed at meeting the huge pharmaceutical demands for small molecules that modulate protein function.

Conformational diversity of proteins

Protein structure is currently classified by the shape of the polymeric backbone. Unfortunately this provides medicinal chemists with very little information as to



the shape or topography of amino acid side-chains on protein surfaces. We have developed the required algorithms and applied these to cluster continuous and discontinuous protein surfaces. These privileged side-chain shapes serve as screens in an in silico assay to identify small molecules that match these shapes in a virtual screening of virtual library approach.

Virtual screening of virtual libraries

We are developing databases of compounds that encapsulate the wealth of chemical diversity available to synthetic chemists. We have developed, and are continually optimising, a drug design environment that allows us to identify compounds in the chemical universe that match the shape of proteins. In this way we are bridging the chemical and biological universes and focusing the resource-intensive combinatorial chemistry process on molecules that mimic protein shapes.

New linkers for library synthesis

We have developed a backbone linker and a safety catch linker for the synthesis of libraries of macrocycles (cyclic molecules like chlorophyll and cyclosporin). In particular we have used the safety catch linker to synthesise large arrays of peptidic macrocycles. We are optimising chemistries for the solid phase synthesis of large arrays of macrocycles containing unnatural polymers and amide bond isosteres on these linkers. We are developing new linkers for the synthesis of macrocycles.

Overcoming the difficult macrocyclisation step

We have developed a novel ring contraction auxiliary (the formation of a larger ring designed to undergo a ring contraction and form a smaller ring) that, via a ring closure/ ring contraction approach, yields monocyclic products unobtainable using existing synthetic methods. We are examining the combination of this strategy with new and existing linkers to provide the solid-phase avenues for the synthesis of highly strained and novel macrocycles.

emistry design

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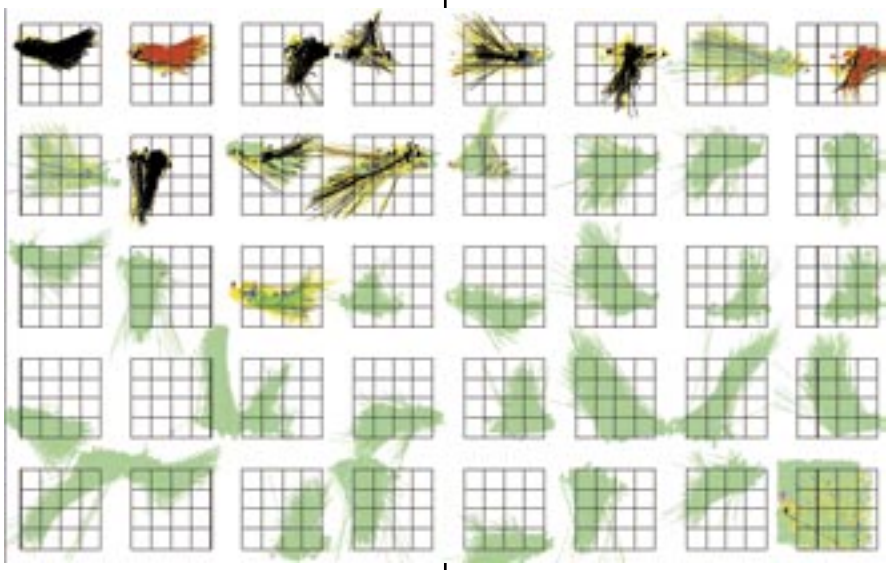
Students • Andrew McDevitt, Doug Horton, Stephen Long, Mikael Kofod Hansen

Research assistant • Simon Golding

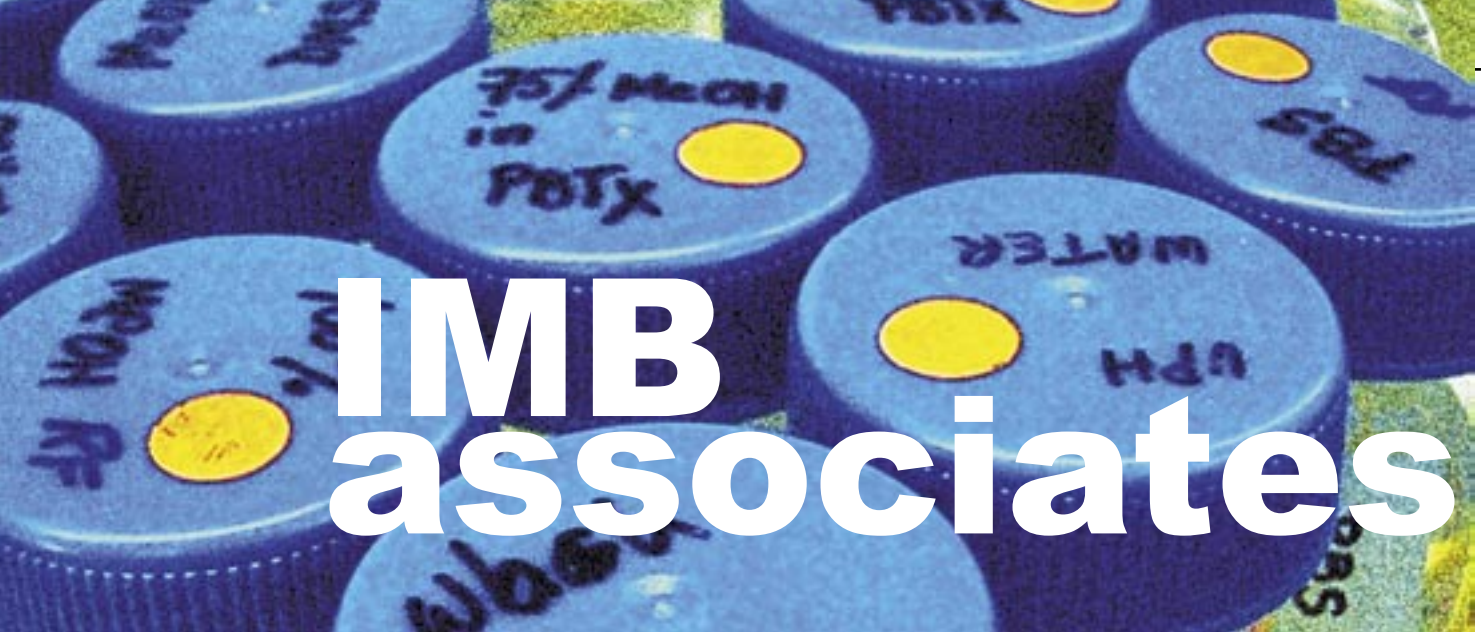
The development of potent G-protein coupled receptor agonists and antagonists

Using our ring contraction auxiliary, we have synthesised a class of macrocycles that are unobtainable using existing chemistries. This class of natural products have shown wide-ranging biological activities including antitumour, herbicide, antimalarial, opiate agonist and tachykinin NK-2 antagonist activities. We are exploring this class of macrocycles as orphan ligands for G-protein coupled receptors.



Cytokine mimetics

Cytokines are a broad class of proteins, including interferons, interleukins, colony stimulating factors, TGF-b and tumour necrosis factor, that regulate cell-cell interactions under both normal and physiological conditions. Although the therapeutic use of cytokines is still at an early stage, early indications suggest that cytokines may be used against cancer, hepatitis C, multiple sclerosis, growth, asthma and arthritis. Several cytokines currently on the market have achieved sales well in excess of $1 billion/year. Considerable effort has therefore been devoted to the search for small molecule agonists and antagonists of key cytokines, but unfortunately these efforts have met with little or no success.
We are developing the required design and synthetic methodologies for the discovery of molecules that modulate cytokine function. Using these structure-based design approaches we have developed an antagonist of Interleukin-4.



Matt Trau: Nanotechnology and biomaterials

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

The overall goal of the research within our centre is to develop biologically related materials and devices that will ultimately improve human health. The two main research categories are genetic screening and drug discovery devices, and artificial tissue matrices for implants into the human body. Both of these areas require the preparation of novel materials and devices which have been fashioned to contain designed nanostructure.

Genetic screening and drug discovery devices

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

Artificial tissue matrices

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

Steve Barker: Evolutionary genomics of arthropods

Most animals are arthropods, yet their genomes and evolutionary genetics are poorly understood. Our research focuses on the ticks of cattle, and the lice of humans and other primates. These parasites cause disease and economic burden, and our research is aimed at novel strategies for their containment and control.

Mitochondrial genomics

Mitochondria have their own genomes, and in most groups of animals the order of genes is remarkably similar. However, we discovered two remarkable exceptions: a group of hard ticks and lice and their kin. The arrangement of the 37 genes in the mitochondria of these animals has changed so many times that it is difficult to reconstruct the evolutionary path of these mitochondria. By studying the exceptions, mitochondria that have changed a lot, we hope to learn about the rule (why the arrangement of genes in the mitochondria evolve so slowly).

Nuclear genomics

We have begun to sequence the genome of *Rhipicephalus appendiculatus*, a tick that infests cattle in Africa and transmits a malaria-like disease. *R. appendiculatus* will be the first chelicerate arthropod to be studied in this way, and we expect to discover much that is new.

Molecular epidemiology and evolutionary genetics of parasitic diseases

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

Bryan Mowry: Molecular genetics of schizophrenia

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

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

Current candidate-gene and genome-wide linkage studies provide some evidence for the involvement of a number of specific genes (eg. serotonin 5HT2a receptor gene and the dopamine D3 receptor gene) and as yet unidentified factors localised to specific chromosomal regions including 6p, 6q, 8p, 13q and 22q. These data provide suggestive, but no conclusive evidence for causative genes

Our work is aimed at identifying these genes. In collaboration with national and international colleagues, we are studying both ethnically diverse (heterogeneous) and genetically isolated (homogeneous) populations, to account for two different possibilities: (1) the same, frequently occurring causative genes occur in all populations and (2) rare genes may exist in one or more genetically homogeneous populations.

Tom Loy: Molecular archaeology

Molecular archaeology provides another dimension of detail to archaeological research. It involves the analysis of DNA and proteins extracted from ancient plant and animal remains. Our areas of interest lie in the preservation of biomolecules, sex determination, species identification, population genetics, identification of diseases in the past and primate/human evolution.

Method development

This year our group has developed three robust methods for the analysis of ancient DNA. We have optimised extraction and PCR amplification techniques from blood and bone, using extremely small sample sizes to minimise the impact on ancient artifacts. We have developed a sex determining test of 90% accuracy and a species determination test that provides useful phylogenetic information. Population analysis uses mitochondrial control region sequences and has been applied to ancient human populations at the Mayan site of Copan in Honduras.

Human genetic and cultural evolution

This research is focusing upon blood residues on tools and bones from hominid sites in South Africa, sequence and phylogenetic analysis using the mitochondrial *16S* and *CytB* genes, variable domains 3, 4, 5 in the *28S rRNA* gene and primate endogenous retroviruses that will serve as a proxy for genomic evolution. We are also investigating ancient diseases, both infectious and hereditary, to determine their age, evolutionary development and any gene linkages. Using a combination of capillary electrophoresis, PCR amplification, decomposition studies and taphonomy we are documenting the pathways of degradation and preservation of ancient biomolecules.

John Hancock: Mammalian signal transduction

Cells in complex organisms must communicate with each other to make correct decisions about their behaviour, whether they should divide, move, do nothing or suicide. The information that cells use to make these decisions is delivered to the outside of the cell and needs to be transmitted across the cell membrane to the nucleus, a process referred to as signal transduction. Disruption of signal transduction networks is a key feature of cancer cells.

Ras genes encode small (21kD) guanine nucleotide binding proteins that operate as molecular switches in signal transduction pathways downstream of tyrosine kinase and G-protein coupled receptors. Ras is activated by guanine nucleotide exchange factors that catalyse exchange of GTP for GDP. The binding of GTP to Ras induces a conformational change that allows RasGTP to activate multiple effector pathways. Ras is returned to the inactive GDP ground state by the hydrolysis of GTP hydrolysis, a reaction that is stimulated by GTPase activating proteins (GAPs). Some 25% of human tumours have point mutations in one of their *Ras* genes which render the GTPase activity of the mutant protein resistant to GAP stimulation. Oncogenic Ras is therefore fixed in the activated GTP bound state and constitutively activates its effector pathways. These include: the Raf/ MEK/ MAP kinase cascade, phosphatidylinositol-3-kinase (PI3K) and networks of other Ras-related proteins including Ral, Rac, Rho, and Cdc42. The consequence of these events is stimulation of cell proliferation. In order to function, Ras proteins must be localized to the inner surface of the plasma membrane. This is achieved by the addition of a C-terminal membrane anchor in the endoplasmic reticulum. From there Ras proteins must be trafficked to discrete regions or microdomains of the plasma membrane. How Ras proteins traffic to these domains and how Ras function is regulated by membrane interactions is a major focus of our work. This has major relevance in the design of new anti-cancer therapeutics.

Ian Frazer: Effective tumour immunotherapy

Tumours are different enough from the normal cells in the person in whom they grow that the body's defences against infection can recognise them as foreign but, unlike infections, tumours are poorly controlled by these defences. There are many reasons for this – some relate to the body's natural reluctance to attack itself, and this problem can be overcome through better vaccines. Our work focuses on development of such vaccines for cancer of the neck of the womb (cervical cancer).

Targeting immunotherapy to epithelial tumours

We use a model in which mice are transplanted with skin transgenic for the E7 protein of HPV16 to mimic the immunobiology of cervical cancer. We observe that E7 transgenic skin is not rejected by immunocompetent animals even if immunised with E7 protein and adjuvant. However treatment of grafted animals with *Listeria* results in prompt graft rejection and acquisition of memory immune responses sufficient to allow subsequent rejection of further E7 transgenic grafts without further *Listeria* exposure. We are currently exploring the molecular and cellular mechanisms of rejection and developing surrogate markers for an effective immune response that could be applied to our clinical trials of E7 specific immunotherapy for cervical premalignancy.

Codon usage and expression of papillomavirus genes

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

Kevin Burrage: Computational biology

Computational biological modelling is a key tool in understanding biological phenomena. We are interested in trying to quantify the mutation rates and error measurements, both of which are uncertainties, inherent in biological systems. We hope to develop mathematical models robust enough to cope with this uncertainty, and then apply this model to genetic regulatory networks with a high degree of confidence.

One particular area of interest is in the use of stochastic processes to attempt to quantify the various issues of uncertainty, mutation rates, error measurements etc in biological models. Various stochastic models are being developed that attempt to provide insight into genetic regulatory networks. This work is feeding into another project based on the use of virtual reality and sophisticated visualization methodologies to understand the dynamics of regulatory networks in biology - such mathematical and visual models will be used as predictive and confirmational tools for the understanding of genomic behaviour in general.

The Australian **Genome Research** *Facility*

Joint

The Australian Genome Research Facility (AGRF), formed through the Major National Research Facilities program, provides Australia's pre-eminent central resource for genomics researchers throughout the country and overseas. The head office and the Brisbane node are hosted by the IMB.

The Brisbane Division provides a wide range of DNA sequencing services to a growing number of clients. The main operational focus in the past year has been to ensure that robust protocols are in place for the various DNA sequencing service options and, where possible, automate work processes. The introduction of an internet-based sample submission process is a major advance in sample handling and was designed by our own staff.

With the new funding initiative from the National Health and Medical Research Council's (NH&MRC) Program in Medical Genomics, designed to stimulate large-scale genomics research, the Facility is expecting a considerable increase in workload. The AGRF is uniquely positioned to provide the resources to handle the increased demand created by this Program. The continued advances in automation and a change to seven-day processing should meet this additional workload.

The Research and Technology Section was officially formed in late 1999 and operates at both the Brisbane and Melbourne nodes. The Brisbane group is focussing on single cell genotyping procedures, robotic instrumentation and high-throughput processing. The success of the single cell processing is evident with the development of a number of collaborative clinical trials in the area of pre-natal diagnostics. Similarly, advances in genetic profiling of single or low cell numbers are proving useful in archaeological identification and forensics. Continued development of the robotics workstation has produced advances in the rate and control of sample processing.

A Microarray Distribution Facility has been established at the Melbourne node. Human, mouse and yeast cDNA libraries have been purchased and will be available as microarrayed slides for individual researchers in Australia. Considerable effort has been expended in replication, validation and amplification of the clones. The development of controls is an important part of ensuring that researchers are comfortable with using the microarrays to quickly generate large amounts of data. The setting up process has taken more than 12 months and will be available for general access in 2001.

This year has seen the AGRF consolidate its processes and refine its procedures, and from this solid foundation it will continue to meet the future demand generated by the growth in genomics research.

ventures

Special Research Centre *for* Functional and Applied Genomics

The Special Research Centre (SRC) was established at the beginning of 2000 with John Mattick as Director and David Hume assuming the role of Deputy Director/Manager. The SRC is unique in that it brings together three major areas of research strength in Computer Science and Information Technology, Molecular Genetics and Cell Biology, and Protein Structure and Chemistry from within the University of Queensland.

Although IMB is a major participant, senior staff also reside in University Departments of Mathematics, Computer Science and Electrical Engineering and the schools of Molecular and Microbial Sciences and Biomedical Sciences.

The strategy of the SRC in its first year has been to establish a number of core technology facilities, not only to eliminate bottlenecks in the pipeline from gene discovery to application, but also to develop new technologies in key areas. Each of the facilities operates on a cost-recovery basis and is available both within the SRC and to external groups. Some highlights of the first year of operation include:

Transgenic animal service Queensland (TASQ)
Transgenic mice are a key research tool for many members of the SRC program. This service currently has three functional micromanipulators and two full time staff, and is working close to capacity. The facility has established methods for freezing of mouse sperm and embryos, and intracytoplasmic sperm injection (ICSI). Elizabeth Williams, the director, recently presented a modified approach to generation of mouse embryo-stem cell chimaeras at the International Mouse Genome Conference in Narita, Japan.

Protein expression facility
Large scale expression of proteins remains a limiting step in structural biology. The protein expression facility was fortunate to recruit Ms Allison McLean, who has extensive industry experience in fermentation technology. Three, 5- and 10-litre fermenters now operate full time in the generation of high yield fed-batch cultures of bacteria producing recombinant proteins for subsequent structural studies. The next phase of development is the establishment of a downstream processing facility to expedite large scale purification.

Microarray facility
Gene expression information provides important clues to the likely functions of both new and known mammalian genes. The SRC has established a gene expression microarray facility, directed by Dr Sean Grimmond, including provision for clone curation and replication, array of clone sets and analysis. Dr Joanne Redburn is a key appointment with experience in many applications of robotics. Large mouse and human cDNA sets have been replicated, and the first publication-quality expression studies in both species have been completed.

Computational biology and data-mining
Two key appointments, Drs Jennifer Hallinan and Rohan Teasdale, permitted rapid advances in applications of information technology within the SRC. Dr Hallinan has developed a new neural net based database for clone curation and is working on new software for analysis of gene expression arrays. Dr Teasdale is an expert in database mining, and is cooperating in several gene discovery projects within the SRC. Other current and future developments within the SRC include infrastructure/technology development in cryoelectron microscopy, proteomics, protein-protein interactions and chemical libraries. The overall aim is to provide world-class infrastructure for biotechnology research and to apply those resources efficiently to the generation of new drugs, bioactive molecules and other technology applications.

joint ventures...

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

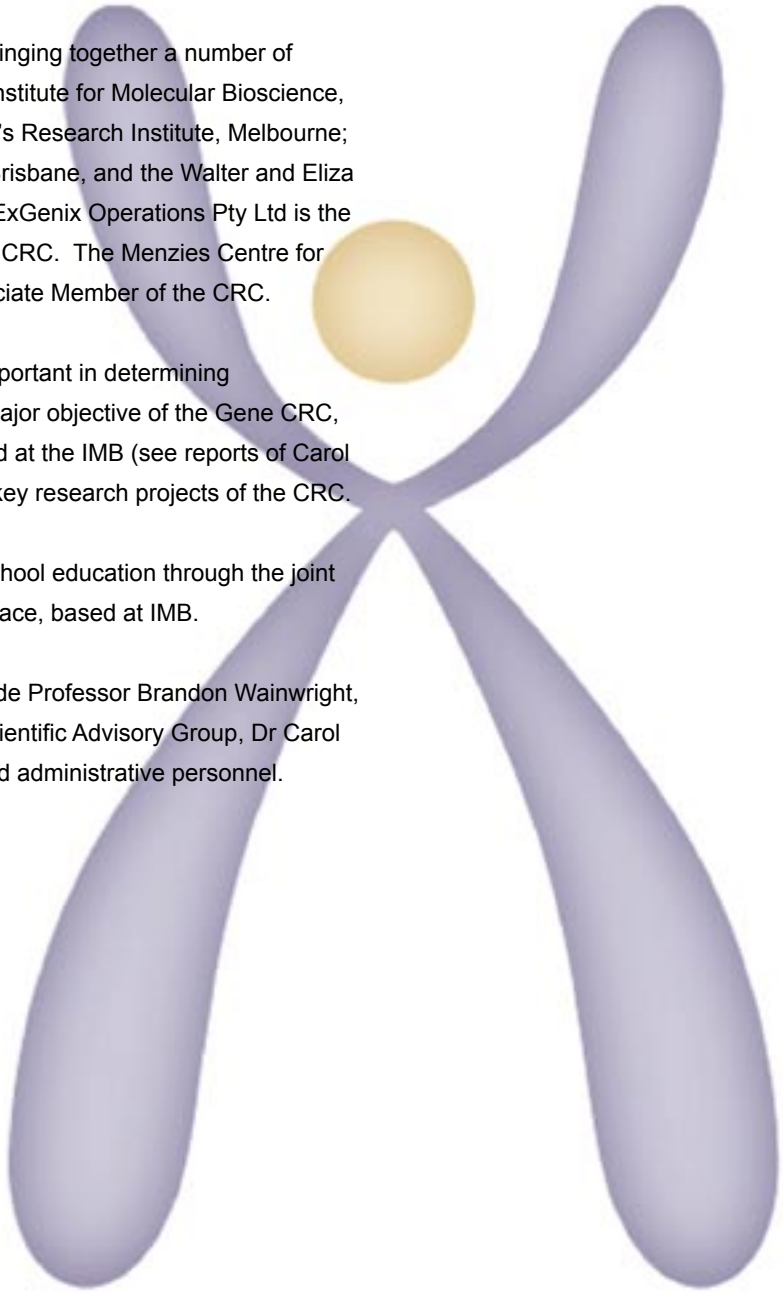
The Institute is a participant in the CRC for the Discovery of Genes for Common Human Diseases (Gene CRC).

The Gene CRC was established in July 1997, bringing together a number of leading Australian human genetics groups: the Institute for Molecular Bioscience, University of Queensland; the Murdoch Children's Research Institute, Melbourne; the Queensland Institute of Medical Research, Brisbane, and the Walter and Eliza Hall Institute of Medical Research, Melbourne. ExGenix Operations Pty Ltd is the Centre Agent and Commercial Participant of the CRC. The Menzies Centre for Population Health Research, Hobart, is an Associate Member of the CRC.

The identification and study of genes that are important in determining susceptibility to common human diseases is a major objective of the Gene CRC, and the basal cell carcinoma research conducted at the IMB (see reports of Carol Wicking and Brandon Wainwright) is one of the key research projects of the CRC.

In addition, the CRC contributes to public and school education through the joint appointment of an education officer, Angela Wallace, based at IMB.

IMB staff who participate in the Gene CRC include Professor Brandon Wainwright, who is the CRC Deputy Director and Chair of Scientific Advisory Group, Dr Carol Wicking, and several research staff, students and administrative personnel.



The establishment of the IMB as an Institute of the University of Queensland invested it with the right to enrol its own research MSc and PhD students. With this in mind, the Institute is developing a Graduate Program aimed at providing broad based career training to equip our students to tackle the scientific challenges of the 21st century. In addition to a primary research project, learning opportunities will be provided in a range of areas covering commercialisation, management, bioethics, patent law and intellectual property, and emerging technologies in the biosciences.

A Graduate Education Committee was convened to oversee the program and make recommendations to the IMB Executive. This committee has two student representatives who provide a dialogue between the student body and staff. The Institute's commitment to graduate education resulted in the creation of a Graduate Coordinator position with the primary responsibility of handling student matters.

Graduate **program**

In its first year the IMB enrolled 10 PhD students; Senali Abayratna, Charlotte Widberg, Nicholas Drinnan, Isabel Morrow, Anthony Cook, James Smith, Christine Wells, Johan Rosengren, Manu Trabi and Kate Irvine.

Honours students undertaking their research project within the IMB will continue to enrol through the various schools of the University, further continuing the IMB's collaborative relationship with the Faculties. IMB staff, particularly those with joint appointments, will continue to lecture in undergraduate courses.

In 2000, PhDs where awarded to six students who began their studies in the laboratories of the then CMCB and DDD; Peter Bailey, Patricia Free, Megan Law, Ailsa McManus, David Pennisi, Edmund Sim, Aaron Smith, Joel Tyndall and Clement Waine.

The IMB actively promoted its graduate program, taking part in the University's Postgraduate Study Information Evening. Staff and students talked to a range of individuals noting that many 2nd year students were already considering the possibility of graduate study. The IMB also hosted an open house weekend for intending graduate students aimed at attracting students from interstate to undertake PhDs at the University of Queensland. Both events were well received and actively supported by staff and students alike.

The students of the IMB actively embraced the new structure, establishing an official association of the University Union. Calling themselves SIMBA (Students of the IMB Association), this group has been very effective in drawing together the students from the two former Centres. SIMBA organised a number of events throughout the year that provided students opportunities to discuss issues pertinent to their studies and role within the IMB. They also organised social events, including a particularly successful barbecue and team sports afternoon aimed at further integrating the staff and students of both Centres.

IMBcom

IMBcom was launched by The University of Queensland in March 2000 to help commercialise outcomes from research programs of the IMB.

IMBcom's mission is to drive an internationally competitive development and commercialisation program based on the research of the Institute. Initially IMBcom was a virtual entity within the University's technology transfer company, UniQuest Pty Ltd, being incorporated as a separate company on 11 October 2000. The Board of IMBcom Pty Ltd comprises the University's Senior Deputy Vice-Chancellor Professor Ted Brown; Deputy Vice-Chancellor (Research) Professor Paul Greenfield; CEO of UniSeed Dr David Evans; Dr Jane Wilson; Start-up Australia Chairman Mr Ken Roberts; and Macquarie Bank Deputy Chairman Mr Mark Johnson.

IMBcom also aims to assist the IMB to ensure that its research strengths are ultimately developed by Australian industry. This in turn will help drive Queensland's economic growth and associated employment, which is a key requirement of the State Government's funding of the IMB. The company intends to participate in the development of incubator facilities and seed funding arrangements to help take spin-off companies to the point where they can compete effectively for early stage venture capital in the open market.

Alliances

IMBcom expects that outsourcing of R&D by pharmaceutical companies to facilitate drug design and development will provide major opportunities for research contracts with the IMB. A particular window of opportunity exists in discovery research aimed at new targets and new approaches to human genetic disease.

In the longer term, the major emphasis of IMBcom will be on establishing partnerships with companies, both pharmaceutical and biotechnology, which benefit the IMB through strengthening its financial and scientific base. The focus will be on the USA, and building on the links already established in some key centres of excellence. We expect that 60 percent of external business development and marketing will be focussed on the USA region.

Another major target for IMB R&D alliances is Asia, notably Japan, China, Korea and Taiwan, where strong relationships have already been established with the pharmaceutical and biotechnology sectors. This has been achieved with the assistance of the Queensland government offices in Tokyo, Osaka, Shanghai and Taiwan, as well as Australian Trade Commissioners. There are clear opportunities in studies of diseases important to the Asian region, and through the development of research programs linked to commercialisation processes.

IMBcom is currently negotiating with several Asian companies including Itochu in Japan and several companies from China, Korea and Singapore with interests in possible joint ventures.

Growth of the Australian biotechnology and pharmaceutical industries is also accelerating and this, along with incentives for companies to conduct R&D, including the PIIP program and new programs announced in the Innovation statement, provides additional opportunities for the IMB.

Spin-Offs

The State Government's investment in IMB is already bearing fruit in the form of several recent biotechnology start-ups driven and staffed by ex-IMB researchers, as well as new companies currently emerging from IMB's research.

Promics Pty Ltd

Promics Pty Ltd was established early in 2000 to commercialise the results of novel technology developed within Associate Professor David Fairlie's laboratory in the IMB. Venture capitalists Start-up Australia and Rothschilds Bioscience of Melbourne have invested $3 million in Promics Pty Ltd.

Promics will develop and market novel small molecules that mimic structural characteristics of proteins to make therapeutic

compounds that retain the activity of proteins but have improved stability and bio-availability. The breakthrough on which Promics is based provides a world-first class of drug candidates that shut down the activity of a protein which is produced in inflammatory disorders such as rheumatoid arthritis, acute respiratory distress syndrome, sepsis and Alzheimer's disease.

Xenome Ltd

Xenome is a public, non-listed company located in Brisbane, in which the current major shareholders are Medica Holdings Limited, a publicly listed biotechnology investment company, and UniQuest Pty Ltd, the commercialisation company of the University of Queensland.

Xenome has an exclusive license to a large portfolio of novel venom peptide compounds, and has filed International PCT applications on compounds with novel chemistry, structure and therapeutic application. Xenome's capacity to produce new intellectual property within its own laboratories, coupled with its links to the IMB, are expected to generate significant new commercialisation opportunities.

Cytokine Mimetics

Cytokine Mimetics has been established to apply a novel generic technology to the development of molecules that inhibit or mimic the action of cytokines. The technology enables the sculpting of cytokine functions onto new frameworks that have improved bioavailability characteristics when compared to the native cytokine. This process has the potential to revolutionise the treatment of many important diseases.

Genset Pacific Ltd

GENSET

Genset Pacific Ltd is a fully integrated genomics company engaged in providing tailored genomics information. Genset Pacific Ltd has developed unique industrial expertise in massive manufacturing of custom-made synthetic DNA fragments. Its mission is to deliver to any oligonucleotide user, anywhere in the world, the most comprehensive, reliable and flexible DNA synthesis. The company is strongly committed to bring innovative solutions to the current DNA manufacturing limitations.

Australian Genome Diagnostics Pty Ltd

Australian Genome Diagnostics (AGD), a joint venture between IMBcom and The Walter and Eliza Hall Institute of Medical Research, is a highly specialised pathology laboratory serving hospital and private pathology laboratories with new and innovative diagnostic tests to aid in patient management and improve health outcomes. AGD is currently focusing on breast cancer diagnosis using BRCA1 and 2 analysis, and haematological cancers with tests such as BCRabl, gene rearrangements and translocations. AGD's role is to improve the quality of testing rather than the development of new tests.

IP Management and Development

The market research activities of our Commercial Intelligence Agency (CIA) are used to generate technical and business packages. These packages guide development milestones and assist in the generation of marketing materials used to attract large pharmaceutical companies and venture capital investors. Working closely with scientists we have developed proposals based on existing and future IP, by conducting market appraisals, developing new strategies and matching research opportunities with investor requirements.

IMBcom is also working to bridge the gap between early stage fundamental research and commercialisation. This involves securing sources of seed funding, and assisting scientists to implement development programs that provide proof of concept and validation of the business opportunity. IMBcom has provided seed funding and helped guide the technical progress of three promising early stage programs in 2000.

IMB seminars

Dr David Leavesley
Hanson Centre for Cancer Research, Adelaide
Innate immunity, fibrosis and sclerosis - lessons from a laboratory approach

Dr Matt Trau
Department of Chemistry, The University of Queensland
Gene balls and drug balls: novel colloidal devices for DNA sequencing and drug discovery

Dr Bryan Mowry
Wolston Park Hospital, Wacol, Queensland
Current findings in the molecular genetics of schizophrenia

Dr Wah Chiu
Baylor College of Medicine, Houston, USA
Structural biology of herpesvirus capsid

Professor Simon Easteal
John Curtin School of Medical Research, Canberra
Information biology and the integration of biomedicine in the genomics era

Professor Chris Marshall FRS
Institute of Cancer Research, London UK
Small GTPase signalling pathways and proliferation control

Dr Jan Slot
University Medical Center and Institute of Biomembranes, Utrecht University, Netherlands
Immunogold labeling of ultrathin cryosections: a morphological study on ER - Golgi transport

Dr Jane Andrews
National Institute for Medical Research, London, UK
Xenopus tropicalis: frogs with glowing genetics

Dr Jennifer Hallinan
Centre for Sensor Signal and Information Processing, The University of Queensland
Digital image analysis for cancer screening

Dr Tony Weiss
Department of Biochemistry, The University of Sydney
Elastin: stretching from synthetic genes to controlled assembly

Dr Brian Key
Anatomical Sciences, The University of Queensland
Axon navigation in the embryonic vertebrate brain

Dr Denis Crane
School of Biomolecular and Biomedical Science, Griffith University, Brisbane

Dr Helen Blanchard
St Vincent's Institute of Medical Research, Melbourne
Three-dimensional structure of caspase-8, an initiator enzyme in apoptosis

Dr Sally-Ann Poulsen
Department of Chemistry, The University of Queensland
Dynamic combinatorial chemistry: an approach to drug discovery

Dr James DeVoss
Department of Chemistry, The University of Queensland
Ironing out bacteria: siderophore biosynthesis; bacterial P450s

Dr Ed Nice
The Ludwig Institute for Cancer Research & The CRC for Cellular Growth Factors, Melbourne
Functionally directed proteomics

Professor H Wagner
Institut für Medical Mikrobiologie, Immunologie und Hygiene, Technische Universität, München, Germany
Bacterial CpG-DNA mediated signalling and activation of dendritic cells

Dr Helen Cooper
Development and Neurobiology Unit, Walter and Eliza Hall Institute of Medical Research, Melbourne
The DCC/Neogenin-netrin guidance system: a molecular strategy for cell and axonal migration

Dr Manuel Baca
Walter and Eliza Hall Institute of Medical Research, Melbourne
Phage display: everything you wished to know but were too afraid to ask

Dr Jackie Wilce
Department of Chemistry/ Biochemistry, University of Western Australia, Perth
Studies of a protein-DNA interaction by NMR spectroscopy and X-ray crystallography

Dr Mike Lawrence
Biomolecular Research Institute, Melbourne
Understanding active site modulation in protein families - two structural examples

Dr Wayne Tilley
Flinders Cancer Centre, Flinders

Medical Centre, Flinders University, Adelaide
Androgen receptor structure and function in breast and prostate cancer

Professor André Menez
Department of Protein Engineering, CEA, Saclay, France
Animal toxins, a source of inspiration for drug design

Professor Heinrich Betz
Max-Planck-Institute for Brain Research, Frankfurt, Germany
Glycine as central neurotransmitter: analysis of its receptor sites

Professor Robert Capon
School of Chemistry, The University of Melbourne
Marine bioprospecting: bioactive metabolites from down under the sea

Professor John McAvoy
Department of Anatomy, University of Sydney
Growth factors in lens developmental biology and pathology: key roles for FGF and TGFß

Professor Ray Rodgers
Department of Medicine, Flinders University, Adelaide
The dynamic ovarian follicular epithelium and its associated extracellular matrix

Dr Merlin Crossley
Department of Biochemistry, University of Sydney
Zinc finger proteins in the control of gene expression

Dr Emma Whitelaw
Department of Biochemistry, University of Sydney
Epigenetic inheritance in mammals

Dr Mike Eccles
Cancer Genetics Laboratories and Department of Biochemistry, The University of Otago, New Zealand
Pax2 and apoptosis: life and death in the developing kidney

Professor Jack Pettigrew
Vision Touch and Hearing Research Centre, The University of Queensland
Brains, biological clocks and bipolar disorder

Dr Chiara Zurzolo
Cellular and Molecular Biology, Università degli Sudi di Napoli Federico II Naples, Italy
Lipid rafts and transport of GPI-anchored proteins in polarized epithelial cells

Dr Paul Pilch
Department of Biochemistry, Boston University School of Medicine, USA
Molecular regulation of insulin action in adipocytes

Dr Andrea Munsterberg
Department of Anatomy and Physiology, University of Dundee, U.K.
Muscle development in mice

Dr Yumik Saga
Department of Toxicology, National Institute for Health, Japan
MesP1 and MesP2 are essential for the development of cardiac mesoderm

Professor Hiroyuki Takeda
National Institute of Genetics, Japan
Dynamic expression of zebrafish hairy-related gene, her1, identifies a molecular clock linked to teleost somite segmentation

Dr Kathryn Howell
Health Sciences Center University of Colorado, USA
Structural evidence for multiple transport mechanisms through the golgi

Dr Mike Quilliam
Institute for Marine Biosciences, National Research Council of Canada, Halifax, Canada
MS and LC/MS for the analysis of bioactive marine natural products

Dr Robert Cappai
Department of Pathology, University of Melbourne
Prion proteins: structure and function in disease and health

Professor Wayne Hall
Executive Director
The National Drug and Alcohol Research Centre, University of New South Wales, Sydney
Heroin use in Australia: lessons for social policy towards biotechnology

Dr Bill Lot
Sir Albert Sakzewski Virus Research Centre, The University of Queensland
Vitamin B12-RNA interactions in Hepatitis C: a novel probe of structure and function

2000

Dr Marilyn Anderson
Department of Biochemistry, La Trobe University, Melbourne
Biosynthesis and function of cyclic knotted proteins in plants

Dr Joel Adelson
College of Physicians and Surgeons, Columbia University, New York, USA
Genomic redundency, development of new functional molecules, and inventiveness in higher genomes

Professor György Kéri
Department of Medicinal Chemistry, Semmelweis Medical University, Budapest, Hungary
Signal transduction therapy - new trends in drug research

Dr Martin Banwell
Research School of Chemistry, Institute of Advanced Studies, Australian National University, Canberra
Enzyme directed synthesis of key drug precursors

Dr Alan Roseman
Laboratory of Molecular Biology, MRC, Cambridge, UK
Building atomic models of macromolecules using cryo electron microscopy

Dr Binks Wattenberg
Molecular Cell Biology Laboratory, Hanson Centre for Cancer Research, Adelaide
Protein trafficking and signal transduction in intracellular membranes: tail-anchored proteins and sphingosine-kinase

Professor Mark von Itzstein
Director, Centre for Biomolecular Science and Drug Discovery, Griffith University, Gold Coast
The synthesis and evaluation of carbohydrate based probes as inhibitors of rotavirus

Dr Matt Cooper
Department of Chemistry, University of Cambridge, UK
Using surface plasmon resonance (SPR) to screen for binders to membrane receptors

Dr Francois Penin
Institute for Biology and Chemistry of Proteins, France
Mechanism of signal peptide process of Dengue viral polyprotein at the membrane C-prM junction. Structure-function analysis by CD, NMR and directed mutagenesis

Dr Terje Dokland
Institute of Molecular Agrobiology, The National University of Singapore
Viral morphogenesis: structural and biochemical approaches

Dr David Owen
Laboratory of Molecular Biology, MRC, Cambridge, UK
A structural and functional dissection of the AP2 adaptor complex - a pivotal player in clathrin mediated endocytosis

Dr Thomas Preiss
Gene Expression Programme, EMBL, Germany
Analysis of mRNA recruitment to ribosomes in eukaryotic cells

Collaboration

is the lifeblood of scientific endeavour, enabling synergies and exchanges that are essential for successful research and development outcomes. IMB scientists list a total of 137 international collaborative projects active in 2000, and a further 140 within Australia. These include partnerships with many of the most prestigious research institutions in the world. Our collaborative partners include:

- European Molecular Biology Laboratory, Germany
- NeuroGadgets Inc., Canada
- National Institutes of Health, Bethesda, USA
- Duke University Medical Centre, Chapel Hill, USA
- Merck Laboratories, Philadelphia, USA
- Oxford University, UK
- Hong Kong University, Hong Kong
- Osaka University, Japan
- Baylor College of Medicine, Houston, USA
- Samuel Lunenfeld Research Institute, Toronto, Canada
- Washington University School of Medicine, USA
- The Mount Sinai School of Medicine, New York, USA
- Wistar Institute, Philadelphia, USA
- Harvard Medical School, Boston, USA
- Imperial College, The University of London, UK
- The Hospital for Sick Children, Toronto, Canada
- Centre National de la Recherche Scientifique, France
- Brain Research Institute, RIKEN Japan
- Garvan Institute of Medical Research, Sydney
- Ludwig Cancer Research Centre, Melbourne
- St Vincent's Institute of Medical Research, Melbourne
- Glaxo Wellcome, USA
- Cambridge University, UK
- Cornell University, New York, USA
- Institute of Molecular Pathology Vienna, Austria
- Massachusetts General Hospital, USA
- Queensland Institute of Medical Research, Brisbane
- The Walter and Eliza Hall Institute, Melbourne
- Children's Medical Research Institute, Sydney
- Institute of Medical and Veterinary Science, Adelaide
- University College, London, UK
- Fox Chase Cancer Center, Philadelphia, USA
- Howard Florey Institute, Melbourne
- National Cancer Institute, Frederick, USA
- Biomolecular Research Institute, Canberra
- Ludwig Institute for Cancer Research, Melbourne
- Scripp's University, San Diego, USA
- Case Western Reserve University, Ohio, USA
- Analytica Therapeutics Inc, San Francisco, USA
- University of California, San Diego, USA
- NovoNordisk, Copenhagen, Denmark
- Washington University, St Louis, USA
- University of the Witwatersrand, South Africa
- San Diego Zoological Society, USA
- John Curtin School of Medical Research, Canberra
- University of Edinburgh, UK
- University of California, San Francisco, USA

Financial statement

Statement of Operating Income and Expenditure

Year Ended 31 December 2000

INCOME:

	Note	
University of Queensland (Operating Grant)	1	2,942,718
University of Queensland Research Grants		200,990
State Government	2	5,500,000
SRC Grant (Australian Research Council)		1,631,153
Australian Research Council	3	1,131,271
Clive and Vera Ramaciotti Foundation		43,546
CRC for Discovery of Genes for Common Human Diseases		220,958
Diabetes Australia Research Trust		33,409
Department of Industry Science and Technology		166,400
Human Frontiers Science Program		127,242
Glaxo Wellcome Australia		670,000
Government Employees Medical Research Fund		45,000
Juvenile Diabetes Foundation International		299,626
Mayne Bequest Foundation		60,000
The Merck Genome Research Institute		261,559
National Health and Medical Research Council	3	2,938,586
National Heart Foundation		45,000
Post Graduate Scholarships		28,209
Queensland Cancer Fund		230,072
Sylvia and Charles Viertel Charitable Foundation		165,000
Wellcome Trust		28,011
Commercial Income		1,371,664
Miscellaneous Income		415,591
TOTAL INCOME:		18,556,004
Funds brought forward from 1999	4	1,009,031
TOTAL FUNDS AVAILABLE		19,565,035

EXPENDITURE:

Salaries-Research		6,549,841
-Administration		1,090,220
-Infrastructure		541,043
Research Services		2,635,745
Education Programs	5	317,726
Administration	6	937,703
Infrastructure	7	357,436
Capital Equipment	8	2,307,116
IMBcom		984,608
TOTAL EXPENDITURE:		15,721,438
Funds carried forward to 2001:	9	**3,843,597**

Explanatory Notes to Statement of Income and Expenditure

1/ In-kind Contributions

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

	Department	*Percentage*
S. Barker	Parasitology	80
D. Hume	Biochemistry	40
	Microbiology	40
T. Loy	Anthropology & Sociology	100
J. Mattick	Biochemistry	20
R.Parton	Microscopy & Microanalysis	10
J. Rothnagel	Biochemistry	100
B.Wainwright	Biochemistry	20
M.Waters	Physiology & Pharmacology	100
A. Yap	Physiology & Pharmacology	100
B. Kobe	Biochemistry	100

2/ State Government Funding received in advance for 2001 **1,750,000**

3/ Fellowship/Projects from Government Agencies

Australian Research Council

Projects	867,324
Fellowships	263,947

National Health and Medical Research Council

Projects	2,593,522
Fellowships	345,064

4/ Funds brought forward from 1999

University of Queensland Operating Grant	784,151
Fellowships (as approved by funding bodies)	-25,633
Project Grants (as approved by funding bodies)	250,512

5/ Education Programs

Postgraduate scholarships	298,786
Postgraduate recruitment & training	18,941

6/Administration

Annual Report	16,670
Marketing	55,714
Personnel Recruitment and Training	155,664
Visiting Scientists/Seminars	19,435
Other fees	233,844
Entertaining	7,806
Equip Lease - Photocopiers	13,178
Legal Expenses	667
Postage and Freight	11,065
Printing and Stationery	57,715
Telephone	39,516
Travel Expenses	30,478
Sundries	39,428
Facility Costs	256,525

7/Infrastructure

General Maintenance	1,880
Rental - Demountables	12,674
Renovations	49,036
Laundry	1,396
Minor Equipment and Furniture	32,160
Animals	58,746
Additional Lab Space	2,609
Computer Services	37,177
Equipment Maintenance	119,047
Glass Washing and Replacement	34,174
Minor Equipment	33,363
Reticulated gases, RO water and dry ice	37,497
Scientific Services	-78,468
Stores	16,146

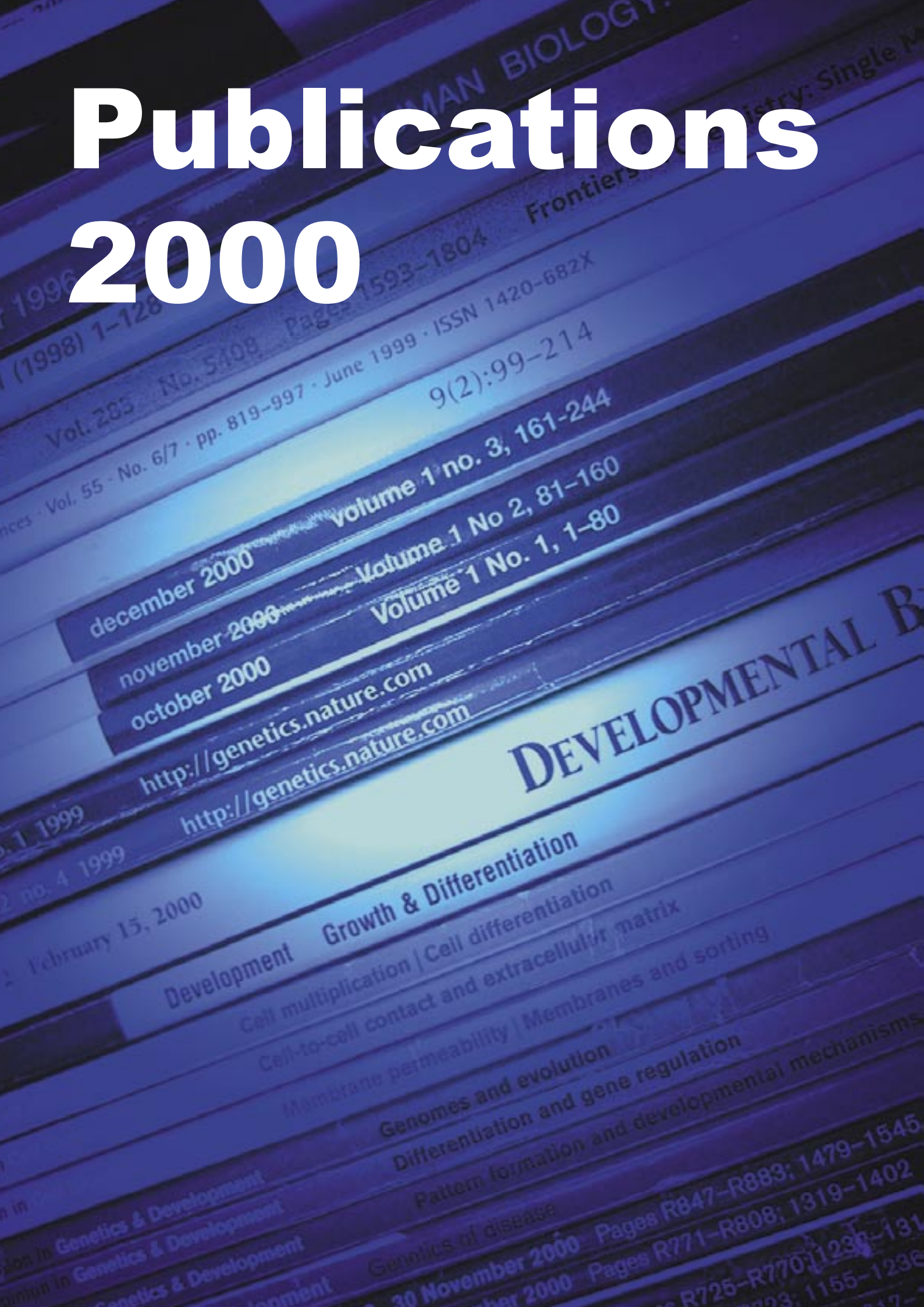
8/Capital Equipment

Scientific & Computing Equipment	2,219,577
Minor Equipment	87,539

9/Funds carried forward to 2001

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

* See note 2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december 2000
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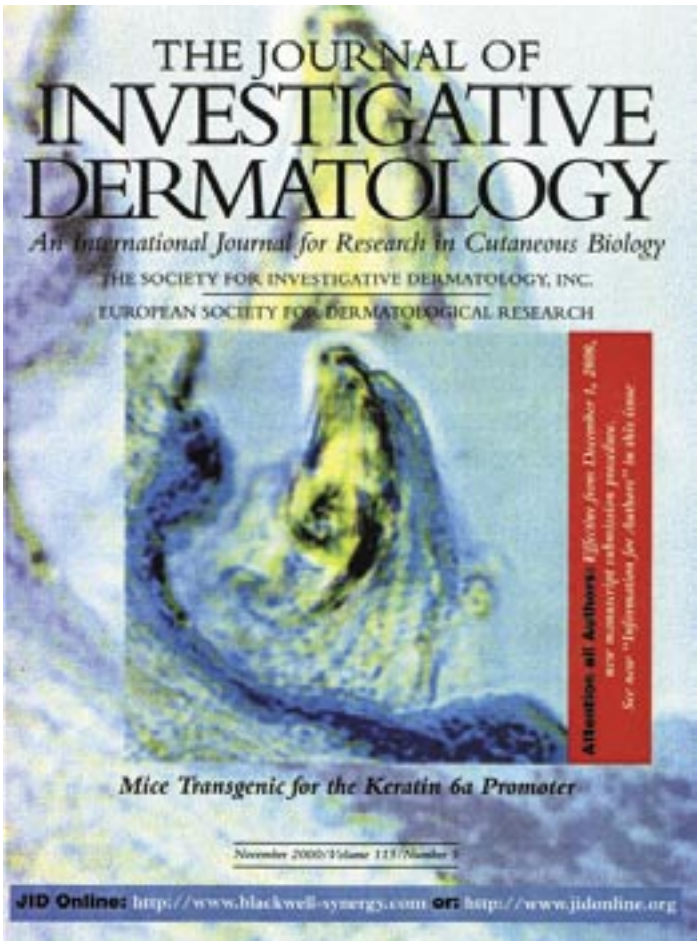

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