LA TROBE UNIVERSITY

LA TROBE INSTITUTE FOR MOLECULAR SCIENCE

Research Report 2011

LA TROBE INSTITUTE FOR MOLECULAR SCIENCE

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A snapshot of our achievements

Development of an anti-malaria vaccine targeting merozoite surface protein 2 that inhibits parasite development in Phase I clinical trial patients

Identification that mutations in the gene 'fused in sarcoma' are linked to the neurodegenerative disease Amyotropic Lateral Sclerosis

Demonstration that the anti-cancer therapeutic TRAIL promotes mutations in surviving cancer cells

Establishment of 'Exocarta' – a database of exosomal molecular components hosted by La Trobe University for the scientific community

Development of novel chemical approaches for the synthesis of molecular cages and polymers

Development and characterisation of polymer inclusion membranes for the removal of Endocrine Disruptor Chemicals from environmental waters

Generation of a new program for the analysis of helix geometry in proteins

Development of genetic tools to monitor drug resistance in parasites in West Africa

Identification of novel mitochondrial proteins MiD49 and MiD51 as receptors for the mediator of mitochondrial fission Drp1

Identification of Sdh3, a component of the respiratory complex II, in the TIM22 protein translocase complex of the mitochondrial inner membrane

Development of ultra-low cost paper microfluidic sensors by ink jet printing for electrochemiluminescence based detection

Synthesis of novel macrocyclic and macrobicyclic ligands for radiopharmaceutical applications

Identification of the stem cell origin of basal cell carcinomas that arise in women carrying a mutation in the BRCA1 gene

Use of next generation sequencing to define population and species level evolution in Antarctic and deep-sea species

Identification of Rbf as a novel regulators of germline stem cell development in Drosophila

Isolation and characterisation of bacteriophage that prevent the stabilization of bacteria-induced foam in wastewater.

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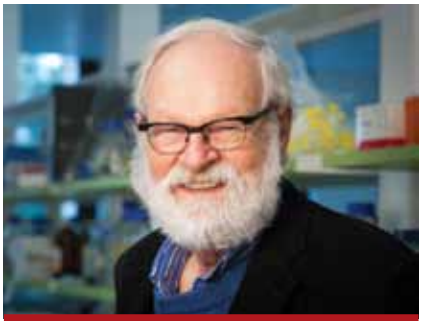


NICK HOOGENRAAD

Executive Director

As LIMS completed its third year of existence, 2011 saw our new building grow from a hole in the ground with the turning of the first sod in February by the Hon Senator Kim Carr, into a grand six storey structure. We look forward to the completion and occupation of the building in November 2012, and the relocation of Genetics into refurbished new space in the adjoining building. Besides the construction of the main LIMS building, we also began construction on a new Specific Pathogen Free (SPF) facility to allow us to expand our ability to work on genetically modified mice. This facility will be completed in June 2012, allowing LIMS to expand its research operations by 30%.

The year began with the announcement of the first Excellence in Research in Australia (ERA) nationwide assessment of research performance by all disciplines in Australian universities. The ERA results for LIMS were outstanding, with a maximum score of five ("well above world rating") for biochemistry and cell biology.

This was the only score of five, making this discipline top ranked in Australia. Chemistry also scored well, obtaining a three ("equal to world rating") for Physical Chemistry and three for Analytical Chemistry. Genetics was also given a three, making them equal to world rating.

The Federal Government has announced a second ERA round in 2012, and we look forward to confirming the outstanding reputation of biochemistry and cell biology at La Trobe. We are confident that we can improve our scores in chemistry and genetics with the recruitment of excellent staff in these disciplines since the last ERA assessment period.

We were disappointed to see some valued members of staff depart – David Vaux, John Silke and Leann Tilley – but were fortunate to recruit some outstanding new staff to LIMS. Professor Richard Simpson and his group relocated from the Ludwig Institute for Cancer Research to LIMS to increase our strength in proteomics and systems biology. Weisan Chen will also transfer from the Ludwig to LIMS in 2012 as Professor of Immunology. We were delighted to recruit Dr Matt Perugini from Bio21. Matt joined us in 2012 as an ARC Future Fellow and Associate Professor in Biochemistry, and will develop a LIMS Protein Interaction Facility. We welcomed Professor Jenny Graves, a Distinguished Professor in Genetics from the Australian National University (ANU), back to La Trobe University. We also recruited four LIMS Fellows: Dr Brian Smith, a molecular modeller and drug design expert joined Chemistry from WEHI; Dr Suresh Mathivanan, a bioinformatics and proteomics expert with an NHMRC training fellowship joined Biochemistry from the Ludwig; and X-ray crystallographers Dr Begona Heras from the Institute for Molecular Bioscience, University of Queensland and Dr Megan Maher from the Centenary Institute, University of Sydney.

Another highlight was the election of Professor Marilyn Anderson to the Australian Academy of Science. She also joined the Council of La Trobe University and was reappointed to the City West Water Board.

A major emphasis in the research effort by LIMS is in translational research. Hexima Ltd, a plant biotechnology company founded by LIMS staff member, Marilyn Anderson, has consolidated its research and development activities in LIMS.

Dr Mick Foley is scientific director of Adalta Pty Ltd, a start-up biotech company arising out of CRC research by Biochemistry staff members. La Trobe University is also the lead institution in the CRC for Biomarker Translation. A team of scientists are working in LIMS on the identification of plasma membrane biomarkers associated with disease, using quantitative proteomics and the production of monoclonal antibodies against these biomarkers. To assist the Institute with its translational research activities, two new external members have been appointed to the LIMS Advisory Board: Dr Tony Radford, a founding director of one of Australia's largest biotechnology companies, Cellestis, which produces diagnostic products such as a highly sensitive blood test for tuberculosis, and Dr Bruce Kefford, Deputy Secretary, Agriculture Research and Development, Victorian Department of Primary Industries, with extensive experience in agricultural research and development.

Each year brings fresh challenges. The external funding situation remains very competitive. Our researchers also require access to state-of-the-art equipment and it is a major challenge to find funding for both the essential equipment and its maintenance. LIMS was particularly fortunate to have more than A$10M from the building budget to equip laboratories and to finance the purchase of mass spectrometers, NMR equipment, a broad range of microscopes, DNA sequencing equipment, and X-ray crystallography equipment, ensuring we not only have a very fine building but that it will be fitted out and equipped with state-of-the-art equipment.

We look forward to 2012 with great anticipation as we create a place for LIMS in the research landscape of Australia.

Mission

LIMS is an institute set within the academic fabric of the School of Molecular Sciences. Its broad mission is to educate students in an environment where world class research is being carried out.

The mission of LIMS is to:

- Train the next generation of scientists to carry out research in biochemistry and cell biology, molecular genetics, biotechnology, chemistry and nanotechnology.
- Carry out both first class basic research and translational research which will lead to the production of commercial products such as therapeutic and diagnostic reagents and biotechnology products such as those used in agricultural production
- Vertically integrate the educational process by placing undergraduate and postgraduate students in the same environment where world class research is performed.
- Stimulate the interest of students in science via an extensive outreach program for secondary school students and their teachers.

The transforming principle of LIMS is the combining of different disciplines (biochemistry, chemistry and genetics) to achieve aims that would not be possible in the traditional academic setting. Thus LIMS brings together diverse scientists for education and training, setting the mould for the next generation of scientists who can pool their talents to work on projects that would not otherwise be possible.

Research Director report

RESEARCH AWARDS AND HONOURS

Biochemistry

Professor Marilyn Anderson was elected as a Fellow of the Australian Academy of Science. This prestigious award is well deserved recognition of Marilyn's research success in plant defence proteins and their application to biotechnology. Professor Nick Hoogenraad was featured in the Australian Academy of Science's *Interviews with Australian Scientists* series, and also as the Annual La Trobe University Alumni Lecturer.

The University acknowledged his long and significant contribution with the award of a Charles La Trobe Professorship. Nick was also awarded Honorary Life Membership of the Australian Society for Biochemistry and Molecular Biology (ASBMB) for his service to the Society. Professor Leann Tilley was awarded the 2011 Beckman Coulter Discovery Science Award from the ASBMB for distinguished contributions to the field of biochemistry and molecular biology. Dr Alex Maier was a Victorian finalist for the Eureka Prizes People's Choice Award for research and innovation.

Alex was also awarded Iran's highest scientific honour, the Khwarizmi Award, by President Mahmoud Ahmadinejad. His work on malaria has revealed a key adaptive strategy used by the malaria parasite to survive in, and cause damage to, its human host.

Dr Diana Stojanovski was a finalist in the life sciences and biological sciences category of the Australian Scopus Young Researcher Awards. Postgraduate students Catherine Palmer and Ayenachew Bezawork-Geleta were awarded student poster prizes at the 2011 Lorne Conference on Protein Structure and Function.

Chemistry

Emeritus Professor John Hill was awarded an honorary B (Univ) degree from the University of Surrey, UK. Dr Conor Hogan's paper entitled "Electrogenerated chemiluminescence detection in paper-based microfluidic sensors" was cited as a Top 10 Most Viewed Articles for Q1 2011 in, *Analytical Chemistry*.

Dr Anne Richards was an invited keynote speaker for a presentation titled "The design and synthesis of molecular cages and polymers," at the RACI Inorganic 2011 Symposium. Jacqui Delaney was awarded the Royal Australian Chemical Institute's (RACI) Analytical Division's original publication award for 2011. Ellen Reid was awarded The Royal Society of Victoria Young Scientist Research Award 2011 (Physical Sciences).

Genetics

Dr Warwick Grant's contribution to parasite research was recognised with his participation in a discipline reference group for helminth diseases, established by the World Health Organisation special program on Tropical Disease Research (WHO/TDR).

The group has prepared several advisory reports for WHO/TDR, three of which are to be published in late 2011 and early 2012 in peer reviewed journals and in WHO publications targeted at policy makers in developed and developing countries. Dr Jan Strugnell was appointed co-leader of the Marine Ecosystem Change and Protecting Marine Biodiversity streams within the Australian Antarctic Program. Jan was also invited to lead the Palaeo-reconstruction and Evolution subgroup of the International Scientific Committee for Antarctic Research (SCAR) Life Sciences program, and was invited to join the organising committee of the international Molluscs conference, to be held in 2012. Jan was an invited participant at three international workshops in the UK and Ireland which focused on genetic monitoring, estimating diversification rates and barcoding in southern ocean species.

She was also recognised by her alma mater, James Cook University, with an Outstanding Alumni Award and by the Australian Academy of Science with an early career investigator prize. Dr Mike Westerman, an emeritus member of the Department, was a co-author on a major paper published in *Science*.

Pharmacy

Dr Joe Tucci was an invited guest speaker at the International Conference on Pharmacy and Pharmaceutical Sciences, Yogyakarta, Indonesia. Joe gave a talk "Genetic polymorphisms of the CYP450 subtypes CYP 2C9, CYP 2C19 and CYP 2D6 in populations of ethnic Makassar Indonesians."

Mark Hulett
Director, Research

Research profiles

PROFILE

Robin Anders

Emeritus Professor
A sexual blood-stage malaria vaccine antigens

With collaborators at the Monash Institute of Pharmaceutical Sciences and the Burnet Institute, we seek to gain an understanding of the structural and antigenic characteristics of merozoite surface antigens considered potential components of a malaria vaccine.

Research focus

- structural determinants of antibody binding to malaria antigens
- vaccine design to overcome antigenic polymorphisms
- significance and mechanism of amyloid formation by merozoite surface protein 2.

Achievements

MSP2 malaria vaccine

With support from the PATH Malaria Vaccine Initiative, a vaccine was developed that contained the 3D7 and FC27 isoforms of MSP2, which represent the two families of MSP2 found in *Plasmodium falciparum* isolates.

The subjects in a phase 1 trial of this vaccine conducted in Brisbane mounted anti-MSP2 antibody responses that were shown to inhibit parasite development in an antibody-dependent cellular inhibition assay.

McCarthy JS, Marjason J, Elliott S, Fahey P, Bang G, Malkin E, Tierney E, Aked-Hurditch H, **Adda C**, Cross N, Richards JS, Fowkes FJ, Boyle MJ, Long C, Druilhe P, Beeson JG, **Anders RF** (2011) A phase 1 trial of MSP2-C1, a blood-stage malaria vaccine containing 2 isoforms of MSP2 formulated with montanide ISA 720, *PLoS One*, 6:e24413.

Merozoite surface protein 2 (MSP2)

MSP2 is an intrinsically unstructured protein, which forms amyloid-like fibrils under physiological conditions. Surprisingly, the 25 residue conserved N-terminal region of MSP2, which is responsible for fibril formation, was found to have some helical propensity in NMR studies. Membrane mimetic conditions that stabilize this helix inhibit fibril formation. The helix is strongly amphipathic and is lipophilic. As MSP2 is a GPI-anchored membrane protein both the N- and C-termini of MSP2 may interact with the merozoite plasma membrane and thereby display the central variable region of the molecule to plasma antibodies.

Zhang X, **Adda CG,** Low A, Zhang J, Zhang W, Sun H, Tu X, **Anders RF**, Norton RS (2012) Role of the helical structure of the N-terminal region of plasmodium falciparum merozoite surface protein 2 in fibril formation and membrane interaction, *Biochemistry*, 51:1380-87.

PROFILE

Marilyn Anderson

Professor
Plant innate immunity proteins

We study defence molecules produced by plants for protection against insect pests and pathogens. The research spans basic work on the structure and function of these molecules to the practical application of creating crop plants which are protected from insect predation and disease. This practical application is being developed within the company Hexima Ltd, which is located in LIMS. Research is funded by the ARC and Hexima.

Research focus

- antifungal molecules, particularly plant defensins
- production of transgenic crop plants with resistance to fungal disease
- insecticidal molecules, mechanisms of action and application in plant protection
- production of cyclic peptides in plants.

Achievements

Mechanism of biosynthesis of cyclic peptides in plants

Cyclic peptides have great potential as pharmaceuticals because they are extraordinarily stable in biological systems and can be used as scaffolds for grafting and delivery of bioactive peptides. To realise this potential there is a need to understand the mechanism of biosynthesis and to develop expression systems for the production of the quantities needed for clinical studies and commercial production. Cyclic peptides from bacteria and plants, unlike the best characterised cyclic peptides from fungi, are encoded by genes and are excised from precursor proteins by a special class of proteolytic enzymes which ligate the newly generated N- and C-termini to produce a cyclic peptide backbone.

Conlan BF, **Anderson MA** (2011) Circular micro-proteins and mechanisms of cyclization, *Current Pharmaceutical Design*, 17:4318-28.

Evolution of cyclic peptides in plants

Cyclotides are cyclic peptides of about twenty-nine amino acids and form the largest family of cyclic peptides produced by plants. Until 2011 cyclotides were thought to be restricted to the Rubiaceae, Vioaceae and Cucurbitaceae families. They have now been discovered in the Fabaceae family which includes plants such as beans and peas that have a major role in human and animal nutrition.

Poth AG, Colgrave ML, Philip R, Kerenga B, Daly NL, **Anderson MA**, Craik DJ (2011) The discovery of cyclotides in the Fabaceae plant family provides new insights into the cyclization, evolution and distribution of circular proteins, *ACS Chemical Biology*, 6:345-55.

PROFILE

Julie Atkin

Lecturer
Mechanisms of neurodegeneration in Amyotrophic Lateral Sclerosis (ALS)

We study the cellular and molecular mechanisms leading to motor neuron death in ALS, with a focus on cellular stress pathways and intracellular trafficking processes. Research is supported by grants from the NHMRC, Motor Neuron Disease Research Institute of Australia, and the Bethlehem Griffiths Research Foundation.

Research focus

- Cellular mechanisms of toxicity induced by proteins recently linked to ALS, such as TAR DNA binding protein 43 (TDP-43), fused in sarcoma (FUS)
- disruption of intracellular trafficking and dysfunction of axonal transport in ALS
- mechanisms of neuroprotection by protein disulphide isomerase (PDI) in ALS.

Achievements

Stress signalling from the endoplasmic reticulum

Recent evidence indicates that endoplasmic reticulum (ER) stress plays a central role in ALS pathogenesis. ER stress activates the unfolded protein response (UPR) and activation of the UPR is one of the earliest events in motor neurons in rodent models of ALS. Furthermore, genetic manipulation of ER stress in these models alters disease onset and progression, implicating the UPR in disease. Perturbation of the ER could occur in ALS cases associated with TDP-43, FUS and VCP, implicating ER stress as a potential upstream mechanism involved in both familial and sporadic forms of ALS.

Walker AK, Atkin JD (2011) Stress signalling from the endoplasmic reticulum: a central player in the pathogenesis of ALS, *IUBMB Life*, 63:754-63.

Mutant FUS induces endoplasmic reticulum stress in ALS

Mutations in the gene encoding fused in sarcoma (FUS) are linked to ALS, but the mechanisms by which these mutants trigger neurodegeneration remain unknown. FUS is normally located in the nucleus but in ALS, FUS redistributes to the cytoplasm and forms inclusions. Our research demonstrates that mutant FUS induces ER stress in motor neuron cell lines, but only in cells in which FUS distributes to the cytoplasm. Mutant FUS also co-localized with PDI, an important ER chaperone, in NSC-34 cells and in human ALS motor neurons.

Farg MA, **Soo KY**, **Walker AK**, **Pham H**, **Orian** J, Horne MK, Warraich ST, Williams KL, Blair IP, **Atkin JD** (2012) Mutant FUS induces endoplasmic reticulum stress in ALS and interacts with protein disulphide ilsomerase, *Neurobiology of Aging,* 33:2855-68.

PROFILE

Suzanne Cutts

ARC Future Fellow
Cellular responses to DNA interacting cancer drugs

We develop new therapeutic strategies for cancer treatment by understanding the mechanism of action of currently used anticancer drugs.

Research focus

- therapeutic strategies for prevention of anthracycline-induced cardiotoxicity
- development of tumour-targeted nanoparticles to activate anthracycline drugs
- elucidation of the mechanism of action of new clinically used anthracenedione drugs.

Achievements

Preventing anthracycline-induced cardiotoxicity

Cardiotoxicity is the most serious adverse event associated with the use of anthracyclines and has been attributed to the death of cardiac cells by the generation of reactive oxygen species. This cardiotoxicity risk and the requirement for surveillance or intervention increase the cost of health care and compromise quality of life.

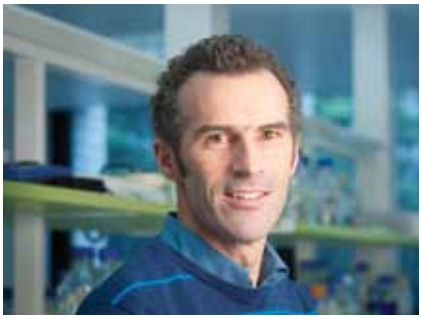
Since anthracyclines will continue to be widely used in the clinic, cardiotoxicity preventative strategies are urgently needed. We have shown that the formaldehyde prodrug AN-7 augments anthracycline anticancer potential while simultaneously reducing cardiotoxicity. We are seeking to identify the mechanism by which the activated anthracyclines protect cardiac cells from undergoing cell death.

Tarasenko N, **Cutts SM**, **Phillips DR**, Inbal A, Kessler-Icekson G-I, Nudelman A, Rephaeli A (2012) Disparate impact of butyroyloxymethyl diethylphosphate (AN-7), a histone deacetylase inhibitor, and doxorubicin in mice bearing a mammary tumor, *PLoS ONE,* 7:e31393.

DNA damage responses

Drugs that bind covalently to DNA are processed by cell response mechanisms that determine whether the damage will be repaired or trigger a signal for cells to undergo apoptosis. We have shown that anthracenediones induce topoisomerase II (TOP2) – mediated double strand breaks efficiently, and activate cell cycle checkpoints via Chk1 and Chk2 phosphorylation, and subsequent G2/M arrest. The rational selection of checkpoint kinase inhibitors may significantly enhance the therapeutic benefit of anthracenediones that can stabilise the TOP2 cleavage complex.

Evison BJ, **Pastuovic M**, **Bilardi RA**, **Forrest RA**, **Pumuye PP**, Sleebs BE, Watson KG, **Phillips DR**, **Cutts SM** (2011) M2, a novel anthracenedione, elicits a potent DNA damage response that can be subverted through checkpoint kinase inhibition to generate mitotic catastrophe, *Biochemical Pharmacology*, 82:1604-18.



PROFILE

David Dougan

ARC Australian Research Fellow
Proteostasis in health and disease

We study how protein homeostasis (proteostasis) is maintained in the cell. In particular, our focus is on the role of ATP-dependent proteolytic machines and how they contribute to proteostasis within bacteria and the evolutionarily related eukaryotic organelle, the mitochondrion. Research is funded by the ARC.

Research focus

- molecular dissection of substrate recognition by ATP-dependent proteolytic machines
- sensing and signaling of key stress response pathways
- deciphering the physiological role of the N-end rule pathway in bacteria.

Achievements

Regulated proteolysis and proteostasis

In the cytosol of the model Gram-negative bacterium, *Escherichia coli,* there are five different ring-shaped proteolytic machines (ClpAP, ClpXP, HslUV, Lon and FtsH). We focus on the mechanism-of-action of two of these machines, namely ClpAP and ClpXP.

A major aim of our current research is to identify the substrates of these machines. Recently, we identified that the ClpAP protease, together with its adaptor protein ClpS, is responsible for the recognition of a handful substrates containing specific "destabilizing" residues at the N-terminus of the protein. The identification of ClpS as the bacterial N-recognin (N-end rule recognition factor) lead us to not only identify the first natural substrates of this degradation pathway, but also, with collaborators at Max Planck Institute, Germany, to solve the structure of ClpS in complex with several N-end rule substrates. Currently we are dissecting the physiological role of several of these putative substrates. These exciting findings lead to the invitation to present our data at several international meetings, including the EMBO conference on the biology of molecular chaperones (Grundlsee, Austria), the first Cold Spring Harbor Asia conference on protein homeostasis (Suzhou, China) and the 9th International meeting on AAA+ proteins (Kumomoto, Japan).

Dougan DA (2011) Chemical activators of ClpP: turning Jekyll into Hyde, *Chemistry and Biology*, 18:1072-74.

Truscott KN, Bezawork-Geleta A, Dougan DA (2011) Unfolded protein responses in bacteria and mitochondria: a central role for the ClpXP machine, *IUBMB Life*, 63:955-63.

PROFILE

Mick Foley

Associate Professor
Biotechnological approaches to disease

We study the molecular mechanisms that allow the malaria parasite to invade the human red blood cell. We use peptides, antibodies and a novel class of shark antibodies to examine the protein-protein interactions of malaria and other diseases.

Research focus

- understanding the role of malaria proteins AMA1 and MSP2 in invasion
- developing the AMA1 protein as a vaccine against malaria
- exploring the use of shark antibodies in diagnosis and therapy.

Achievements

Apical membrane antigen 1 as a potential drug target

The *Plasmodium falciparum* protein AMA1, plays an important role in facilitating the invasion of parasites into human red blood cells which can lead to malaria.

Our research confirms that a variety of protein reagents such as peptides, single domain protein and monoclonal antibodies that target a hydrophobic trough on AMA1 are all able to block red blood cell invasion and inhibit the growth of malaria parasites in vitro. In collaboration with researchers at Monash University we have shown that this hydrophobic trough has deep cavities that may be amenable to small drug molecules that could be used to block parasite invasion.

Macraild CA, **Anders RF**, **Foley M**, Norton RS (2011) Apical membrane antigen 1 as an anti-malarial drug target, *Current topics in Medicinal Chemistry*, 11:2039-47.

Shark antibody technology

AdAlta Pty Ltd is a spin-off company from the Cooperative Research Centre for Diagnostics. AdAlta is pioneering a new technology that uses modified shark antibodies for therapeutic interventions or diagnostic markers in disease. The process involves taking genes from sharks and modifying them in a laboratory by inserting random sequences – essentially mimicking the way the human immune system works – to develop antibodies capable of a repertoire of defensive responses. These novel libraries can then be screened in the lab against a target to identify a diagnostic or therapeutic lead candidate. In January 2012 AdAlta signed an agreement with international pharmaceutical company, Roche, to evaluate and identify shark antibody binders.

PROFILE

Christine Hawkins

ARC Future Fellow
Apoptosis research

We study the molecular regulation of cell death. An NHMRC grant funds an investigation into how viruses enforce survival of infected cells to enable viral propagation and a Cancer Council funded project explores agents that may induce apoptosis specifically and directly in cancer cells.

Research focus

- identification and characterisation of viral anti-apoptotic proteins
- comparing the mutagenicity of direct apoptosis inducers and chemotherapy drugs
- developing a method for screening compounds for anti-cancer potential.

Achievements

Characterisation of the viral caspase inhibitor MaviP35

Many viruses express proteins which prevent the host cell death that their infection would otherwise provoke. Some insect viruses suppress host apoptosis through the expression of caspase inhibitors belonging to the P35 superfamily.

The *Maruca vitrata* M nucleopolyhedrovirus encodes a P35 family member (MaviP35). We found that MaviP35 shared with other P35 relatives the ability to inhibit mammalian and insect cell death. MaviP35 potently inhibited human caspases 2 and 3, DCP-1, DRICE and CED-3 in vitro, but (in contrast to AcP35) only weakly suppressed the proteolytic activity of the initiator human caspases 8, 9 and 10.

Brand IL, **Green MM**, **Civciristov S**, **Pantaki-**Eimany D, **George C**, Gort TR, Huang N, Clem RJ, **Hawkins CJ** (2011) Functional and biochemical characterization of the baculovirus caspase inhibitor MaviP35, *Cell Death and Disease*, 2:e242.

Mutagenicity of TRAIL

Chemotherapy and radiotherapy commonly damage DNA and secondarily provoke cancer cell death. Unfortunately, this can lead to mutagenesis of non-malignant surviving cells which can provoke second malignancies. TRAIL directly stimulates apoptosis, and may be a useful anti-cancer agent. As TRAIL-induced apoptosis does not require DNA damage, we hypothesized that surviving cells would remain genetically unscathed. Surprisingly, treatment with sub-lethal concentrations of TRAIL was mutagenic. Although death ligands do not need to damage DNA in order to induce apoptosis, surviving cells nevertheless incur DNA damage after treatment with these agents.

Lovric MM, Hawkins CJ (2010) TRAIL treatment provokes mutations in surviving cells, *Oncogene*, 29:5048-60.

PROFILE

Nick Hoogenraad

Charles La Trobe Professor and Head of School
Mitochondrial-unfolded protein response and protein targeting to mitochondria

We research two aspects of mitochondrial biology in mammalian cells: the response of cells to the accumulation of unfolded proteins in mitochondria and the role of molecular chaperones in targeting proteins to the mitochondria.

Research focus

- the role of molecular chaperones in protein targeting to mitochondria
- characterization of cytosolic chaperone complexes in protein targeting
- identification of sensing and signalling components in the mitochondrial unfolded protein response (mtUPR).

Achievements

The role of molecular chaperones in protein targeting to mitochondria

We have previously discovered a mechanism for targeting of pre-proteins to mitochondria. In this process, two cytosolic chaperones Hsp70 and Hsp90 co-operate to deliver pre-proteins to mitochondria (Young, Hoogenraad and Hartl [2003] *Cell* 112, 41-50). The size of this complex is large, (850kDa) suggesting that the complex contains more than Hsp90 and Hsp70. We have now identified a cochaperone called Tom34, which is an integral component in the targeting complex and exhibits an affinity for mitochondrial preproteins.

Faou P, Hoogenraad NJ (2012) Tom34: A cytosolic cochaperone of the HSP90/ Hsp70 protein complex involved in mitochondrial protein import, *BBA Molecular Cell Research*, 1823:348-57.

Characterization of a mitochondrial unfolded protein response

The accumulation of unfolded proteins in mitochondria leads to a mtUPR and the activation of nuclear genes encoding quality control proteins (chaperones and proteases). This pathway is through an extended promoter element which incorporates a CHOP element. Recently, the mtUPR has been found to be linked to the pathogenesis of inflammatory bowel disease through the induction of the dsRNA activated protein kinase (PKR) which is activated by a signal from the stressed mitochondrion. This leads to the attenuation of protein translation through phosphorylation of eIF2a and activation of mtUPR responsive genes through the phosphorylation of c-Jun and activation of AP1.

Rath E, Berger E, Messlik A, Nunes T, Liu B, Kim S, **Hoogenraad N**, Sans M, Sartor R, Haller D, (2012) Induction of dsRNA activated protein kinase links mitochondrial unfolded protein response to the pathogenesis of intestinal inflammation, *Gut, 61:1269-78.*

PROFILE

Mark Hulett

Senior Lecturer
Regulators of cancer and inflammation

We study the molecular processes that promote the growth and spread of cancer, and inflammatory disease, to develop new therapeutic treatments. Research is supported by grants from the NHMRC and ARC, as well as the Melbourne biotechnology company, Hexima.

Research focus

- role of the heparin-sulphate degrading enzyme in tumour angiogenesis, metastasis, and inflammatory disease
- function of the serum protein, histidine-rich glycoprotein (HRG) in tumour progression and inflammation
- innate defence molecules as novel anti-cancer treatments.

Achievements

Heparanase is a novel promoter of leukocyte migration

Heparanase has been implicated in leukocyte migration but the lack of an *in vivo* model has hampered defining the contribution of the enzyme to this important process.

We have generated heparanase deficient mice ($HPSE^{-/-}$) using gene targeting and shown using *in vivo* models that the $HPSE^{-/-}$ mice exhibit impaired dendritic cell (DC) migration. These findings indicate an important role for heparanase in DC migration, a fundamental process in the immune response.

The multifunction role of Histidine-rich glycoprotein in cell clearance

Histidine-rich glycoprotein (HRG) is an abundant mammalian serum protein. We have identified HRG as a novel serum pattern recognition molecule that forms a complex with IgG to enhance necrotic cell clearance through an Fc receptor-mediated mechanism that is also accompanied by a pro-inflammatory response. Based on these observations we have defined HRG as a member of a previously unrecognized "family" of serum proteins involved in necrotic/late apoptotic removal.

Plant innate defence molecules as novel anti-cancer agents

Innate defence molecules represent an attractive source of novel therapeutics for the treatment of cancer and inflammatory disease. We have identified a subfamily of plant molecules that are potent killers of human tumour cells. Furthermore, we have defined their mechanism of action as a new method of cell lysis. Preclinical studies are currently being carried to assess the potential of these molecules as anti-cancer drugs.

Poon IK, **Patel KK**, Davis DS, Parish CR, **Hulett MD** (2011) Histidine-rich glycoprotein: the Swiss Army knife of mammalian plasma, *Blood*, 117:2093-101.

PROFILE

Marc Kvansakul

NHMRC CDA Fellow
Structural biology of cell death and host-pathogen interactions

We research the molecular basis of the regulation of cell death during viral infection. A second area of interest at the host-pathogen interface is the use of small proteins in the defence against microbial threats.

Research focus

- subversion of host cell death during viral infections
- role of viral cell death inhibitors in the development of virus-associated cancers
- structural basis of small plant innate defence molecules' anti-cancer activity.

Achievements

BHRF1, a key inhibitor of cell death in Epstein-Barr virus

The ability of pathogenic viruses to disable the cell death machinery of invaded host cells is of critical importance for viral infectivity, persistence and replication. Viral infections, such as those by Epstein-Barr virus (EBV), have been shown to be intimately linked to malignancies including Burkitt lymphoma.

A key group of virulence factors that allows gamma herpesviruses to overcome the apoptotic machinery of host cells and persist in the host are viral Bcl-2 proteins. Using X-ray crystallography we revealed the molecular basis for cell death inhibition by BHRF1, an EBV Bcl-2 like protein, and showed using a mouse tumour model of Burkitt lymphoma that BHRF1 may contribute to the development and maintenance of Burkitt's lymphoma.

Kvansakul M, Wei AH, Fletcher JI, Willis SN, Chen L, Roberts AW, Huang DC, Colman PM (2010) Structural basis for apoptosis inhibition by Epstein-Barr virus BHRF1, *PLoS Pathogens*, 6(12):e1001236.

Structural basis of small plant innate defence molecules' anti-cancer activity

Innate defence molecules represent an attractive source of novel therapeutics for the treatment of cancer and inflammatory disease. Certain plant molecules have been shown by our collaborators (Hulett, LIMS) to be potent killers of human tumour cells. We are now defining their mechanism of action using biophysical methods to study their ability to induce cell lysis.

PROFILE

Peter Lock

Senior Research Fellow
Cancer cell signalling pathways in invasion and metastasis

We investigate the cell signalling pathways that control the formation and activity of invadopodia, extracellular protease-enriched cytoskeletal structures associated with invasive and metastatic cancer cells.

Research focus

- identification and functional analysis of novel molecular regulators of invadopodia
- actin cytoskeletal regulators in invadopodia
- clinical relevance of invadopodia components in cancer.

Achievements

The invadopodia regulator Tks5 is a prognostic marker of reduced survival in glioma patients

We previously discovered the adaptor protein, Tks5, as a substrate of the Src tyrosine kinase. Subsequently Tks5 was found in invadopodia and shown to be necessary for invadopodia to proteolytically degrade extracellular matrix and for cancer cells to invade through matrices such as Matrigel.

While Tks5 expression has been detected in invasive breast tumours and melanomas, its relevance in human cancer has not been investigated until now. In collaboration with researchers at the Royal Melbourne Hospital and Melbourne University, we retrospectively analysed survival in fifty-seven patients with glioma tumours and found that Tks5 expression is linked to reduced patient survival. Notably, the link with survival was most striking in patients with lower grade tumours. These studies are the first to identify Tks5 as a prognostic biomarker in glioma.

Stylli SS, I ST, Kaye AH, **Lock P** (published online 2012) Prognostic significance of Tks5 expression in gliomas, *Journal of Clinical Neuroscience*. This paper has been selected for recommendation by the Faculty of 1000 (F1000) who have rated it in the top 2% of articles in the fields of biology and medicine.

Discovery of novel invadopod regulators

We have developed a strategy based on affinity purification, mass spectrometry and confocal microscopy to screen for novel invadopodia proteins in metastatic melanoma cells. Several candidate proteins which localise to invadopodia have been identified in this screen with two of these proteins currently confirmed by RNA interference technology to be functionally required for invadopodia-mediated matrix degradation.

PROFILE

Suresh Mathivanan

NHMRC Peter Doherty and LIMS Fellow
Exosomes, secretome and systems biology

The research focus of the lab is to explore exosomes (40-100 nm diameter vesicles secreted by various cell types) and soluble secreted proteins in the context of intercellular signalling and cancer. Research is supported by NHMRC.

Research focus

- role of oncogenic events in altering proteins that are secreted
- exosomes in intercellular signalling
- systems biology approaches to analyse multi-omic datasets.

Achievements

ExoCarta – a compendium of exosomal molecular components

ExoCarta is a compendium of previous exosomal protein, RNA and lipid studies. It is a manually curated repository hosted in La Trobe University and is freely available for the scientific community.

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For more information on ExoCarta, please visit:
exocarta.org

Currently, ExoCarta (Version 3.1) contains information on 11 261 protein entries, 2375 mRNA entries and 764 miRNA entries that were obtained from 134 exosomal studies.

Mathivanan S, Fahner CJ, Reid GE, **Simpson RJ** (2012) ExoCarta 2012: database of exosomal proteins, RNA and lipids, *Nucleic Acids Research*, 40:D1241-44.

Extracellular Microvesicles

Extracellular microvesicles (eMVs) are a class of membrane bound organelles secreted by various cell types. It includes exosomes, ectosomes and apoptotic blebs. The field of eMVs currently faces obstacles with relevance to the purification protocols and the terminologies used in naming these vesicles. The invited editorial highlights these issues and prompts biomedical researchers to name the vesicles with consensus and use stringent purification protocols.

Simpson RJ, Mathivanan S (2012) Extracellular microvesicles: the need for internationally recognised nomenclature and stringent purification criteria, *Journal of Proteomics & Bioinformatics*, 5: ii-ii.

PROFILE

Jacqueline Orian

Senior Research Fellow
Multiple Sclerosis research

We study the mechanisms underlying neurodegeneration in multiple sclerosis (MS), with the view of contributing to improved drug design for this condition. Research is supported by grants from the National Multiple Sclerosis Society, Multiple Sclerosis Research Australia and Novartis Australia.

Research focus

- role of astrocytes in neuroinflammation
- mechanisms of grey matter damage in neuroinflammation, in the experimental autoimmune encephalomyelitis (EAE) model of MS.

Achievements

Modulation of astrocytic function during neuroinflammation

Glial fibrillary acidic protein (GFAP) is an astrocyte-specific intermediate filament (IF) protein, belonging to a complex isoform family. In collaboration with colleagues at Monash University, we revealed a novel isoform associated with 3' end splicing.

With colleagues at Bio21 Institute, we demonstrated region-specific GFAP enrichment prior to the first evidence of pathology, by 2D-difference image gel electrophoresis (DIGE), thus making it a potential marker for disease progression.

Pham H, Doerrbecker J, Ramp AA, D'Souza CS, Gorasia DG, Purcell AW, Ayers MM, **Orian JM** (2011) Experimental autoimmune encephalomyeltis (EAE) in C57bl/6 mice is not associated with astrogliosis, *Journal of Neuroimmunology*, 232:51–62.

Mechanisms of grey matter damage in the EAE model of MS

Similarly to MS, the emphasis of EAE investigations has been on white matter disease, whilst the contribution of grey matter damage to overall pathology has been overlooked. Our investigations reveal concurrent grey and white matter pathological onset. Mechanisms driving parenchymal entry of inflammatory cells into grey matter show regional variability, manifested by differences in the spectrum of parameters of neuroinflammation in different CNS regions.

Orian JM, **Pham H**, **Ramp AA**, Downs LL, Briscoe R, Ayers MM (2011) Grey matter changes in experimental autoimmune encephalomyelitis, *Horizons in Neuroscience Research*, Andres Costa and Eugenio Villalba (eds), Nova Science Publishers, New York, *5:1-17.*

PROFILE

Hamsa Puthalakath

ARC Future Fellow
Regulation of apoptosis in health and disease

We study apoptosis regulation by Bcl-2 family protein (specifically Bim) in a variety of physiological contexts using *in vitro* techniques and using *in vivo* mouse models.

Research focus

- regulation of cardiomyopathy and heart failure
- regulation of apoptosis in the adaptive immune system including thymic and peripheral T cells, B cells and immune modulation during chronic stress and obesity
- regulation of apoptosis in tumorigenesis.

Achievements

Regulating apoptosis by stabilizing the BH3-only protein Bim

The proapoptotic Bcl2 homology domain 3(BH3)-only protein Bim is controlled by stringent post-translational regulation, predominantly through alterations in phosphorylation status.

To identify new kinases involved in its regulation, we carried out a yeast two-hybrid screen using a non-spliceable variant of the predominant isoform, Bim(EL), as the bait and identified the regulatory subunit of cyclic-AMP-dependent protein kinase A, PRKAR1A, as an interacting partner. We also show that protein kinase A (PKA) is a Bim(EL) isoform-specific kinase that promotes its stabilization. Inhibition of PKA or mutation of the PKA phosphorylation site within Bim(EL) resulted in its accelerated proteasome-dependent degradation. These results might have implications for human diseases that are characterized by abnormally increased PKA activity, such as the Carney complex and dilated cardiomyopathy.

Moujalled D, **Weston R**, Anderton H, **Ninnis R**, Goel P, **Coley A**, Huang DC, Wu L, Strasser A, **Puthalakath H** (2011) Cyclic-AMP-dependent protein kinase A regulates apoptosis by stabilizing the BH3-only protein Bim, *EMBO Reports*, 12:77-83.

PROFILE

Mike Ryan

Professor and Head of Department
Mitochondrial biogenesis and disease

We research the nature of the mitochondrial network within the cell and the dynamics of protein complexes within the mitochondrial inner and outer membranes. Our research is supported by grants from the NHMRC, ARC and ARC Centre of Excellence for Coherent x-ray Science.

Research focus

- mitochondrial dynamics in health and disease
- assembly of mitochondrial complex I and defects in disease
- regulation of pro-apoptotic factors on the mitochondrial outer membrane.

Achievements

MiD49 and MiD51, new mediators of mitochondrial fission

Mitochondria form intricate networks through fission and fusion events. These networks are essential for the maintenance of the mitochondrial population and defects in fission and fusion lead to neurological diseases, including Parkinson's disease.

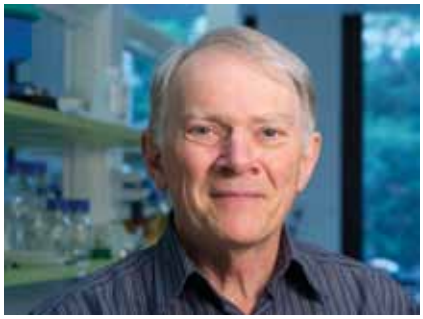
We have recently discovered two proteins which we named MiD49 and MiD51, to be involved in mitochondrial fission in chordates. MiD49 and 51 are receptors for the master mediator of fission, dynamin-related protein 1 (Drp1). We are characterising the mechanism by which the MiD proteins can regulate Drp1 action and the consequences of their loss to the organism as a whole.

Palmer CS, Osellame LD, Laine D, Koutsopoulos OS, Frazier AE, Ryan MT (2011) MiD49 and MiD51, new components of the mitochondrial fission machinery, *EMBO Reports*, 12:565-73.

Characterization of mitochondrial defects in patient cells

In collaboration with researchers at the Murdoch Childrens Research Institute, we have investigated defects in cells from patients diagnosed with mitochondrial disorders. We recently found a new protein termed c8orf38 to be involved in the synthesis of a crucial mitochondrial-encoded subunit of respiratory chain complex I. We have also found that mutations in the mitochondrial protein MTFMT impaired general translation of mtDNA encoded proteins leading to defects in energy generation. Our work provides new insights into the function of proteins that are involved in lethal mitochondrial disorders.

McKenzie M, Tucker EJ, Compton AG, Lazarou M, **George C**, Thorburn DR, **Ryan MT** (2011) Mutations in the gene encoding C8orf38 block complex I assembly by inhibiting production of the mitochondria-encoded subunit ND1, *Journal of Molecular Biology*, 414:413-26.



PROFILE

Richard Simpson

Professor
Colorectal cancer – molecular basis to targeted therapeutics

Cancer of the colon (CRC) is the most common form of cancer in Australia. Our research aims to discover new ways to detect CRC early by identifying cancer signature proteins /RNAs, and develop smart nanoparticle delivery systems (exosomes) for destroying all types of CRC cells. We will then test our new anti-cancer reagents in clinical trials with CRC patients. Research is supported by a program grant from the NHMRC.

Research focus

- exosomes in colon cell maturation (crypt biology), cancer metastasis, and drug delivery
- exosome membrane topography, target recognition and signalling complexes
- extracellular modulators of epithelial-mesenchymal transition (EMT) process.

Achievements

EMT

EMT, a process essential for morphogenesis during embryonic development, has been implicated in tumour metastasis. Using oncogenic H-Ras/TGF-β-mediated EMT in the MDCK model system, we have identified extracellular modulators of the EMT process, and shown, using plasma membrane proteomic profiling, that MDCK cells switch from cadherin mediated to integrin-mediated adhesion following Ras/TGF-β-induced EMT. We are characterizing the functional role of exosomes in EMT and pursuing a number of identified extracellular effectors as potential markers of CRC metastasis.

Chen Y, **Mathias R**, **Mathivanan S**, Kapp EA, Moritz RL, Zhu H, **Simpson RJ** (published online 2011) Proteomic profiling of MDCK plasma membranes reveals Wnt-5a involvement during oncogenic H-Ras/TGF-β-mediated epithelial-mesenchymal transition, Molecular & Cellular Proteomics, 10(2):M110.001131.

Isolating exosomes

Exosomes, a distinct class of membranous nanovesicles (40-100 nm diameter) released from most cell types, play a critical role in cell-cell communication. We recently developed an immunocapture method for isolating exosomes from the CRC cell line LIM1215 which led to the definition, for the first time, of a CRC-specific exosomal signature. We have extended these studies to the LIM1863 cell line and discovered two discreet populations of exosomes (apical and basolateral) that differ at the level of protein, RNS (miRs and mRNA), and lipid content. Future studies are directed towards elucidating the functional role of exosomes in colonic crypt morphogenesis, dissecting their membrane topography to identify and characterize membrane complexes associated with cell-target recognition and exocrine/juxtacrine cell signalling.

Tauro BJ, **Greening DW**, **Mathias RA**, **Ji H**, **Mathivanan S**, **Scott AM**, **Simpson RJ**, et al (2012) Comparison of ultracentrifugation, density gradient separation, and immunoaffinity capture methods for isolating human colon cancer cell line LIM1863-derived exosomes, Methods, 56:293-304.

PROFILE

Diana Stojanovski

ARC Australian Postdoctoral Fellow
Protein trafficking

We study the mechanisms that govern trafficking of mitochondrial precursors to and within mitochondria. We are also interested in the role of cytosolic factors in this process. Research is supported by grants from the ARC, Clive and Vera Ramaciotti Foundation and an ECR Establishment Grant from La Trobe University.

Research focus

- precursor trafficking through the cytosol
- understanding mitochondrial transport machineries
- mitochondrial import and assembly in mammalian cells and links to disease.

Achievements

Understanding mitochondrial trafficking machineries

The intermembrane space of mitochondria contains a dedicated chaperone network, the small TIM family, for the trafficking of hydrophobic precursors through this aqueous environment. We have discovered that these essential chaperones require at least a single disulfide bond to function and maintain cell viability in yeast cells.

However the mutant versions of the proteins are prone to instability and turnover. I was recently awarded a Short Term Fellowship from the European Molecular Biology Organisation to explore the machineries that modulate the turn-over of these proteins in the lab of Professor Thomas Langer at the University of Cologne, Germany. The results from this international stay are currently being compiled for a manuscript.

Schmitdt O, Harbauer AB, Rao S, Eyrich B, Zahei RP, **Stojanovski D**, Schönfisch B, Guiard B, Sickmann A, Pfanner N, Meisinger C (2011) Regulation of mitochondrial preprotein translocase by casein kinase 2 and protein kinase A, *Cell*, 144:227-39.

Gebert N, **Ryan MT**, Pfanner N, Wiedemann N, **Stojanovski D** (2011) Mitochondrial protein import machineries and lipids: A functional connection, *BBA Biomembranes*, 1808:1002-11.

Mitochondrial import and assembly in mammalian cells

There has been little focus on how problems in mitochondrial protein import can contribute to human health and disease, although evidence supporting this notion is mounting. We have recently embarked on projects that aim to characterise the mechanisms and machineries that mediate protein import in mammalian cells.

PROFILE

Kaye Truscott

ARC Future Fellow
Mitochondrial protein homeostasis

We study the molecular mechanisms of mitochondrial protein biogenesis and the inherent protective mechanisms that maintain protein integrity in this organelle. Our knowledge in this area is extended by complimentary studies of related protein quality control proteins and stress response pathways in bacteria. Research is supported by grants from the ARC.

Research focus

- regulated degradation of mitochondrial proteins in health and disease
- signalling components of the mitochondrial unfolded protein response
- mitochondrial protein import, processing and assembly.

Achievements

Characterisation of mitochondrial proteostasis components

Maintaining a functional population of proteins for the lifetime of a cell is critical for good health and for aging well. Disruptions to mitochondrial protein homeostasis are linked to a range of diseases and premature aging.

We have examined the substrate specificity of ATP-dependent proteases in the matrix of mammalian mitochondria. Tracking the fate of newly imported model unfolded and disease-relevant mutant mitochondrial matrix proteins has revealed their degradation pathway and provided insight into the substrate specificity of the proteases. Also, unfolded protein response pathways are critical for maintaining cellular protein homeostasis. These signal transduction pathways often involve a proteolytic element as part of the signalling pathway. We have determined how the matrix proteases influence the mitochondrial unfolded protein response. Finally a new player in the TIM22 protein translocation machinery of yeast mitochondria was revealed. Surprisingly, this protein was identified as Sdh3, a component of respiratory complex II. Thus Sdh3, is dual located in the inner membrane and hence functions in mitochondria bioenergetics and protein translocation.

Truscott KN, Bezawork-Geleta A, Dougan DA (2011) Unfolded protein responses in bacteria and mitochondria: a central role for the ClpXP machine, *IUBMB Life*, 63:955-63.

Gebert N, Gebert M, Oeljeklaus S, von der Malsburg K, Stroud DA., Kulawiak B, Wirth C, Zahedi RP, Dolezal P, Wiese S, Simon O, Schulze-Specking A, **Truscott KN**, Sickmann A, Rehling P, Guiard B, Hunte C, Warscheid B, van der Laan M, Pfanner N, Wiedemann N, et al (2011) Dual function of Sdh3 in the respiratory chain and TIM22 protein translocase of the mitochondrial inner membrane, *Molecular Cell*, 44:811-18.

Chemistry

PROFILE

Belinda Abbott

Lecturer
Design and synthesis of medicinal compounds

We study the design, synthesis, and evaluation of novel molecules which are needed to understand, prevent, and treat conditions such as motor neurone disease, cancer and malaria.

Research focus

- design and synthesis of small molecule enzyme inhibitors
- development of synthetic oligonucleotides for antisense therapy
- synthesis of natural products of medicinal interest.

Achievements

Synthesis of enzyme inhibitors

Our work involves the design, synthesis, purification and characterisation of novel heterocyclic compounds as inhibitors of enzymes. These targets include several protein kinases and cyclic nucleotide phosphodiesterases which are implicated in a wide range of significant health problems including cancer, abnormal blood clotting and malaria.

We have developed a new tetrazole-based compound which has excellent potency against phosphatidylinositol-3-kinase and also, when delivered as a prodrug, against the MCF7 cancer cell line.

Antisense therapy using peptide nucleic acid

Peptide nucleic acid (PNA) is synthetic analogue of the biopolymers deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), which carry and encode genetic information. Potential applications of PNA include the areas of diagnostics, biosensors and antisense therapy. Our research is focused on improving the cellular uptake of PNA sequences which have shown efficacy in a transgenic mouse model for amyotrophic lateral sclerosis, a form of motor neurone disease. As part of this work, we have developed a convenient and efficient method for the synthesis of Fmoc/Boc protected PNA monomers.

Browne EC, Langford SJ, **Abbott BM** (2012) Peptide nucleic acid monomers: a convenient and efficient synthetic approach to Fmoc/Boc monomers, *Australian Journal of Australian Journal of Chemistry,* 65:539-44.

PROFILE

Peter Barnard

Lecturer
Synthesis and development of novel optical (fluorescent) and radiopharmaceutical agents for biological imaging applications

We are interested in the preparation and development of metal coordination complexes of N-heterocyclic carbenes and macrobicyclic ligands for use as diagnostic imaging agents (radiopharmaceuticals) and fluorescent probes for imaging and sensor applications.

Research focus

- synthesis of novel chelating ligands, including N-heterocyclic carbenes (NHCs) and macrocyclic/macrobicyclic ligands
- synthesis, spectroscopic and structural studies of coordination complexes
- ligand radio-labelling studies with metallic radioisotopes (^{99m}Tc, ^{64}Cu, ^{68}Ga and ^{89}Zr)
- conjugation of novel imaging agents to biomolecules (lipids and peptides).

Achievements

Radiopharmaceutical and luminescent applications of N-heterocyclic carbene ligands

N-heterocyclic carbenes (NHCs) are among the most important and widely studied ligand types in contemporary organometallic chemistry. Previously we reported a series of Au-NHC complexes that have anti-tumour properties and are active via an anti-mitochondrial mechanism. In an effort the extent the potential medicinal applications of these ligands we recently developed a rapid method for labelling chelating NHCs with the radioisotope ^{99m}Tc for radiopharmaceutical imaging applications. We have also prepared a range of novel luminescent Ru and Ir coordination complexes of chelating NHC ligands. These compounds show a range of emission wavelengths and we are investigating potential of these molecules in electrochemiluminescent sensor applications.

Synthesis of novel macrocyclic and macrobicyclic ligands for radiopharmaceutical applications

Metal-tagged radiopharmaceuticals usually consist of a bioactive molecule, such as a peptide or monoclonal antibody (mAb), labelled with a metallic-radioisotope. For such imaging agents to function successfully the metal chelate complex must be inert to ligand exchange reactions. We have developed a series of novel macrocyclic and macrobicyclic (sarcophagine) ligands that form highly stabilised complexes with the positron emitting isotope of copper, ^{64}Cu. Ligand challenge experiments (histidine and cysteine) for one macrobicyclic ligand labelled with ^{64}Cu clearly demonstrate that transmetallation does not occur with these common metal binding amino acids. These radiopharmaceutical projects are collaborative with researchers from the Australian Nuclear Science and Technology Organisation (ANSTO) and are supported by funding from the Australian Institute of Nuclear Science and Engineering (AINSE).

PROFILE

Jason Dutton

Lecturer

Synthesis of highly reactive, cationic compounds and functional organometallic polymers

We investigate new structure, bonding and reactivity for main group and transition metal elements. In particular our focus is the synthesis of highly charged or high-oxidation state species. These reactive molecules will be used as reagents for generating compounds implicated as intermediates in important metal-based catalytic cycles. Investigation of these intermediates will allow for a greater understanding of the processes involved in catalytic transformations. The other primary research project is the synthesis of functional polymers containing organometallic "backbones," with the goal of producing processable polymers that can act as catalysts.

Research focus

- synthesis of ligand stabilized dicarbon (L-C=C-L) compounds as building blocks for supramolecular organometallic frameworks
- development of iodine and oxygen polycations as oxidizing agents for the synthesis of high-oxidation state, catalytically relevant transition metal complexes
- synthesis of a perfluoronated analogue of the trityl cation ($[C(C_6F_5)_3]^+$) for the generation of highly activated transition metal and main group cations.

Achievements

Theoretical identification of ligand stabilized C2 as a promising synthetic target

In conjunction with Dr David Wilson, a neutral C^2 fragment stabilized by either phosphine or N-heterocyclic carbene ligands was identified as a promising bifunctional ligand for the formation of polymeric (supramolecular) organometallic complexes. The identification of this new class of carbon compound warranted publication of the theoretical calculations in the prestigious journal Angewandte Chemie. Efforts towards the synthesis of the compounds are now in progress.

Dutton JL, **Wilson DJD** (2012) Theoretical identification of ligand stabilized C2 as a promising synthetic target, *Angewandte Chemie International Edition*, 51: 1477-80.

Synthesis of iodine polycations

Iodine dications based on a $[PhI(L)_2]^{2+}$ (L = neutral ligand) framework have been successfully synthesized. The first ligand exchange reactions at an iodine centre have been performed. The structural (X-ray) characterization of the complexes is in progress. The next step is using these compounds to oxidize transition metals.

PROFILE

Conor Hogan

Senior Lecturer
New sensing strategies based on electroactive and luminescent materials

We research new chemistries, technologies and sensing strategies based on electroactive and luminescent materials which will result in exquisitely low detection limits, enhanced selectivity and miniaturised instruments which can be used outside of the laboratory setting. Our research is supported by LIEF Infrastructure and ARC Discovery grants.

Research focus

- low cost diagnostics for the developing world
- electrochemiluminescence: new optically and electrochemically active materials for sensing applications
- electrochemical control of emission wavelength for multiplexed detection.

Achievements

A new approach to sensing for resource-poor environments and remote communities

Ultra-low cost paper microfluidic sensors produced by ink jet printing were used for electrochemiluminescence based detection for the first time.

Significantly we demonstrated that the electrochemically initiated emission could be captured using a mobile phone camera and used as the basis for quantitation.

Delaney JL, **Hogan CF**, Tian JF, Shen W (2011) Electrogenerated chemiluminescence detection in paper-based microfluidic sensors, *Analytical Chemistry*, 83:1300-06.

Tuning luminescent emission color via electrode potential

ECL in 3D: We have demonstrated that selective electrochemiluminescence (ECL) of several ruthenium and iridium complexes in solution could be controlled simultaneously by electrode potential. These luminescent redox systems create a range of new possibilities for multianalyte ECL detection, assessment of interdependent electrochemical/spectroscopic properties, and colour tuning in light-emitting devices.

Doeven EH, Zammit EM, Barbante GJ, **Hogan CF**, Barnett NW, Francis PS (2012) Selective excitation of concomitant electrochemiluminophores: tuning emission color by electrode potential angew, *Angewante Chemie International Edition,* 51:4354-57. (Chosen as a "Hot Paper" by the editors "for its importance in a rapidly evolving field of high current interest").

PROFILE

Adam Mechler

Senior Lecturer
Chemistry of self-assembly: from molecules to macrostructures

We investigate the physicochemical properties of surfaces, interfaces and self-assembled macrostructures such as lipid membranes and protein fibres. Research is also conducted into the design and novel characterization methods of surface nanostructures.

Research focus

- the molecular mechanism and environmental controls of phospholipid self-assembly into liposomes and supported biomimetic membranes
- the action mechanism of membrane-disrupting antimicrobial peptides: origins of membrane specificity and selectivity
- design and characterization of functional nanomaterials, such as self-assembling conductive β-peptide fibres.

Achievements

Development of inverted cubic phase lipid biosensors

A feasibility study of using functionalized lipid nanostructures: inverted cubic phase "cubosomes" for the detection of chemical warfare agents, such as cholera toxin B, has been successfully completed in a multi-institute collaboration with Melbourne University, CSIRO and Monash University. Cubosomes have a greatly enhanced active surface area compared to flat supported membranes, due to the porous inverted bicontinuous cubic structure. This feature was successfully used to enhance the sensitivity of detection per surface area when immobilizing the cubosomes on a quartz crystal microbalance sensor chip and measuring the mass change upon the binding of the analyte.

Fraser STJ, Mulet XR, Martin L, Praporsk Si, **Mechler A**, Hartley PG, Polyzos AS, Separovic F (2012) Surface immobilization of bio-functionalized cubosomes: sensing of proteins by quartz crystal microbalance, *Langmuir*, 28: 620-27.

Micro-nano surface structuring enhances the sensitivity of Raman spectroscopy

By using numerical simulations, the origin of Raman enhancement in inverted pyramidal micro-nano structures was identified as the near-field electromagnetic resonance. With collaborators at Monash University, and the University of Pecs, Hungary, we established that the resonance effects are not plasmonic – thus the shape of the structure, not the material, determines the Raman response. This observation opens new avenues of designing integrated spectroscopic elements in lab-on-a-chip sensors.

Mechler M, Kukhlevsky SV, Mechler, A, McNaughton, D (2011) Resonance effects in Raman-enhancing pyramidal pit microstructures, *Physical Chemistry Chemical Physics*, 13: 20772-78.

PROFILE

Ian Potter

Senior Lecturer and Head of Department
Biochemical responses: stimulus and detection

Our lab seeks to develop methods to induce and quantify favourable biochemical responses in plants. We also develop extraction and sensing platforms for Endocrine Disruptor Chemicals (EDCs) and Pharmaceutical Personal Care Products (PPCPs) for environmental and biological applications.

Research focus

- applications of polymer inclusion membranes incorporating molecular recognition sites
- development of new polymer types and sensor reagents for specific chemical types
- metabolomics of naturally occurring biomarkers.

Achievements

Biochemical responses in plants

In collaboration with staff from the Department of Primary Industries Victoria (DPI) we are developing methods to identify and detect chemical biomarkers that will indicate early levels of stress in vines. We have successfully identified chemical biomarkers resulting from grape phylloxera infestation. This work is supported by grants from the Grape and Wine Research and Development Corporation. In another project with DPI staff, we are investigating indole glucosinolates that are induced in Brassica plants upon infection by plant bacterial pathogens. This work will identify bioactive compounds to be used in screening and breeding programs aimed at producing Brassica varieties with high human bio efficacy and plant disease resistance.

Benheim D, Rochfort S, Ezernieks V, Powell KS, Korosi GA, **Robertson E**, **Potter ID** (2011) Early detection of grape phylloxera (Daktulosphaira vitifoliae Fitch) infestation through identification of chemical biomarkers, *Acta Horticulturae*, 904:17-24.

Polymer membranes as extraction and sensing devices for EDCs and PPCPs

We have collaborated with colleagues at The University of Melbourne, Curtin University, DPI, CSIRO, and Energy Technology to develop and characterise polymer inclusion membranes for the removal of EDCs from environmental waters. Preliminary investigations have demonstrated the effectiveness of PIMS to remove chlorinated acidic herbicides.

O'Rourke M, Duffy D, De Marco R, **Potter I** (2011) Electrochemical impedance spectroscopy – a simple method for the characterization of polymer inclusion membranes containing aliquat 336, *Membranes*, 1:132-48.

PROFILE

Anne Richards

ARC Future Fellow, Senior Lecturer
The design and synthesis of molecular cages, clusters and polymers

Using a variety of synthetic strategies, organic, inorganic and organometallic, we prepare novel chelating ligands that are used as support molecules for the synthesis of molecular cages, clusters and polymers. These structural properties of these complexes are probed by X-ray crystallography and other pertinent techniques. These materials are both of fundamental scientific importance and have functional applications, such as gas storage and magnetic materials.

Research focus

- development of a novel ligand library of functionalized phosphonic acids
- synthesis of magnetic materials
- design and synthesis of gas storage and sequestering materials.

Achievements

Molecular cages and coordination polymers
With collaborators at Texas A&M University, we have prepared a nano-sized iron cage containing 36 iron centers which showed anti-ferromagnetic coupling. The synthesis and coordination preference of organophosphonates is an ongoing area of research in our laboratory. These versatile ligands have been used as support molecules for cages polymers.

Zavras A, Fry JA, Beavers CM, **Talbo GH**, **Richards AF** (2011) 2-pyridylmethylphosphonic acid: a flexible, multi-dentate ligand for metal phosphonates, *CrystEngComm.*, 13: 3551-61.

Synthesis of main group cages and clusters

The synthesis of main group cages and clusters is an emerging research field. These novel materials, with their unique architectures are highly active reactants for gas sorption and can be used as model compounds for the interface between molecular and solid state chemistry to establish structure-property relationships and as molecular building blocks.

Beavers, CM, **Talbo GH**, **Richards AF** (2011) Ketiminate supported aluminum(III) complexes: Synthesis, characterization and reactivity, J. Organomet. *Chemistry*, 696: 2507-11.

PROFILE

Evan Robertson

Senior Lecturer
Optical spectroscopy for understanding atmospheric, interstellar and biomolecular chemistry

We use the power of optical spectroscopy to explore the properties of molecules relevant to pharmaceutics, the atmosphere, and even interstellar chemistry. Research is supported by ARC grants, the Australian Synchrotron and National Computing Infrastructure.

Research focus

- laser spectroscopy and conformational shape of biomolecules
- characterisation of atmospheric aerosols
- synchrotron IR spectroscopy of atmospheric and interstellar molecules and aerosol clusters.

Achievements

Conformer selective infrared spectroscopy of p-amino-phenethylamine

Neurotransmitter analogue p-aminophenethylamine (APEA) was studied in a jet-cooled gas phase environment using laser-based spectroscopic techniques along with theoretical chemical calculations.

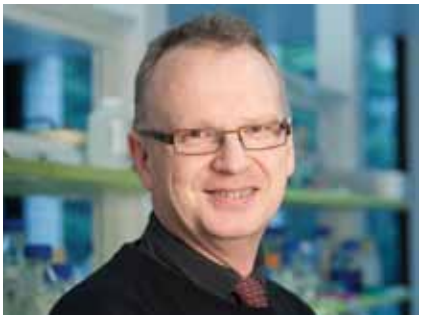
Conformer-specific IR spectra in the NH/CH stretch region reveal a consistent pattern of spectral signatures associated with the four distinct conformations of the ethylamine side chain in this molecule and related analogues such as tyramine. The two most populated conformers are stabilised by non-covalent, intramolecular NH...π type hydrogen bonding.

High-resolution FTIR spectroscopy of ketenimine

Ketenimine, a molecule found in the interstellar medium has been studied in collaboration with colleagues at the Australian Synchrotron and Monash University. Unusual sets of IR transitions have been observed, of a type normally forbidden by quantum mechanical "selection rules". The Coriolis coupling mechanism that bends the rules has been teased out.

Bane MK, **Robertson EG**, Thompson CD, Medcraft C, Appadoo DRT, McNaughton D (2011) High-resolution FTIR spectroscopy of the Coriolis coupled ground state and ν_7 mode of ketenimine, *Journal of Chemical Physics*, 134: 234-306.

Bane MK, Thompson CD, **Robertson EG**, Appadoo DRT, McNaughton D (2011) High-resolution FTIR spectroscopy of the ν_8 and Coriolis perturbation allowed ν_{12} bands of ketenimine, *Physical Chemistry Chemical Physics*, 13:6793-98.



PROFILE

Brian Smith

Associate Professor, LIMS Principal Research Fellow
Molecular modelling of biochemical systems

We use computational methods to study biochemical processes, the structures of proteins, and the interactions of proteins with other molecules. Techniques include quantum mechanics, molecular dynamics, comparative modelling, protein X-ray crystallography, and cheminformatics.

Research focus

- drug discovery and development of inhibitors of Alzheimer's BACE-1
- structural studies of small molecule modulators of apoptosis
- structure and function of proteins from malaria.

Achievements

PS – a program for helix analysis

The structure of helices within proteins is invariably distorted from the ideal linear topology. Curvature of the helix axis can be measured by determining the radius of a circle fit to the axis.

In this study we review existing methods that describe the geometry of helices in proteins, and describe a new approach of defining a curved helix axis. The helix axis is defined by a set of parametric equations that describe the intersection of a sphere and a plane. These equations are obtained by minimizing the variance in the distance of backbone atoms to the helix axis, thereby placing backbone atoms equidistantly from the axis. Several geometric properties of the helix, including helix radius, radius of curvature and pitch, can be readily obtained from these equations. The approach does not rely on a regular spacing of peptide monomers in the polypeptide chain, is applicable to any form of helix (including alpha and 3_{10} helices), can use any atom in the peptide to determine the axis, and can be applied to any polypeptide including mixed α/β peptides.

Smith BJ (2012) PS – a program for the analysis of helix geometry, *Journal of Molecular Graphics and Modelling*, 33: 52-60.

PROFILE

Michelle Spencer

Lecturer
Materials and nanomaterials for electronic devices, sensors and batteries

We study a variety of materials and nanomaterials (including metals, oxides and semiconductors) which have applications in electronic devices, sensors and batteries. We seek to understand the structure, properties and dynamical processes of these (nano) materials using a computational modelling approach.

Research focus

- novel metal oxide nanostructures for gas sensing
- nanoscale silicon for advanced electronic devices and batteries.

Achievements

Novel silicon nanosheets

In collaboration with researchers at the AIST Japan, Toyota Central R&D Labs Japan and RMIT University, we have investigated ultrathin silicon nanosheets. Nanosheets are characterised by their nanometre thickness and large lateral dimensions up to micrometres.

By using a computational approach we discovered a new surface reconstruction that is specific to a double-layer Si nanosheet, classified as Si(111)-2x2. This reconstruction is not seen on thicker nanosheets and is different to the 2x1 reconstruction observed on the bulk Si(111) surface. We are currently determining the effect of other surface modifications on the properties of these materials.

Spencer MJS, Morishita T, Mikami M, Snook IKS, Sugiyama Y, Nakano H (2011) The electronic and structural properties of novel organomodified Si nanosheets, *Physical Chemistry Chemical Physics*, 13:15418-22.

ZnO nanostructures for gas sensing

One-dimensional ZnO nanostructures, such as nanowires and nanotubes, show great promise for gas sensing device applications. Their unique size and morphology often result in a better sensor response than the traditional thin films. We are using density functional theory calculations to determine the gas-sensing mechanism of ZnO nanostructures. We found that the surface morphology, including the presence of surface defects, has a significant effect on the gas-sensor surface reaction. Specifically, we showed that NO_2 dissociates on oxygen-deficient ZnO surfaces, resulting in 'healing' of the surface and production of NO gas.

Spencer MJS (2012) Gas sensing applications of 1D-nanostructured zinc oxide: insights from density functional theory calculations, *Progress in Materials Science*, 57:437-86.

PROFILE

David Wilson

Senior Lecturer
Computational quantum chemistry

We carry out research in the general area of computational quantum chemistry. We use computer calculations to model molecular structures and properties as well as energetics and mechanisms of reactions, with a particular focus on the interaction of molecules with light and electric/magnetic fields. Our research is supported by substantial grants of high-performance computing.

Research focus

- development of fundamental understanding of molecular properties as they relate to the electronic structure of molecule and atoms
- the interaction of molecules with electric and magnetic fields
- application of computational quantum chemical methods to chemical problems.

Achievements

Modeling molecular properties

Luminescent metal complexes have captured the interest of many scientists, principally as organic light emitting diode devices, and increasingly for potential applications in biological and chemical sensing and bioimaging.

In collaboration with experimental colleagues, we have demonstrated that, with appropriate choice of ligand functionality, it is possible to manipulate emission wavelengths while keeping the redox ability of the complex relatively constant. That is, we have demonstrated an ability to design (by prediction of molecular properties), new sensing and light-emitting materials.

Kiran RV, Hogan CF, James BD, Wilson DJD (2011) Photophysical and electrochemical properties of phenanthroline-based bis-cyclometallated iridium complexes in aqueous and organic media, *European Journal of Inorganic Chemistry*, 31:4816-25.

Biomolecular modelling

We study biomolecular modeling for the purpose of drug design. One example system is HIV-1 protease, for which resistance remains a major issue, despite the availability of numerous HIV-1 protease inhibitors. We have investigated the flexibility of HIV-1 protease in an effort to understand how HIV-1 protease is able to "outsmart" new drugs. Our work provides insight into the changes that occur in HIV protease due to stress (cause and effect), which will aid in the understanding of resistance and the design of new drugs.

Oehme DP, Wilson DJD, Brownlee RTC (2011) Effect of structural stress on the flexibility and adaptability of HIV-1 protease, *Journal of Chemical Information and Modeling*, 51:1064-73.

Genetics

PROFILE

Warwick Grant

Associate Professor
and Head of Department
Evolutionary genetics of nematode parasites

We research the evolution of drug resistance in nematode parasites of medical and veterinary importance as an approach to conserving the efficacy of the few drugs that are available. Other projects in the lab are aimed more broadly at understanding how parasitism evolved in this group of organisms, with a view to mining these data for novel, nematode specific, targets for drug or vaccine development.

Research focus

- drug resistance genetics in *Onchocerca volvulus* and *Teladorsagia circumcincta*
- application of large scale next generation sequencing methods to parasite population and evolutionary genetics
- development of a model system in which to investigate the genetic basis of parasitism in nematodes.

Achievements

Helminth parasite research

Helminth (nematode and flatworm) parasites are major contributors to diseases of poverty, as well as major agricultural pests, yet little is known of their basic biology and few compounds are available for their control. Work in the Grant lab is directed at understanding the evolution of drug resistance in nematode parasites, and includes analyses of the genetic structure of parasite populations and searches for regions of the genome that are under recent selection. Research involves the use of next generation sequencing technologies in addition to more conventional genotyping approaches.

Drug resistance and tropical disease

In collaboration with colleagues at McGill University in Canada, I have played a role in the establishment of a research consortium that is supported by the World Health Organisation special program on Tropical Disease Research (WHO/TDR) and the African Program for Onchocerciasis Control (APOC), and involves collaborations with research labs and ministries of health in Burkina Faso, Ghana and Cameroon. The project, which aims to define genetic markers for surveillance of drug resistance selection in the causative organism of River Blindness, also involves a capacity building component that will see graduate students from endemic countries undertake research degrees in the Genetics Department.

PROFILE

Adam Hart

Lecturer
Molecular regulation of stem cells and cancer

Our research focuses on the transcription factors that control pluripotency and lineage commitment in embryonic, germline, haematopoietic and cancer stem cells. Research is supported by NHMRC, Australian Stem Cell Centre, Victorian Life Science Computation Initiative and the National Collaborative Research Infrastructure Strategy.

Research focus

- pluripotent stem cells from the testis
- marsupial stem cells
- molecular regulation of mesoderm differentiation.

Achievements

Periostin, a key regulator of kidney development and regeneration

Working with researchers at Monash University, we have discovered a key regulator of kidney development and regeneration.

In this study we used genetically modified, BMP-EGFP mice to identify and isolate the kidney mesoderm stem cells from renal epithelial cells, then analysed the transcriptional profile of the isolated cell populations by micro-array analysis.
We discovered that that Periostin, a secreted extracellular matrix protein is a key regulator of kidney growth and differentiation.
This work could have significant impact on treating patients with acute or chronic renal failure and in identifying the genetic cause of congenital kidney defects.

Sorocos K, Kostoulias X, Cullen-McEwen L, **Hart AH**, Bertram JF, Caruana G (2011) Expression patterns and roles of periostin during kidney and ureter development, *The Journal of Urology*, 186:1537-44.

Breast cancer stem cell identified

In collaboration with researchers at seven major Australian universities and research institutes, we identified the breast epithelial stem cell that gives rise to tumours in familial (BRCA1) breast cancer. By comparing the transcriptional profile of normal and BRCA1 mutated epithelial stem cells, we were able to identify the stem cell origin of basal cell carcinomas that arise in most women carrying a BRCA1 mutation. This study has implication for the development of enhanced screening and therapeutic strategies for managing familial and sporadic breast cancer.

Lim E, Vaillant F, Wu D, Forrest NC, Pal B, **Hart AH**, Asselin-Labat ML, Gyorki DE, Ward T, Partanen A, Feleppa F, Huschtscha LI, Thorne HJ, ConFab K, Fox SB, Yan M, French JD, Brown MA, Smyth GK, Visvader JE, Lindeman GJ, et al (2009) Aberrant luminal progenitors as the candidate target population for basal tumor development in BRCA1 mutation carriers, *Nature Medicine*, 15:907-13.

PROFILE

John Mitchell

Associate Professor
Human evolutionary genetics and forensic science

Our research seeks to understand human origins and migrations over the last 100,000 years focusing on Southeast Asia and Australasia. To do this we use DNA sequence variation to create maternal and paternal lineages.

Research Focus

- mitochondrial and Y chromosome lineages and phylogeny
- forensic implications of trace DNA
- pharmacogenetics – cytochrome P450 genes.

Achievements

Forensic aspects of DNA

The issue of transfer DNA is increasingly being raised in court cases with the advancement of DNA analytical techniques. Minute quantities of DNA (trace DNA) can appear at crime scenes and their origin is often disputed.

This area was underappreciated in forensic science, but since our review paper, more attention is being paid by forensic labs.

van Oorschot RAH, Ballantyne KN, **Mitchell RJ** (2010) Forensic trace DNA: a review, *Investigative Genetics*, 1:1-14.

Human settlement of Oceania

The human settlement of Oceania (including Australia) is both poorly understood and controversial. One reason for this is that we have lacked appropriate DNA markers for the populations in this region. We identified key SNPs to define mitochondrial lineages unique to the region as well as those that are restricted to subpopulations. In particular, the uniqueness of Australian mitochondrial lineages was observed.

Ballantyne K N, van Oven M, Arwin R, Stoneking M, **Mitchell RJ**, van Oorschot RAH, Kayser M (2012) MtDNA SNP multiplexes for efficient inference of matrilineal genetic ancestry within Oceania, *Forensic Science International – Genetics,* 6:425-36.

PROFILE

Nick Murphy

Lecturer
Molecular ecology

We use molecular methods to address issues in ecology, conservation biology and evolution. The major emphasis of the research is in fragmented and isolated terrestrial and freshwater habitats.

Research focus

- the evolution of desert spring invertebrates
- the impact of fire on terrestrial arthropods
- range limits in freshwater species.

Achievements

Trapped in desert springs

The desert springs surrounding Lake Eyre in central Australia are home to a unique suite of animals that exist nowhere else. Phylogenetic and phylogeographic studies of three different groups, amphipods, isopods and snails all show remarkably similar evolutionary histories, with a large degree of cryptic speciation reflecting a previously unknown level of diversity.

Most of the diversity within these groups has its origins prior to the formation of both deserts and the spring systems. To date, results suggest that the endemic fauna have no close relatives outside of the springs. Thus, the desert spring ecosystem represents one of the last remnants of a time when inland Australia was much wetter and supported species such as crocodiles and flamingos.

Murphy NP, Breed MF, Guzik MT, Cooper SJB, Austin AD (2012) Trapped in desert springs: phylogeography of Australian desert spring snails, *Journal of Biogeography,* 36:1573-82.

Guzik, MT, Adams MA, **Murphy NP**, Cooper SJ, Austin AD (forthcoming 2012) Phylogeographic structure of an ancient endemic crustacean (*Phreatomerus latipes*), *PLoS ONE,* 7(7): e37642.

PROFILE

Greg Somers

Lecturer
Molecular regulation of stem cell development

Our research seeks to identify and understand the molecular mechanisms regulating stem cell characteristics, including self-renewal and differentiation.

Research focus

- genetic screens involving *in vivo* stem cell populations
- understanding the molecular machinery involved in niche-stem cell interactions
- identify novel tumour-suppressor factors, responsible for generating cancer stem cells.

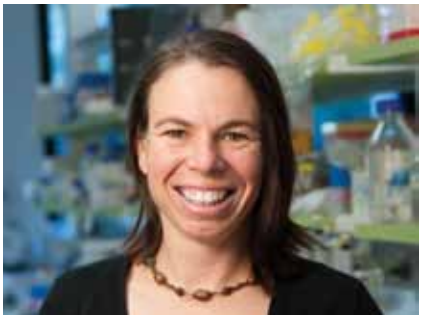
Achievements

Identifying novel regulators of Drosophila germline stem cell development

We have developed an in vivo screening strategy, using the male gremlin of *Drosophila melanogaster*, to identify novel conserved factors important for stem cell self-renewal and differentiation.

Our screen has presently identified alleles that behave as putative tumour-suppressors, as well as alleles essential for stem cell maintenance. One of the factors identified from our screen is the *Drosophila* orthologue (Rbf) of the Retinoblastoma protein (pRb). Disruption of Rbf results in supernumerary stem cells at the expense of more differentiated cell-types, a phenotype similarly seen with mammalian pRb proteins. However, the biological mechanisms of mammalian pRb proteins remain poorly understood. We have shown *Drosophila* Rbf functions non-cell-autonomously to regulate GSC differentiation. We have also shown *Drosophila* Rbf normally functions to restrict the self-renewing signals of the Bone Morphogenetic Pathway (BMP). Our work provides new insights into the mechanisms regulating stem cell development as well as shedding light on the evolution of multicellularity and tissue differentiation, one of the fundamental questions of animal biology.

Chang KC, Garcia-Alvarez G, **Somers G**, Sousa-Nunes R, Rossi F, Lee YY, Soon SB, Gonzalez C, Chia W, Wang H (2010) Interplay between the transcription factor Zif and aPKC regulates neuroblast polarity and self-renewal, *Developmental Cell*, 19:778-85.



PROFILE

Jan Strugnell

Lecturer
Molecular biodiversity

We apply next generation sequencing tools to help solve bottlenecks in fisheries and aquaculture industries (e.g. lobster, abalone). We also investigate population and species level evolution in molluscs and Antarctic and deep-sea species in the context of past climatic change.

Research focus

- stress transcriptomics of commercially important abalone
- evolution in Antarctica and the deep sea
- cephalopod (octopus, squid) evolution.

Achievements

The southern ocean: source and sink?

Many fauna of the Antarctic continental shelf share close relationships to the deep-sea fauna of other ocean basins. Connections between the Antarctica and the deep sea are thought to have been facilitated by the deep Antarctic continental shelf coupled with submerging Antarctic bottom water and emerging circumpolar deep water.

We examined the evolutionary history of the octopus genus, *Benthoctopus*, present in the world's deep-sea basins and Antarctica. Using sequence data in a relaxed Bayesian framework, we showed that the *Benthoctopus* clade originated in shallow Northern Hemisphere waters. *Benthoctopus* species in Antarctica are representative of polar emergence and occur at shallower depths than non-polar species.

Strugnell JM, Cherel Y, Gleadall IG, Hochberg FG, Ibanez CM, Jorgensen E, Laptikhovsky VV, Linse K, Norman M, Vecchione M, Voight JR, Allcock AL, et al (2011) The southern ocean: source and sink? *Deep-Sea Research II*, 58:196-204.

What can the mitochondrial genome reveal about cephalopod phylogenetics?

We presented the first analysis of cephalopod (squid, octopus) mitochondrial gene order and constructed phylogenies based on gene order using Bayesian, distance, and parsimony analysis methods. Analyses included all cephalopods for which the mitochondrial genome has been sequenced. We constructed a phylogeny based on amino-acid sequence data of all mitochondrial protein coding genes. As well as supporting Octopodiformes and Decapodiformes analyses established support for Teuthoidea to the exclusion of Sepiidae (cuttlefishes). Morphological characters and paleontological evidence suggests that our phylogeny reflects true evolutionary relationships.

Allcock AL, Cooke IR, **Strugnell JM** (2011) What can the mitochondrial genome reveal about higher-level phylogeny of the molluscan class Cephalopoda? *Zoological Journal of the Linnean Society*, 161:573-86.

Pharmacy

PROFILE

Mike Angove

Senior Lecturer and Head of Department
Colloid and environmental chemistry

We research surface phenomena responsible for the retention and transport of toxic organic and inorganic chemical species through the environment. Various spectroscopic and computer modelling techniques are employed to elucidate chemical processes so that environmental transport can be predicted. Research is supported by grants from EPA Victoria.

Research focus

- study, modelling and prediction of chemical transport in soil and sediment systems
- removal of toxic species from contaminated soils
- spectroscopic determination of chemical binding at surfaces.

Achievements

EPA Victoria Hazwaste

We received funding from EPA Victoria to investigate possible strategies of removal of heavy metals from contaminated soils. This project looks at optimizing acid extraction methods after investigation of metal binding using XPS and IR measurements of the surface chemistry.

Inositol hexaphosphate sorption

Investigation of Inositol hexaphosphate sorption on goethite was studied as a function of pH and concentration, and by use of Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (ATR-FTIR). While adsorption was highest at low pH, a significant amount remained adsorbed above pH 10 where, in the absence of IP_6, the surface is expected to have a net negative charge. ATR-FTIR spectra of IP_6 solutions in the pH range from 2 to 12 were fitted with a single set of IR bands which were assigned primarily by analogy with phosphate spectra. From its variation in intensity with pH the band at 1040 cm^{-1} was assigned to the effect of hydrogen bonding on the PO vibration. No additional bands were required to fit the spectra of IP_6 adsorbed to goethite, indicating that adsorption occurs by outer-sphere complexation in this system. At all pH values studied the band associated with hydrogen bonding was more intense for the adsorbed species than in solution at the corresponding pH indicating that hydrogen bonding plays an important role in binding IP_6 to goethite.

Johnson BB, Quill E, Angove MJ (2011) An investigation of the mode of sorption of inositol hexaphosphate to goethite, *Journal of Colloid and Interface Science*, 367:436–42.

PROFILE

Daniel Tillett

Senior Lecturer
Bacteriophages for control of problematic environmental and clinical bacteria

We seek to discover and characterise novel bacteriophages for biocontrol of problematic bacteria in both the environment and clinic. Research is supported by grants from the ARC.

Research focus

- isolation and characterisation of novel bacteriophages
- use of bacteriophages to control problematic bacteria in the wastewater industry
- use of bacetriophages to control medically important microbes on the skin.

Achievements

Prevention stabilized foam formation in activated sludge plants

Most activated sludge treatment plants suffer from the presence of foams on the surfaces of their aeration reactors. These are often stabilized by hydrophobic mycolic acid-synthesizing actinobacterial species. We have isolated and characterised a range of bacteriophages that in laboratory scale experiments, prevents stabilization of foams by the hydrophobic mycolic acid-synthesizing bacterial.

Petrovski S, Seviour RJ, Tillett D (2011) Prevention of gordonia and nocardia stabilized foam formation by using bacteriophage GTE7, *Applied & Environmental Microbiology*, 77 7864-67.

Non-target sites with single nucleotide insertions or deletions are frequently found in 16S rRNA sequences and can lead to false positives in fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) has impacted profoundly on our knowledge of the in situ ecophysiology and biodiversity of bacteria in natural communities. However, it has many technical challenges including the possibility of false positives from the binding of probes to non-target rRNA sequences.

We have shown that probe target sites containing single-base insertions or deletions can lead to false FISH positives, the result of hybridization with a bulge around the missing base. Experimental and *in silico* data suggest this situation occurs at a surprisingly high frequency. We have developed software to identify potential non-target sites resulting from single-base insertions or deletions in rRNA sequences.

McIlroy SJ, Tillett D, Petrovski S, Seviour RJ (2011) Non-target sites with single nucleotide insertions or deletions are frequently found in 16S rRNA sequences and can lead to false positives in fluorescence in situ hybridization (FISH), *Environmental Microbiology,* 13:33-47.

Seminar program

FEBRUARY

16 February

Dr Oliver Rackham and Dr Aleksandra Filipovska (Western Australian Institute for Medical Research)
A universal code for RNA-protein recognition and RNA processing in human mitochondria

25 February

Dr Brian Smith (Walter and Eliza Hall Institute of Medical Research)
Application notes on the use of molecular modelling in drug discovery

28 February

Dr Ian Cade (Australian National University)
Borabenzene – an aromatic lewis acid

Dr Dan Li (Monash University)
Nanomaterials and membranes for separation technology

Dr Michelle Spencer (RMIT University)
Molecules, materials and nanostructures: a modelling approach

MARCH

2 March

Dr Matt Perugini (Bio21, The University of Melbourne)
Multiple personalities in quaternary structure and regulation of an enzyme antibiotic target

Dr Germane Cavigliasso (Australian National University)
Computational modelling of dinuclear metal systems of synthetic and biological interest

Dr Ian Gass (Monash University)
Any old iron: spin switching and exchange coupling in clusters, supramolecular arrays and metal-radical systems

8 March

Dr Melissa Latter (University of Western Australia)
From molecular capsules to fluorescent dyes: synthesis, supramolecular assembly and colourful chemistry

9 March

Dr Jason Dutton (University of Calgary, Canada)
Novel structure, bonding and reactivity for selenium and tellurium: carbene analogues, ligand exchange and dicationic complexes

16 March

Dr Suresh Mathivanan (Ludwig Institute for Cancer Research)
Exosome and secretome based analysis of colorectal cancer cells

24 March

Dr Nick Murphy (La Trobe University)
Evolution in Australian desert springs

30 March

Dr Jacqui Gulbis (Walter and Eliza Hall Institute of Medical Research)
Conduction in inwardly rectifying potassium channels is regulated by an intracellular assembly

APRIL

7 April

Dr Gregory Somers (La Trobe University)
Regulation of stem cell differentiation by the tumor suppressor pRb

12 April

Dr Spas Kolev (University of Melbourne)
Application of polymer inclusion membranes for the on-line extractive separation of metal Ions in flow injection analysis

13 April

Professor Bostjan Kobe (The University of Queensland)
Structural basis of TIR domain function in both human and plant innate immune pathways

MAY

5 May

Dr Michael Westerman (La Trobe University)
Kangaroo and bandicoot evolution

11 May

Dr Kurt Lackovic (Walter and Eliza Hall Institute of Medical Research)
Drug discovery via high-throughput and high-content screening

SEMINAR PROGRAM

19 May

Dr Adam Hart
(La Trobe University)
Transcriptional regulation of ESC pluripotency

25 May

Dr Siew Yeen Chai
(Monash University)
Development of a new clas s of cognitive enhancers targeting the enzyme IRAP

31 May

Professor Don McNaughton
(Monash University)
Raman microspectroscopy and imaging of single cells

JUNE

2 June

Dr Jan Strugnell
(La Trobe University)
The octopus ink sac clouds its evolutionary history

14 June

Dr Colin Smith
(La Trobe University)
Liquid chromatography isotope ratio mass spectrometery and its use in analysing ancient proteins

15 June

Dr David Curtis
(The Royal Melbourne Hospital)
The role of apoptosis in leukemic transformation – staying alive isn't so bad after all

JULY

13 July

Professor Adrian Goldman
(University of Helsinki)
Flipping the switch: how Factor H distinguishes you from E. coli

20 July

Dr Melanie Rug
(Walter and Eliza Hall
Institute of Medical Research)
New insights into the trafficking of the major virulence protein PfEMP1 to the surface of malaria parasite infected red blood cells

AUGUST

2 August

Professor Frances Separovic
(University of Melbourne)
Interaction of antimicrobial and amyloid peptides in membranes

9 August

Dr David Lupton
(Monash University)
Normal polarity NHC catalysis: mechanistic insights into the N-heterocyclic carbene catalyzed all-carbon [4 + 2] cycloaddition/ decarboxylation

11 August

Dr Tony Papenfuss
(Walter and Eliza Hall Institute)
Tasmanian devil genomics comes of age

17 August

Professor John Mattick
(Institute for Molecular Bioscience,
University of Queensland)
RNA at the epicentre of human development

25 August

Dr Susan Hoebee
(Department of Botany,
La Trobe University)
Genes, individuals and populations: connecting ecology and genetics

31 August

Dr Simon Barry
(University of Adelaide)
Using genome wide approaches to identify the key targets of FOXP3 in human regulatory T cells

SEPTEMBER

6 September

Dr Jonathan Baell
(Walter and Eliza Hall
Institute of Medical Research)
Hit-to-lead medicinal chemistry with screening, design or the literature as starting points: from antiparasitics to anticancer

7 September

Professor Emma Whitelaw
(Queensland Institute of Medical Research)
Epigenetics and the determination of phenotype

SEMINAR PROGRAM

8 September

Dr Robert Ramsey
(Peter MacCallum Cancer Centre)
Earliest events in intestinal cancer

13 September

Dr Colette Boskovic
(University of Melbourne)
Functional molecules for molecular nanoscience

14 September

Dr Jörg Heierhorst
(St Vincent's Institute)
A breath-taking phenotype: unexpected roles of a DNA damage response protein as a developmental transcription factor

15 September

Dr Craig Sherman
(Deakin University)
Evolution of mating systems

22 September

Dr Gawain McColl
(The Mental Health Research Institute)
Models for neurodegenerative disease in Caenorhabditis elegans

28 September

Dr Marina Carpinelli
(Walter and Eliza Hall Institute)
Using mouse genetics to identify genes involved in hearing loss

OCTOBER

4 October

Professor Peter Quinn
(King's College, London)
Lipid-lipid interactions in membranes: casual liaisons and marriage partners

6 October

Dr Richard Burke
(Monash University)
The cell biology of heavy metal homeostasis in Drosophila

12 October

Professor Xiao-Jun Du
(Baker Heart and Diabetes Institute)
Beta adrenergic signalling in heart function

13 October

Dr Roland van Oorschot
(Victoria Police-Forensic Services)
Transfer of DNA: aspects relevant to criminal investigations

18 October

Dr Paul Francis
(Deakin University)
Max O'Connor Award Lecture 2011

20 October

Dr Jim Vadolas
(Murdoch Children's Research Institute)
Gene therapy for the treatment of genetic disorders

26 October

Dr Sarah Russell
(Peter MacCallum Cancer Centre)
T-cell polarity

NOVEMBER

9 November

Dr Terry Kwok-Schuelein
(Monash University)
Integrins: mammalian receptors that integrate Helicobacter with cancer

23 November

Dr Ygal Haupt
(Peter MacCallum Cancer Centre)
Regulation of p53/PML tumor suppressor network

29 November

Dr Elizabeth Sawyer
(Biophysical Institute of the Chinese Academy of Sciences, Beijing)
From nature to nanotechnology: exploring the potential of amyloid fibrils as biomaterials


LA TROBE INSTITUTE OF MOLECULAR SCIENCE

Publications

BIOCHEMISTRY

Book chapters

Gentle I, Silke J (2011) New perspectives in TNF-R1-induced Nf-KB signaling, *Advances in TNF Family Research*, 79-89.

Tilley L, Charman S, Vennerstrom J (2011) Semisynthetic artemisinin and synthetic peroxide antimalarials, *Neglected Diseases and Drug Discovery*, 33-64.

Journal articles

Anders R (2011) The case for a subunit vaccine against malaria, *Trends in Parasitology*, 27:330-34.

Banadyga L, Lam S-C, Okamoto T, **Kvansakul M**, Huang D, Barry M (2011) Deerpox virus encodes an inhibitor of apoptosis that regulates bak and bax, *Journal of Virology*, 85:1922-34.

Bhatt T, Khan S, Dwivedi V, Banday M, Sharma A, Chandele A, Camacho N, de Pouplana L, Wu Y, Craig A, **Mikkonen A**, **Maier A**, Yogavel M, Sharma A (2011) Malaria parasite tyrosyl-tRNA synthetase secretion triggers pro-inflammatory responses, *Nature Communications*, 2:E1-10.

Brand I, **Lovric M, Civciristov S**, **Pantaki D**, **George C**, Gort T, Huang N, Clem R, **Hawkins C** (2011) Functional and biochemical characterization of the baculovirus caspase inhibitor MaviP35, *Cell Death and Disease*, 2:E1-10.

Breakefield X, Frederickson R, **Simpson R** (2011) Gesicles: microvesicle cookies for transient information transfer between cells, *Molecular Therapy*, 19:1574-76.

Casey J, Sanalla A, **Tamvakis D**, Thalmann E, Carroll E, **Parisi K, Coley A**, Stewart D, Vaughan J, Michalski W, Luke R, **Foley M** (2011) Peptides specific for Mycobacterium avium subspecies paratuberculosis infection: diagnostic potential, *Protein Engineering Design and Selection*, 24:589-96.

Chandrashekaran I, **Adda C, Anders R**, Norton R (2011) EGCG disaggregates amyloid-like fibrils formed by Plasmodium falciparum merozoite surface protein 2, *Archives of Biochemistry and Biophysics*, 513:153-57.

Coley A, **Puthalakath H** (2011) The PKA paradox: Is BIM the answer? *Cell Cycle*, 10:1-2.

Conlan B, **Anderson M** (2011) Circular micro-proteins and mechanisms of cyclization, *Current Pharmaceutical Design*, 17:4318-28.

Conlan B, **Gillon A**, **Barbeta B**, **Anderson M** (2011) Subcellular targeting and biosynthesis of cyclotides in plant cells, *American Journal of Botany*, 98:2018-26.

Darding M, **Feltham R**, Tenev T, Bianchi K, Benetatos C, **Silke J**, Meier P (2011) Molecular determinants of Smac mimetic induced degradation of cIAP1 and cIAP2, *Cell Death & Differentiation*, 18:1376-86.

Dixon M, **Kenny S**, **McMillan P**, Hanssen E, Trenholme K, Gardine D, **Tilley L** (2011) Genetic ablation of a Maurer's cleft protein prevents assembly of the Plasmodium falciparum virulence complex, *Molecular Microbiology*, 81:982-93.

Donker N, **Foley M**, **Tamvakis D**, Bishop R, Kirkwood, C (2011) Identification of an antibody-binding epitope on the rotavirus A non-structural protein NSP2 using phage display analysis, *Journal of General Virology*, 92:2374-82.

Dougan D (2011) Chemical activators of ClpP: turning Jekyll into Hyde, *Chemistry & Biology*, 18:E1-3.

Dougan D, **Micevski D**, **Truscott K** (2011) The N-end rule pathway: from recognition by N-recognins, to destruction by AAA+proteases, *Biochimica et Biophysica Acta*, 1823:83-91.

Dunse K, **Anderson M** (2011) Towards the next generation of pest resistant plants, *ISB News Report, Virginia Tech University*, 1-5.

Evison B, **Pastuovic M**, **Bilardi R**, **Forrest R**, **Pumuye P**, Sleebs B, Watson K, **Phillips D**, **Cutts S** (2011) M2, a novel anthracenedione, elicits a potent DNA damage response that can be subverted through checkpoint kinase inhibition to generate mitotic catastrophe, *Biochemical Pharmacology*, 82:1604-18.

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