IMB RESEARCHERS

The People & Their Passion

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

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

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

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

Division of Genomics & Computational Biology

RESEARCH FOCUS

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

Research Group Leaders
Tim Bailey
Sean Grimmond
John Mattick
Mark Ragan
Rohan Teasdale

Division of Molecular Genetics & Development

RESEARCH FOCUS

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

Research Group Leaders
Peter Koopman
Melissa Little
George Muscat
Andrew Perkins
Rick Sturm
Brandon Wainwright
Carol Wicking

Division of Molecular Cell Biology

RESEARCH FOCUS

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

Research Group Leaders
John Hancock
Brad Marsh
Alan Munn
Rob Parton
Jennifer Stow
Matt Sweet
Michael Waters
Alpha Yap

Division of Chemical & Structural Biology

RESEARCH FOCUS

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

Research Group Leaders
Paul Alewood
Robert Capon
David Craik
David Fairlie
Ben Hankamer
Glenn King
Richard Lewis
Jenny Martin
Mark Smythe

Joint Appointments at the IMB

RESEARCH FOCUS

The purpose of joint appointments is to foster collaborations in teaching, research and related activities between the IMB and Schools at The University of Queensland. Joint appointments involve a split of salary between the IMB and the relevant University of Queensland School and a joint appointee's commitment to the research and teaching activities at the IMB is greater than that of affiliate appointees. Joint appointees participate in all Institute activities including laboratory research, supervision of research higher degree students, and attendance at seminars, Divisional meetings and IMB Group Leader retreats.

Research Group Leaders
Kevin Burrage
Geoff Goodhill
Alan Mark
Geoffrey McLachlan

Pattern Recognition & Machine Learning in Biology

Tim Bailey

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

Our recent work has focused mainly on developing computational tools for studying the process of transcriptional regulation. These include better algorithms for discovering the DNA-binding profiles of transcription factors, search algorithms for comparing DNA-binding profiles, search algorithms for predicting transcription factor binding sites (TFBSs), and a computational model of transcriptional control by a cis-regulatory element in *Drosophila*. We also developed an algorithm for predicting the statistical power of comparative genomics approaches to TFBS prediction.

We are also interested in proteins, and recently developed GLAM2, a motif discovery algorithm that allows for gaps in the motif, and DEME, a motif discovery algorithm that discovers motifs that discriminate between two sets of protein or DNA sequences. We are also studying machine learning approaches for improving protein design.

We place a strong emphasis in delivering useful computational tools to biologists. We make the algorithms we develop available as interactive tools over the web. We support these tools via websites located at IMB and UCSD. These include MEME, a tool for discovering motifs (sequence patterns) in protein and DNA sequences; MAST, a tool for scanning sequence databases for matches to known patterns; MCAST, a tool for scanning sequences for clusters of transcription factor binding sites; and Meta-MEME, a general-purpose sequence modelling tool. Some of these tools are among the most widely used bioinformatics algorithms. For example, the MEME algorithm is used via the UCSD website by over 1000 biologists around the world each month. Maintaining these websites and supporting the biologists who use them is an important commitment for us.

RESEARCH PROJECTS

- Identifying the targets of key transcription factors involved in erythropoiesis
- Identifying targets of transcription factors using functional annotation data
- Improving TFBS prediction using epigenetic modification data
- Improving TFBS prediction using comparative genomics
- Improving the training and application of models of regulation
- Improving motif discovery algorithms

KEY PUBLICATIONS

Bodén, M. (2008). Predicting nucleolar proteins using support-vector machines, in *Proceedings of the Asia-Pacific Bioinformatics Conference – APBC 2008*, Accepted.

Hawkins, J., and Bailey, T.L. (2008). "The power of phylogenetic motif models" accepted for publication at Recomb 2008.

Buske, F., and Bodén, M. (2007). Decoupling signal recognition from sequence models of protein secretion, in *Proceedings of 2007 International Symposium on Computational Models for Life Sciences – CMLS'07*, Accepted.

Dufton, L. and Bodén, M. (2007). Reducing the number of support vectors to allay inefficiency of large-scale models in computational biology, in *Proceedings of 2007 International Symposium on Computational Models for Life Sciences – CMLS'07*, Accepted.

Frith, M.C., Carninci, P., Kai, C., Kawai, J., Bailey, T.L., Hayashizaki, Y., and Mattick, J.M. (2007). Splicing bypasses 3' end formation signals to allow complex gene architectures. *Gene* **403**: 188-193.

Gupta, S., Stamatoyannopolous, J.A., Bailey, T.L., and Noble, W.S. (2007). Quantifying similarity between motifs. *Genome Biology* **8**: R24.

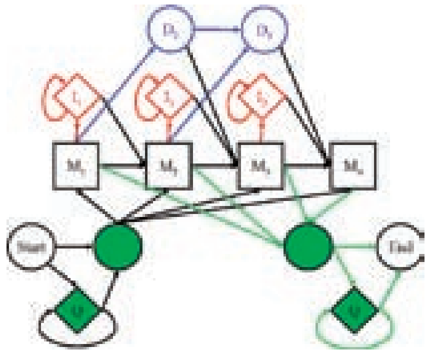
Hawkins, J., Davis, L., and Bodén, M. (2007). Predicting Nuclear Localization. *Journal of Proteome Research* **6**: 1402-1409.

Hawkins, J., Mahony, D., Maetschke, S., Wakabayashi, M., Teasdale, R.D., and Bodén, M. (2007). Identifying Novel Peroxisomal Proteins. *Proteins: Structure, Function and Bioinformatics* **69**: 606-616.

Redhead, E., and Bailey, T.L. (2007). Discriminative motif discovery in DNA and protein sequences using the DEME Algorithm. *BMC Bioinformatics* **8**: 385.

Tino, P., Hammer, B., and Bodén, M. Markovian bias of neural-based architectures with feedback connections, *Perspectives of Neural-Symbolic Integration*, Hitzler and Hammer (eds.), Springer Verlag, 2007. In press.

You, L., Zhang, P., Bodén, M. and Brusic, V. L. Understanding Prediction Systems for HLA-Binding Peptides and T-cell Epitope Identification, in *Proceedings of the 2nd IAPR Workshop on Pattern Recognition in Bioinformatics*, Singapore, Springer Verlag, 2007.



Hidden Markov model.

LAB MEMBERS

Research Fellow: Dr Mikael Bodén (seconded from ITEE)

Research Officers: Dr Martin Frith, Dr John Hawkins

Programmers: Emma Redhead, Stefan Maetschke

PhD Students: Denis Bauer, Tom Whitington

MPhil Student: Isye Arieshanti

Visitors: Professor Osamu Maruyama, Fabian Buske, Zuzana Cienikova, Liang Ma

Expression Genomics

Sean Grimmond

The central theme to my research to date has been the capture of information contained within the transcriptome and the study of transcriptome dynamics to identify key genes or transcriptional programs.

The central focus of my research is to perform global surveys of the transcriptome and to use computational mining and genomic screening techniques to uncover the genes and transcriptional programs controlling important biological processes such as cell differentiation, organogenesis, and tissue repair, as well as pathological states such as tumour initiation and progression. Over the last six years we have worked with the FANTOM consortia to re-define transcriptional output for each locus in mouse and man, with particular attention paid to: genes whose products are associated with developmental pathways, the phosphoregulators network, and the extracellular space.

Central to our research is the ability to rapidly survey transcriptome content and dynamics in model systems. The laboratory is heavily involved in creating and exploiting platform technologies to create accurate catalogues of gene expression in model systems. Microarray profiling is used to monitor the gene activity of loci, next-generation sequencing approaches have been developed to survey transcriptional complexity, and robotic in situ screening is used to put gene expression into a histological context.

The next five years will build upon these recent efforts and focus on the integration of transcriptome content, the accurate surveying of transcriptional complexity in multicellular organisms and integrating these with existing forms of data. These focus areas are outlined in more detail below:

Integration of transcriptome content is necessary to identify key transcripts and novel gene products driving key phenotypes in model systems. The combination of array and sequence tag-based profiling approaches are providing the unprecedented opportunity to survey all variant transcripts expressed from each locus in model systems. Furthermore we are able to study the role of novel RNA species in RNA-mediated control of processes (such as non-coding RNAs, repeat expression, miRNAs etc) in a non-biased fashion using next-generation sequencing approaches. We are actively pursuing these studies in models of the role of cell-cell communication in ES cell-directed differentiation and survival, the control of normal cell division and for the identification of new bio-markers associated with different subtypes of breast cancer.

Accurately surveying transcriptional complexity in multicellular organisms has the added complexity that gene expression needs to be surveyed in a histological context, if one is to accurately model gene networks controlling development and pathology. We are pioneering a joint microarray-in situ hybridisation screening regime to develop a temporal and spatial gene expression atlas of urogenital organogenesis in the mouse (as part of the NIH Genito-Urinary Development MAP program GUDMAP).

With the avalanche of data being created by these approaches, we are actively pursuing new ways to integrate these surveys with genomic, transcriptomic and epigenomic data, in an effort to make more accurate molecular control of biological processes.

RESEARCH PROJECTS

- Redefining total transcriptome content and dynamics of the mammalian transcriptome and studying the role of novel RNAs controlling cellular differentiation and development
- Creating complete transcriptional programs of models of ES differentiation, cell division and organogenesis
- Creating a combined microarray and in situ transcriptome atlas for the mammalian urogenital tract
- Analysing the transcriptome of the extracellular space in mammalian development
- Developing next-generation sequencing technologies to allow for combined genomic, transcriptomic and epigenomic profiling of model systems

KEY PUBLICATIONS

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

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

LAB MEMBERS

Senior Research Officer: Dr Paul Leo

Research Officers: Dr Brooke Gardiner, Dr Alistair Forrest, Dr Nicole Cloonan, Dr Gabriel Kolle, Dr Nicola Waddell, Dr Logan Walker, Dr Ehsan Nourbkash, Dr Ben Wilson

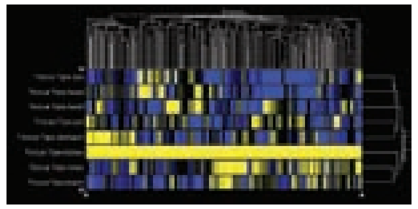
Senior Research Assistants: Graeme Bethel, Anita Steptoe

Research Assistants: Milena Gongora, Shivangi Wani, Michelle Chan

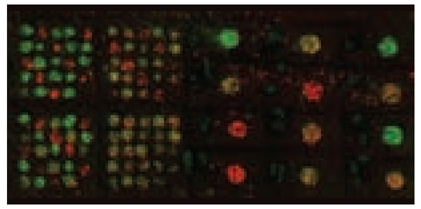
PhD Students: Geoff Faulkner, Melissa Brown

Masters Students: Rathi Thiagarjan, Ajay Panwar

Honours Student: Alan Robertson



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

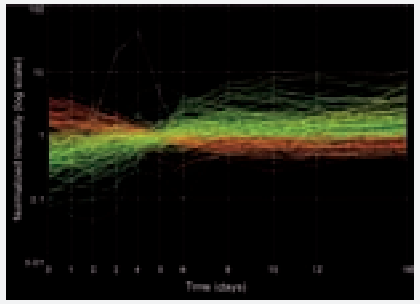


Photomicrograph of HEK cells transfected using a robotically generated cell microarray.

Rnomics: Noncoding RNA in Mammalian Evolution & Development

John Mattick

We are exploring the thesis that the genetic programming of higher organisms has been fundamentally misunderstood for the past 50 years, because of the assumption that most genetic information is transacted by proteins. It is now clear, despite the fact that only a small fraction encodes proteins, that the majority of the genomes of mammals and other complex organisms is transcribed, apparently in a developmentally regulated manner, and that most complex genetic phenomena in these organisms are RNA-directed. Working in conjunction with collaborators in Japan, Europe and the United States, we are working to characterise and understand the functions of the mammalian transcriptome, and to validate the prediction that most genetic information in mammals is conveyed by RNAs that control the trajectories of our differentiation and development. This includes the identification of small regulatory RNAs that control gene expression at various levels, including transcription and splicing, and to determine the expression patterns and function of the tens of thousands of longer non-coding RNAs that are dynamically expressed in mammalian cells. Among our recent findings we have shown that it is possible, if not likely, that most of the mammalian genome is under evolutionary selection, and demonstrated that the majority of long non-coding RNAs are expressed in the brain, many in precise cellular and subcellular locations. We also participated in the international ENCODE project to functionally analyse one percent of the human genome, and further characterised unusual features of the non-coding landscape of the genome, including ultraconserved sequences and transposon-free regions. We use advanced computational and experimental methods, integrating in silico, in vitro and in vivo approaches. The outcomes of our research will be to refine our understanding of the genomic factors underpinning human development, diversity and disease, with practical implications in medicine, genetic engineering and advanced programming of self-assembling information systems.



Dynamic expression of non-coding RNAs during embryonal stem cell differentiation.

RESEARCH PROJECTS

- Bioinformatically predicting and experimentally validating new microRNAs and other small RNAs in mouse and human
- Analysing the dynamic expression of long non-coding RNAs during differentiation of embryonal stem cells, neural stem cells, muscle, macrophages, T-cells and developing tissues such as the male and female genital ridge
- Analysing the cellular and subcellular expression patterns of non-coding RNAs in brain and other tissues
- Targeted functional analysis of selected non-coding RNAs involved in developmental processes and neurogenesis
- Re-aligning the human genome with other mammalian genomes on the basis of RNA structural rules
- Developing new algorithms for the prediction of different classes of functional non-coding RNAs
- Identifying non-coding RNAs as diagnostics and prognostic markers in cancer

KEY PUBLICATIONS

Mattick, J.S. (2007). A new paradigm for developmental biology. *Journal of Experimental Biology* **210**: 1526-1547.

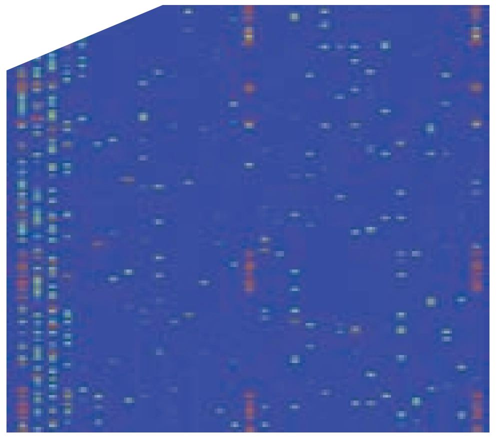
Taft, R.J., Pheasant, M., and Mattick, J.S. (2007). The relationship between non-protein-coding DNA and eukaryotic complexity. *Bioessays* **29**: 288-299.

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

Ravasi, T., Suzuki, H., Pang, K.C., Katayama, S., Furuno, M., Okunishi, R., Fukuda, S., Ru, K., Frith, M., Gongora, M., Grimmond, S., Hume, D.A., Hayashizaki, Y., and Mattick, J.S. (2006). Experimental validation of the regulated expression of large numbers of noncoding RNAs from the mouse genome. *Genome Research* **16**: 11-19.

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

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



LAB MEMBERS

Research Officers: Dr Marjan Askarian-Amiri, Dr Larry Croft, Dr Marcel Dinger, Dr Martin Hansen, Dr Igor Makunin, Dr Harald Oey, Dr Michael Pheasant, Dr Giulia Solda, Dr Lorenzo Malquori

Senior Research Assistant: Ke-lin Ru

PhD Students: Paulo Amaral, Michael Clark, Chol Hee Jung, Darren Korbie, Tim Mercer, Satu Nakhuri, Cas Simons, Stefan Stanley, Stuart Stephen, Ryan Taft

MSc Students: Emmanuelle Billon, Jan Szubert

Validation of bioinformatically predicted small RNAs from mice using high-density arrays.

Computational Genomics

Mark Ragan

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

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

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

For more information on two specific projects, the Visible Cell™ e-project and the Modelling and Analysis of Biological Network Activity (BioMANTA) project, please see: www.visiblecell.com and www.biomanta.org

RESEARCH PROJECTS

- Automatically inferring vertical and lateral gene transmission, genetic recombination and breakpoints in pathogenic bacteria
- Investigating genome dynamics and the evolution of new protein functions in teleosts
- Fine-scale mapping of orthologous and paralogous regions of mammalian genomes
- Studying protein-protein interaction networks in cellular context
- Computationally discovering novel miRNA targets in mammalian genomes
- Integrating bioinformatic information using Semantic Web technologies
- Implementing the Visible Cell™ Project: software and data infrastructure
- Implementing a data grid for very large molecular and image datasets

KEY PUBLICATIONS

Höhl, M., and Ragan, M.A. (2007). Is multiple-sequence alignment required for accurate inference of phylogeny? *Systematic Biology* **56**: 206-221.

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

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

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

Garcia Castro, A., Rocca-Serra, P., Stevens, R., Taylor, C., Nashar, K., Ragan, M.A., and Sansone, S-A. (2006). The use of concept maps during knowledge elicitation in ontology development processes. *BMC Bioinformatics* **7**: 267.

Beiko, R.G., Chan, C.X., and Ragan, M.A. (2005). A word-oriented approach to alignment validation. *Bioinformatics* **21**: 2230-2239.

Beiko, R.G., Harlow, T.J., and Ragan, M.A. (2005). Highways of gene sharing in prokaryotes. *Proceedings of the National Academy of Sciences USA* **102**: 14332-14337.

Garcia, A., Thoraval, S., Garcia, L.J., and Ragan, M.A. (2005). Workflows in bioinformatics: meta-analysis and prototype implementation of a workflow generator. *BMC Bioinformatics* **6**: 87.

Mar, J.C., Harlow, T.J., and Ragan, M.A. (2005). Bayesian and maximum likelihood phylogenetic analyses of protein sequence data under branch-length differences and model violation. *BMC Evolutionary Biology* **5**: 8.

LAB MEMBERS

Senior Research Officers: Dr Nicholas Hamilton

Research Officers: Dr Aaron Darling, Dr Karin Kassahn, Dr Simon Wong

Research Webmaster: Dr J. Lynn Fink (to 4/2007)

Database and Application Developers: Oliver Cairncross, Dr Ingrid Jakobsen, Dr Tim McComb, Tim Sullivan, David Wood

Data Grid Developers / Administrators: Kimberly Begley (Griffith University/APAC), Mhairi Marshall (ARC Centre of Excellence/APAC)

Queensland Facility for Advanced Bioinformatics Senior Team: Jeremy Barker (CEO), Dr Dominique Gorse (Technical Manager from 5/2007), Dr David Hansen (Technical Manager to 5/2007)

BioMANTA-Pfizer: Dr Melissa Davis, Dr Muhammad Shoaib Seghal

QosCosGRID: Dr Pamela Burrage, Dr Krzysztof Kurowski

Scientific Programmer: Chikako Ragan

Manager, ARC Centre of Excellence in Bioinformatics: Lanna Wong

PhD Students: Cheong Xin Chan, Alex Garcia, Chang Jin Shin

Masters Student: JooYoung Choi

Honours Student: Andrés Esteban-Marcos

International Interns: Arnab Saha Mandal (Indian Institute of Technology, Kharagpur)

Research Trainees: Vinh Dang, Liam McIntyre

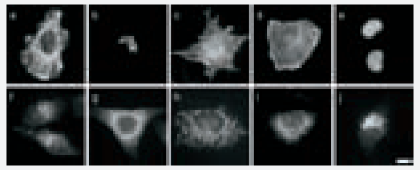
Computational Cellular Biology

Rohan Teasdale

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

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

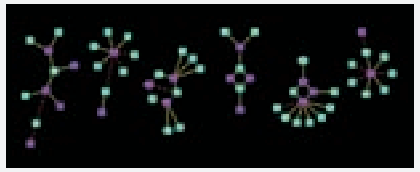
Subcellular Localisation - Determination of the subcellular localisation or compartmentalisation is an essential step in characterising the protein's function across all types of biomedical research, and its modulation needs to be considered when developing pharmaceutical agents. Our major long-term objective is to document the subcellular localisation of every protein within the mouse proteome. This will be achieved by a combination of experimental evidence, computational prediction and data mining.



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

RESEARCH PROJECTS

- Annotating the membrane organisation of mammalian secretory pathway proteins
- Maintaining and updating LOCATE: A Mouse Protein Subcellular Localisation Database - http://locate.imb.uq.edu.au
- Developing algorithms for prediction of protein features
- Developing computational approaches to analyse image and real-time microscopy data
- Studying endosome dynamics, macropinocytosis and retromer
- Investigating the systems biology of the mammalian endosome



KEY PUBLICATIONS

Hamilton, N.A., Pantelic, R.S., Hanson, K., and Teasdale, R.D. (2007). Fast automated cell phenotype image classification. *BMC Bioinformatics* **8**: 110.

Sprenger, J. Fink, J.L., Karunaratne, S., Hanson, K., Hamilton, N., and Teasdale, R.D. (2007). LOCATE: A Mammalian Protein Subcellular Localization Database. *Nucleic Acids Research* **36** (Database issue).

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

Davis, M.J., Hanson, K.A., Clark, F., Fink, J.L., Zhang, F., Kasukawa, T., Kai, C., Kawai, J., Carninci, P., Hayashizaki, Y., and Teasdale, R.D. (2006). Differential use of endoplasmic reticulum signal peptides and transmembrane domains is a common occurrence within the variable protein output of transcriptional units. *PLOS Genetics* **2**: e46.

Kerr, M., Lindsay, M., Luetterforst, R., Hamilton, N., Simpson, F., Parton, R., Gleeson, P.A., and Teasdale, R.D. (2006). Visualisation of macropinosome maturation by the recruitment of sorting nexins. *Journal of Cell Science* **119**: 3967-3980.

LAB MEMBERS

Senior Research Officers: Dr Brett Collins, Dr Nick Hamilton, Dr Zheng Yuan

Research Officers: Dr Lynn Fink, Dr Markus Kerr, Dr Stefan Maetschke, Dr Suzanne Norwood

Research Assistants: Seetha Karunaratne, Shane Zhang

PhD Students: Rajith Aturaliya, Melissa Davis, Daniel Shaw, Josefine Sprenger, Jack Wang

How Genes Regulate Embryo Development

Peter Koopman

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

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

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

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

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

RESEARCH PROJECTS

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

KEY PUBLICATIONS

Wilhelm, D., Palmer, S., and Koopman, P. (2007). Sex determination and gonadal development in mammals. *Physiological Reviews* **87**: 1-28.

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

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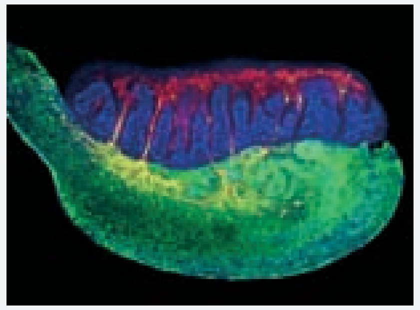

Recombinant organ culture with GFP expressing mesonephros (green) and wild type testis allows analysis of cell migration into the testis during development. Migrating endothelial cells integrate with endogenous vasculature (yellow and red respectively) which separate forming testis cords (blue).

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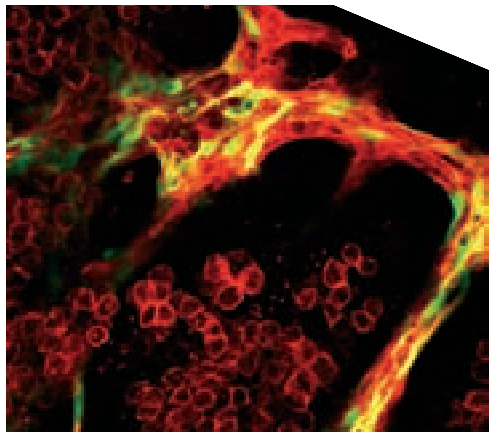

Platelet endothelial cell adhesion molecule (red) vividly outlines germ cell clusters and endothelial cells in a recombinant organ culture. Migrating endothelial cells marked by GFP (green) integrate into the endogenous population to establish testis vasculature.