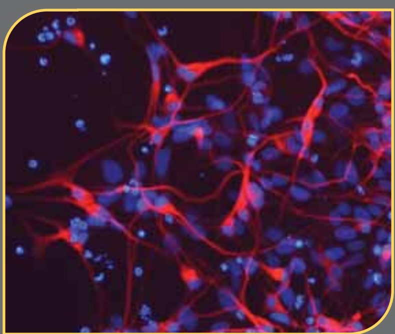
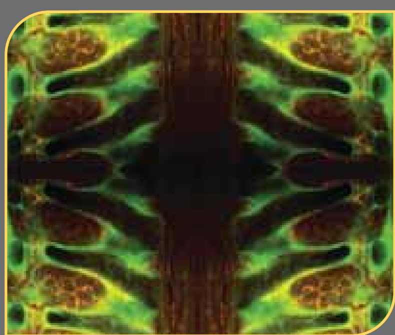
PHARMACOLOGY

annual report

volume 11





Contents

Head of Department's Report

Head, Department of Pharmacology
Professor Peter McIntyre

2007 was a good year for the Department of Pharmacology in a wide range of activities. Pharmacology was one of five areas identified as areas of strength within the University by a recent Thomson Scientific report, which puts the University of Melbourne in the 'Top 3' in Australia in both citations and impact in five fields – neurosciences, physics, microbiology, pharmacology and psychology/psychiatry. The Department of Pharmacology is one of the few independent, discipline-based departments of pharmacology in Australia and has a proud history of achievement in our discipline.

New staff members of 2007 include Ms Maya Kesar who became the first combined Biomedical Departments Animal House Manager, a key initiative in the closer relationships that the key Biomedical departments are building to forge a new Biomedical "Cluster" in the Faculty of Medicine Dentistry and Health Sciences. Other new faces were Dr Lucy O'Donovan from the UK who joined the Crack group as a postdoctoral fellow. Dr Kade Roberts joined the Hughes group as a postdoctoral fellow. Lindsay Kosack, Debbie Allen, Huei Jiunn Seow joined the Anderson Lab and Geraldine Fitzgerald, Clare Savage, Sarah Brand joined the Royse Group. In addition, the State Neuropathology Laboratory has temporarily relocated to the Level 9.

Professor Peter McIntyre, Dr Elizabeth Shaw, Professor James Angus

The Department was honoured by the visit of Dr Elizabeth Shaw, the daughter of the founding Chairman of the Department, Professor Frank H. Shaw (Chairman from 1954 until 1964). Dr Shaw was hosted by the Dean of the Faculty of Medicine, Dentistry and Health Sciences, Professor James Angus and I, where she learned more about the Department and the faculty and we discussed other eminent members of her family who have been associated with the University of Melbourne.

Undergraduate teaching went smoothly, with continued strong demand for places in our core second and third-year subjects, 534-201 and 534-301. We had good responses to our Quality of Teaching surveys. Our active Teaching Committee monitored courses and developed new offerings and oversaw the beginnings of the development of New Generation Courses for our contribution to the "Melbourne Model".

The Department Honours program remains as our main entry portal into research higher degrees and is therefore of great importance to us for maintaining our traditional strength in research. This year the course was near capacity as we recruited 13 honours students in addition to 8 Advanced Medical Science students. Ms Christina Tan (McIntyre and Ziogas) was the Dux of the class this year. Please see the honours & AMS Student page of our website for more details of our courses and the projects that we offer.

Many postgraduate students presented their final talks this year: PhD: Chris Choy (M van den Buuse, MHRI), Cindy Chiu (P Beart, HFI), Linda Lau (P Beart, HFI), Ken Liu (G Anderson Lab), Heneu Tan (S Petrou, HFI, & C Wright Lab), SR Datla (Prof G Dusting, BOBIM & Woodman Lab), Christina Koulis (T Cocks Lab); and Masters student Julia Griffiths (P Marley Lab & R Pearson, Peter MacCallum Cancer Institute).

Eight Graduate Research students successfully completed their PhD this year: Lakshimi Diwakarla (P Beart, HFI), Mark Farso (P Beart, HFI), Melissa Gresle (B Jarrott, HFI), Mr Heneu Ong Tan (S Petrou, HFI) and Chrissandra Zagami (P Beart, HFI), including three that have been awarded NHMRC postdoctoral fellowships overseas, Ms Klaudia Budzyn (C Sobey), Ms Lauren May (A Christopoulos, Monash) and Nicola Smith (Baker). We offer our warm congratulations and wish them good luck in their future careers.

Congratulations to Mr Ran Li, an AMS Student with Dr Ken Winkel, who won 3rd place in the Anatomy Department "Under the Coverslip" Competition for his photo "Holey Apparition"; Francis Shand, Honours student with Professor Alastair Stewart was nominated to attend the U21 conference in Montreal where he presented his work from his Honours year. He also received a high commendation for his poster at the ASMR meeting; Honours students, Dian Samijono (with Dr James Ziogas) and Suang Suang Koid (with Dr Graham McKay) were finalists in the Poster Prize at the annual ASCEPT Conference in Adelaide; Jane Ward was awarded the best oral presentation in the Interstitial Lung Disease Assembly at the Asia Pacific Society of Respirology; and J Ziogas was awarded a Carrick Institute Grant.

Our research income was a little over four million dollars this year and we are very pleased that we are experiencing more success in competing for NH&MRC competitive grants as well as having several labs funded by the Neurotrauma grants from the TAC/Neurotrauma Initiative (Saunders, Hughes and Crack labs), to fund work into spinal cord damage, repair and identification of new targets for treating traumatic brain injury.

Successful applicants for NHMRC Project Grants to begin in 2008 were: Alastair Stewart, Peter Crack, Mike Hubbard, Steve Bozinovski & Ross Vlahos, Jane Ward, Gary Anderson (with Margaret Hibbs), Tony Hughes (2 grants with John Wade & Ross Bathgate, HFI). In addition, Colin Royse was awarded funding from ANZCA and I was awarded a University of Melbourne "near miss" grant. This is in addition to our continuing success in attracting funding from commercial and philanthropic sources.

The Department continues to strongly support our research teams with the best infrastructure we can obtain. This year we purchased new equipment through Department funds and external funding for AMAXA nucleofector, a Microwave Peptide synthesizer, a new preparative ultracentrifuge, superspeed centrifuge, five figure analytical balance and an autoclave. This investment in high-quality equipment is essential to allow us to attract and retain the best researchers.

Pharmacology was in the news once again. These include our Research Higher degree student David Williams '60 Minutes' interview "The venom hunters" on 25 February 2007; Professor P McIntyre radio interview with Red Symons & Podcast on "Brains Matter", and The Anderson & Morris Lab extensive news coverage of the paper: "Smoking causes muscle weight loss not fat loss". In addition, Rosa Gualano was Australian Council for Educational Research "Principal for a Day" at her former alma mater, Koonung Secondary College (see University of Melbourne VOICE Vol 1 No. 16 15-21 Oct 2007).

In finishing my introduction, I would like to encourage potential Honours and Graduate Research students to come and talk to us if you are interested in pursuing a career involving biomedical research and pharmacology. We have world-class facilities and equipment and a passion for our subject that will make your time with us stimulating and exciting and will present numerous opportunities for building your career, either in Australia or beyond our shores in Europe, the Americas or in our fast-growing Asian region. Come and see what we have to offer.

Professor Peter McIntyre

Department Staff

Academic & Teaching Staff

Head of Department and Professor
Professor Peter McIntyre, BSc PhD Latrobe

Deputy Head of Department and Professor of Pharmacology
Alastair George Stewart, BSc PhD

Professor of Pharmacology
James Alexander Angus, BSc PhD Syd FAA
Gary Peter Anderson, BSc PhD

Associate Professors
Owen Llewyn Woodman, BSc PhD
Christine Eva Wright, BSc PhD Monash
Alistair Royse, MB BS MD FRACS FCSANZ
Colin Royse, MB BS MD FANZCA

Senior Lecturers
Richard Anthony Hughes, BPharm VCP PhD Lond
Michael Julian Lew, BSc PhD Monash
Elizabeth McIntyre Tudor, BVSc PhD
James Ziogas, BSc PhD

Lecturer
Peter Crack, BSc, PhD Monash
Graham Mackay, BSc PhD UK
Jane Elizabeth Ward, BSc PhD

National Health and Medical Research Council - Principal Research Fellow
Thomas Matthew Cocks, BSc NSW PhD Lond

Principal Research Fellow
Kate Magdelena Dziegielewska, MSc Pol PhD Lond

Neuroscience Victoria Senior Research Fellow
Mark David Habgood, BSc MSc PhD

Senior Research Fellow
Kenneth Daniel Winkel, MB BS Qld BMedSc PhD FACTM

CJ Martin Fellow
Sophocles Chrissobilis, BSc PhD

Research Fellows
Carl Joakim Ek, BSc, PhD Tas
Steven Bozinovski, BSc LaTrobe PhD
Brett Cromer, BSc PhD
Mirella Dottori, BSc DMB
Pia Johansson, BSc Tas PhD
Rosa Claire Gualano, BSc PhD Monash
Michelle Joan Hansen, BSc PhD
Brenda Leung, BSc PhD
Roger Lowe, BSc BNurs PhD Latrobe
Jon Magnum, MSc Otago
Alice Pebay, DocNeurosci Paris
Michael Schuliga, BSc Melb PhD Deakin
Helen Stolp, BSc Tas PhD
Ross Vlahos, BSc PhD

Research Officers
Mark Graeme Devlin, BSc PhD
Ruth Park, BSc PhD

Senior Research Assistants
Trudi Harris, DipAppSc RMIT
Elizabeth Guida, BSc LaTrobe
Danielle Nicholas, BSc Deakin Grad Dip MLA SA

Research Assistants
Heather Daykin, BSc
Jessica Jones, BSc
Shenna Langenbach, BSc Monash
Mark Ross-Smith, BSc
Lovisa Dousha, BSc Monash
Catherine Jones, DipAppSc
Ben Wheaton, BSc

Technical Officers
Linda Cornthwaite-Duncan
Ann Potter, CBiolSci

Professional Staff

Departmental Manager
Victor Iwanov, BSc BEd MSc

Administrative Officer
Jennifer Steen

Personal Assistant to the Head
Fanoula Mouratidis

Administrative Assistant
Hong Nguyen

Administrative Assistant (Postgraduate Diploma in Perioperative and Critical Care Echocardiography)
Marcelle Wood
Lindsay Middleton

Practical Class Technical Staff
Carol Horsman, BAgSc (HortSci) Adel
Melissa Patterson

Biological Research Facility Staff
Damaris Delgado, DipAnimalTech(TAFE)
Sonya Pannenborg, DipAnimalTech(FIT)
Andrea Lonsdale

Resident Fellows

Professorial Fellow
Michael Hubbard, BDSurg PhD(Biochem) Otago

Research Fellow
Jew Kon, BSc, PhD Otago

Honorary Researcher
Garry Nervo, BDSc, MDSc

Honorary Staff

Professorial Fellows
Phil Beart, BSc PhD DSc
Geoffrey Burnstock, PhD DSc FAA FRCS FRCP FMedSci FRS
Bevyn Jarrott, BPharm Qld PhD Camb
Norman Saunders, BSc PhD MB BS Lond ECFMG USA

Principal Fellows with the title Associate Professor
Duncan Blake, MB BS BMedSc PhD FANZCA
David Pilkington Crankshaw, MB BS PhD FLEX Calif FFARACS FANZCA
Noel Cranswick, MB BS BMedSc FRACP
Margaret Morris, BSc PhD Monash
Greg Dusting, BSc PhD
Kate Leslie, MB BS FANZCA
Anders Linden, MD PhD Gottenb
Frederick Mitchelson, MSc PhD Lond PhC MRPharmS MPS
James Tibballs, MB BS Monash BMedSc MBA MD MEd FFARACS FANZCA FFICANZCA
Maarten van den Buuse, PhD N'lands
David Warrell, MA Lond DM DSc FRCP
John Wilson, BSc MB BS PhD FRACP FCCP

Senior Fellows
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Christopher Bolton, MB BS FANZCA
Malcolm Brown, MB BS PhD FFARACS FANZCA
Andrew Davidson, MB BS FANZCA
Michael Davies, MB BS FANZCA
Roman Klugar, MB BS FANZCA
Andrew Lawrence, BSc PhD UK
Clive May, BSc PhD
Desmond McGlade, MB BS FAFRACS FANZCA ECFMG
Phillip Reece, BSc Adel PhD ANU
David Scott, FFARACS FANZCA
Patrick Sexton, BSc PhD
Paul Soeding, BSc MB BS FANCA
David Story, BSc PhD
Jennifer Trinca, MB BS FFARACS FANZCA
Michael Veltman, MB BS UWA FANZCA PTXeXAM
Kostantin Yastrebov, MD PhD FACRRM
Arthur Christopoulos, BSc PhD Monash
John Faris, BSc MBChB BA FANZCA
Christopher Sobey, BSc PhD

Fellows
Katia Barbaro, BSc MSc PhD São Paulo
Jennifer Callaway, BSc PhD Monash
Fiona Carroll, BSc PhD Monash
Kim Connelly, MB BS FRACP
Grant Drummond, BSc PhD
Trisha Jenkins, BSc PhD Monash
Nichole Jones, BSc PhD Monash
Ajay Kumar, MB BS FANZCA
Nadine Levick, MB BS MPH Baltimore FACEM FRACGP
Forbes McGain, MB BS
Vasilios Nimorakiotakis, MB BS FACEM
Andrew Nash, BSc PhD
Ross O'Shea, BSc PhD
Rebecca Ritchie, BSc PhD Adel
Malcolm Shepherd, PhD BSc MB ChB MRCP UK
David Sidebotham, MB ChB FANZCA
Mark O'Shea BSc PhD UK
Simon Jensen, BSc MSc MSChB Dunedin NZ

Teaching in Pharmacology

TEACHING STRUCTURE AND SUBJECT COORDINATORS FOR 2007

SCIENCE
BSc
BBiomedSci
BOptom

Second Year — 534-201: G Mackay

Third Year
- 534-301: MJ Lew
- 534-302: J Ward
- 534-304: J Ziogas
- 534-305: GP Anderson
- 534-306: RA Hughes
- 534-311: C Wright (discontinued)

Optometry — 534-307: J Ziogas

Honours & Postgraduate Diploma in Science
534-496 &
534-497: RA Hughes & P McIntyre

MEDICINE DENTISTRY & HEALTH SCIENCES
MB BS
BDSc
BPhysio

Medical Curriculum & Advanced Medical Science
510-210: OL Woodman

Dentistry — 511-323: J Ziogas

Nursing — 534-401 & 534-402: G Mackay

Graduate Diploma in Drug Evaluation & Pharmaceutical Sciences
534-802: A Frauman & J Ziogas

Postgraduate Diploma in Perioperative and Critical Care Echocardiography
534-825: C Royse

VETERINARY SCIENCE
BVSc

Second Year — 250-218 & 250-219: EM Tudor

The Department of Pharmacology contributes to the undergraduate teaching of degrees in Science (BSc and BSc(Hons)), Biomedical Science (BBiomedSci), Medicine (MB BS and BMedSci), Dentistry (BDSc), Physiotherapy (BPhysio), Optometry (BOptom) and Veterinary Science (BVSc). In addition, we contribute to teaching in the Masters of Nursing. The details of these courses may be obtained from the University of Melbourne Handbook of Undergraduate Courses at: http://www.unimelb.edu.au/HB/

Science and Biomedical Science

The Department of Pharmacology offers a number of subjects to students as part of the BSc and BBiomedSci courses. These units may be taken in combination with subjects from other Departments such as Physiology, Anatomy and Cell Biology, Biochemistry and Molecular Biology, Pathology, Microbiology and Immunology, and Chemistry. Students wishing to study pharmacology at the undergraduate level as part of the BSc or BBiomedSci degree begin by taking Pharmacology (534-201) in second year. This unit — the basis for all further studies in pharmacology — comprises a combination of lectures and practical classes. In the third year of the BSc and BBiomedSci degrees, the Department offers a selection of subjects consisting of a combination of lectures and practical classes:

Cellular and Molecular Pharmacology (534-301) is the foundation for study in this discipline, covering the mechanisms of drug-receptor interactions, handling of drugs by the body and the pharmacology of the autonomic nervous system, intracellular signalling and autacoids.

Neuropharmacology (534-302) is concerned with the action of chemical transmitters and drugs in the nervous system.

Pharmacology of Therapeutic Substances (534-304) deals with the use of drugs in the treatment of a variety of systemic diseases.

Toxicology (534-305) introduces students to mechanisms by which drugs and other chemicals exert toxic effects in living systems.

Drug Discovery (534-306) describes approaches used in the discovery of new pharmacological agents.

Drug Development Techniques (534-311), introduces students to pharmacological techniques used to evaluate actions of potential drug candidates in vitro and in vivo. This subject will be discontinued in 2008.

Bachelor of Science (Honours)

Students who major in pharmacology and achieve Faculty Honours in third year, (usually second class honours or higher), are eligible to enrol in the fourth year Bachelor of Science (Honours) course (BSc(Hons)). This additional year of study is centred around an original research project carried out under the supervision of a member of the academic staff. As well as participating in the ongoing research conducted in the Department of Pharmacology, students attend lectures and seminars in advanced topics in pharmacology and recent advances in research. Assessment is by a number of formats: a thesis describing the results of the student's research, oral presentations and written assignments spread through the year.

Medicine

The Department of Pharmacology contributes to the problem-based learning (PBL) curriculum in Medicine. This curriculum is systems-based – the Department contributes teaching in the form of lectures and practical laboratory exercises, as well as providing PBL tutors for small group teaching, throughout the first 5 semesters. Furthermore, the Department is directly responsible for the co-ordination of the third semester of the course (510-210 Cardiorespiratory and Locomotor Systems), while individual staff members head some of the teams that develop the weekly problems which form the basis of the PBL approach. Thus, in an integrated context, medical students learn the principles of drug action, as well as therapeutic use of drugs and their side effects – a foundation of the safe and effective clinical use of drugs.

Advanced Medical Science

As part of the medical course, students enrol in Advanced Medical Science to undertake a year of supervised research. Similar to students participating in the BSc(Hons) program, students who choose to do a project in the Department of Pharmacology will carry out a one year original research project under the supervision of an academic staff member.

Dentistry

As part of the third year of the Bachelor of Dental Science degree, students are required to undertake a unit where Pharmacology is taught together with Pathology and Oral Health Sciences. In this unit, students are introduced to the principles of drug action and disposition, and the molecular and functional rationale behind the treatment of a variety of diseases. This knowledge is vital to the effective use of therapeutic agents that will be prescribed or otherwise encountered during clinical dental practice.

Physiotherapy

Pharmacology contributes to components of the Physiotherapy course. The aim of the course is to provide students with a background to the mechanism of action and adverse reactions of drugs that are most likely to be used by patients treated by a physiotherapist. The subject covers the principles of drug action and disposition as well as the actions of drugs on the cardiovascular, respiratory, nervous and skeletal muscle systems.

Optometry

Ocular Pharmacology (534-307) is taught in the third year of the Optometry course. The aim of the subject is to make the students aware of the basic mechanisms of drug action with specific emphasis on drugs used in optometry and that might impact on their work as optometrists.

Veterinary Science

Pharmacology is taught second year (250-218 & 250-219) Veterinary Pharmacology and Toxicology to students in Veterinary Science. Over the two units, students are taught the mechanisms of drug action, particularly as they relate to their use in veterinary practice, and the principles and pharmacology of intoxications.

Practical Class

The Department of Pharmacology provides undergraduate students with the opportunity to complete a variety of tasks to complement their lecture material in science, medicine, veterinary science, dentistry and optometry. The laboratory is a multimedia teaching environment, equipped with organ baths and other experimental equipment. It has networked computer systems for data collection and access to teaching resources such as computer simulations.
The laboratory has capacity for up to 60 students per class in sessions lasting up to 6 hours. Academic staff are supported by postgraduate students, acting as demonstrators, and technical assistants in these classes. Undergraduate students work either independently or in teams to complete assessable tasks. In obtaining their experimental results, the students gain skills in time management and learn to critically analyse experimental design and their own data. They also develop confidence in the written and oral presentation of material. The student benefits from these activities in acquiring a variety of generic skills and specific pharmacological knowledge.

Student performance and teaching outcomes are constantly monitored through self-appraisal tasks in multimedia packages, and traditional teacher assessment of written reports and tests. Students also give oral presentations encompassing experimental results or reviews of relevant literature. As another alternative to written reports, data obtained during a practical class is sometimes presented as a poster using a similar format to a scientific conference presentation.
In order to illustrate aspects of the principles of pharmacology and mechanisms of action of both therapeutic substances and toxic agents, classes utilise a variety of experimental modalities:

In vitro pharmacology - Classical organ bath experiments are performed on various tissue preparations of cardiac muscle and gastrointestinal, vascular, and bronchial smooth muscle. Students work in small groups to perform these tasks and interpret their results as the experiment progresses.

As well as tissue practicals, other in vitro pharmacology assays utilise subcellular fractions to examine the role of enzymes in pharmacokinetics, and membrane fragments containing receptors to perform pharmacodynamic analyses and interpret ligand-receptor interactions.

In vivo pharmacology - Students have the opportunity to do some experimental work on live animals. Following ethical guidelines approved by the Animal Ethics and Experimentation Committee of the University, students examine the effects of various drugs on parameters such as blood pressure and heart rate, respiration rate and airway tone.

In order to demonstrate the mechanism of action of some pharmacological agents, students voluntarily ingest agents such as a β-adrenoceptor antagonist and subsequently measure and record various cardiovascular parameters (blood pressure, heart rate, skin temperature, etc).

Multimedia teaching of pharmacology can enhance certain learning objectives, and is employed to allow students access to experimental protocols that are not feasible in a teaching environment, and to minimise the use of animals. Several resources have been developed in this Department with these specific goals in mind. Interactive computer-aided learning packages cover important principles of drug delivery, distribution and elimination, and allow the students to observe aspects of behavioural pharmacology in response to drugs not normally available in the laboratory. The potential toxicity of a drug is now illustrated using images of tissue samples obtained previously, which allow quantitative on-line analysis of the effects of the drug on the immune system. These alternative modes of delivery can overcome problems with animal handling and inappropriate interpretation of responses due to student inexperience, significantly enhancing learning outcomes.

Honours & AMS Students 2007

Honours Students 2007

Shand, Francis H.W.: The mechanism of macrophage modulation by 2-methoxyestradiol
Ong, Siau Chi: Collagen fibrils attenuate mesenchymal cell phenotypic modulations
Koid, Suang Suang: Lyn and Dok-1 as negative regulators of mast cell function
Hunt, Liam Cambell: The effects of leukaemia inhibitory factor on myogenic cells
Li, Xin: Mechanisms of matrix remodelling by airway smooth muscle
Chan, Jiaying Linda: Design, synthesis and pharmacological characterisation of novel inhibitors of EphA4 signalling
Ting, Karen: Beta-adrenoceptor agonist and IL-6 generation from human airway smooth muscle
Samijono, Dian Wulandari: Nitrolipids as potential modulator of 17beta-estradiol signalling
Bogeski, Marijana: Role of serotonin-1A receptors in schizophrenia: Prepulse inhibition studies in mice
Leo, Chen Huei: Effect of 3', 4'-dihydroxyflavonol treatment on vascular function in streptozotocin-induced diabetic rats
Hartley, Brigham J: Investigating the potential functional dimerisation of RXFP1 and RXFP2, the cognate receptors for relaxin and INSL3
Tan, Christina Yan Ru: Effects of N-linked glycosylations on the function of human TRPV1 and TRPV4 channels

Top honours Student
Christina Tan

Honours & AMS Students 2007

AMS Students 2007/8

Patricia Ky
Fahmi Abdul Jalil
Andrew Huynh
Sahaila Mohamad Bharoraji
Ran Li
Mohd Fakhry MD Nnor
Rizq Fazzali Abdul Raes
En'en Tong

Francis Shand (right) accepts high commendation for his poster at the ASMR conference in December 2007

Achievements:

This year, the award for the top Honours student in Pharmacology was presented to Christina Yan Ru Tan (P McIntyre's Laboratory).

Francis Shand was nominated to attend the U21 conference in Montreal where he presented his work from his Honours year. He also received a high commendation for his poster at the ASMR meeting.

Dian Samijono & Suang Suang Koid were finalists in Poster Prize at ASCEPT Conference in Adelaide.

Ran Li (AMS student with Ken Winkel - AVRU Lab) won 3rd place in the Anatomy Department "Under the Coverslip" Competition for his photo "Holey Apparition". (picture on page 15)

Francis Shand and Catherine Downes are continuing their research careers as PhD students with their former Honours Supervisors.

POSTGRADUATE STUDIES IN PHARMACOLOGY 2007

Upon completion of the BSc(Hons) degree, students achieving high H2A or higher grades may be accepted to undertake postgraduate studies toward the MSc (two years study) or PhD (three years study) degrees. In addition, candidates for these degrees are often graduates of Science or Medicine from other universities in Australia or overseas. The student conducts research in the laboratory of a member of the academic staff and becomes a member of the research team.
Students regularly report the results of their research to their supervisory panel, as well as through departmental seminars and at national and international scientific conferences. Assessment is based on the submission of a major thesis which is assessed by national and overseas experts in the field of research.

The Department offers a range of support to assist postgraduate students. There is a postgraduate student room in the Department, where each student has 24 hour access to a desk and computer facilities. To assist in the presentation of the results of their research, the Department offers financial support to students to attend a national scientific conference each year and one international conference, usually in the second or third year of study. Students are encouraged to take advantage of the range of facilities and services offered by the School of Graduate Research such as counselling, health, careers and employment, and childcare.
A normal prerequisite to undertaking studies at this level is financial support in the form of a scholarship, for example from the University, Government or foundations that support research.

Nursing

In collaboration with the School of Nursing, a Pharmacology and Therapeutics unit (534-401/501) at Masters level was introduced in 2003. The aim of the unit is to provide students with a fundamental understanding of the processes of drug action and the major groups of therapeutic agents. This knowledge is critical to an understanding of the use of therapeutic agents, and in extending clinical practice, particularly with the emergence of Nurse Practitioners.

Graduate Diploma in Drug Evaluation and Pharmaceutical Sciences

The Graduate Diploma in Drug Evaluation and Pharmaceutical Sciences expands the knowledge base of pharmacists, scientists and physicians in the pharmaceutical industry and regulatory bodies with respect to basic pharmacology, toxicology, pharmaceutical sciences, quality control issues, clinical trial methodology and interpretation, and therapeutics as they relate to drug evaluation. The course is available to graduates with a degree in medicine, pharmacy or science, or applicants with other approved qualifications. The course is also available as a distance learning program for international students who do not wish to undertake the course on campus.

Postgraduate Diploma in Perioperative and Critical Care Echocardiography

The Post-Graduate Diploma of Perioperative and Critical Care Echocardiography (PGDipEcho) is an entirely distance-based diploma designed to provide medical specialists such as anaesthetists or intensive care physicians with the knowledge base to become expert in echocardiography. Students are sent interactive tutorials and workbooks, which contain the text and audiovisual material to illustrate the echocardiography images. Students can complete the course over one or two years. The first cohort were enrolled in 2004, and all 30 full-time students completed their diploma successfully. In 2007, we have 30 students completing their diploma, and a new cohort of an additional 60 students. The course was set up and developed using a steering committee of experts from across Australia and New Zealand, with approximately 60 people contributing with tutorials or case studies. As a measure of its importance, the Australian and New Zealand College of Anaesthetists has granted it recognition as a qualification in the highest category for echocardiography - “that a graduate of the diploma is suitably qualified to be a “supervisor of training in echocardiography”.

PhD Students 2007

Theses Passed 2007

Budzyn, Klaudia: Importance of Rho-Kinase in blood vessel function
Diwakarla, Lakshimi Prashanti: Mitochondria, reactive oxygen species and neuronal apoptosis
Farso, Mark Christopher: Molecular and cellular pharmacology of type III metabotropic glutamate receptors
Gresle, Melissa Michelle: Investigation and pharmacological modulation of white matter damage following transient forebrain ischemia in rats
May, Lauren Therese: Allosteric modulation of G protein-coupled receptors
Smith, Nicola Jennifer: G protein-coupled receptors and activation of growth factor receptors
Zagami, Chrissandra Julia: Strategies for the management of neurodegeneration: Studies in a transgenic model of motor neuron disease

Theses in Progress 2007

Andrews, David Tomas: The effects of anaesthetic agents on ischaemia-reperfusion injury
Chan, Sheau Pyng Jamie: Targetting macrophage growth factors in COPD
Chiu, Cindy Hsin-Yi: Animal models of inherited human epilepsies
Choy, Kwok Ho: Neurodevelopmental aspects of schizophrenia
Chu, Percy Wai Yin: Mechanisms involved in tolerance to neuronal injury
Datla, Srinivasa Raju: Modulation of vascular NADPH oxidase in vivo and cardiovascular disease
Donald, Amanda: Selective inhibition of G protein signalling by membrane-permeable peptide inhibitors
Jackman, Katherine Ann: Nox4 derived reactive oxygen species and neuroprotection following ischaemia stroke
Joshi, Anjali: Effects of chronic flavonol treatment on endothelial function in normal and diabetic rats
Jani, Nitya Vipin: Investigating novel angiotensin II receptor antagonists
Khau, Thippadey: Identification of molecular targets of 2-methoxyestradiol using chemical biology approaches
Koulis, Christine: Role of protease-activated receptor-2 (PAR2) in skin graft rejection
Lau, Chew Ling: Roles and regulations of glutamate transporters in neurodegenerative disease
Lilja, Andrew Robert: Therapeutic stem cells
Liu, Kenneth Wing-Kee: Acquired somatic mutations in the molecular pathogenesis of COPD
Lohman, Rink-Jan: Role of PAR2 in brain of genetic epileptic rats and epileptogenesis
MacDougall, Phoebe Eleanor (Chemistry): Improved anti-inflammatory steroids: Introduction of radical scavenging activities.
MacLaren, Graeme: Strain rate imaging as a means of assessing ventricular function and its application during open heart surgery
Morfis, Maria Nikolau: Characterisation of the interaction of class II G protein-coupled receptors and receptor activity-modifying proteins
Prior, Larissa Jane: Cardiovascular consequences of obesity
Qin, Chengxue (Helena): Structure/activity relationships of novel synthetic flavanols
*Reid, Amanda: Evaluation of cardiac function using pressure-volume loops in the rat
Ryan, Olivia Marlene: Molecular mechanisms of G protein-coupled receptor cross-talk
Soeding, Paul Francis: The assessment of levosimendan on myocardial systolic and diastolic functions using pressure-volume loops
Tan, Heneu Ong: Characterisation and analysis of a novel mouse model harbouring a human epilepsy mutation
*Tan, Hock Meng: Role of neuropeptides in the regulation of appetite
Tan, Xiahui: Exploring the effects of thiazolidinediones on Lung Fibroblasts and Alveolar Epithelial cells stimulated by profibrotic cytokines
Wallis, Nicole: Neuropharmacology of oxidative and exicototoxic injury to spinal motoneurons
Wan, Li: Mechanisms of acute renal failure in septic shock
Williams, David John: Snakebite morbidity and mortality in Papua New Guinea: a prospective clinical and epidemiological study of the clinical syndromes of envenomation and the determinants of poor clinical outcomes
Xia, Connie: New anti-allergic drugs based on the enigmatic actions of the chromones
Yap, Suwan (Chemistry): Synthesis and evaluation of ionizable flavonols for vascular disease
*Masters

A few of our postgraduate students. Left to Right: A Lilja, N Jani, A Bhaskaracharya, XH Tan, C Downes, F Shand, T Khau, C Xia, J Chan.

Members of the Department regularly contribute to items in the media. These contributions are important in helping educate the public about drug-related issues, a key component of the Department "Knowledge Transfer" duties.

In 2007, contributors included:

Our Research Higher Degree student, Mr David Williams who is studying with the Australian Venom Unit was interviewed by 60 minutes "The Venom Hunters" on 25 February, 2007. David is currently studying snakebites in Papua New Guinea. David Williams was also awarded best student presentation and Dr Ken Winkel awarded the ACTM Medal of Outstanding Contribution to Tropical Medicine at the Annual Scientific Conference of the Australian College of Tropical Medicines in Townsville.

P McIntyre was interviewed by Red Symons on 774 ABC Radio and an interview via podcast on www.brainsmatter.com on 6/11/2007 - Episode 47 - Taste and Pain Part 1 and 13/11/2007 - Episode 48 - Taste and Pain Part 2. Peter talked to them about how we sense pain, the different types of pain, and their relationship to taste.

Dr Rosa Gualano accepted an invitation from Koonung Secondary College to be 'Principal for a Day' in August 2007. She was a former student of this school, and her visit was part of a national program co-ordinated by the Australian Council for Educational Research. She was interviewed by Katherine Smith from The University of Melbourne Voice (Vol 1. No. 16, 15-29 October 2007) on the "Complexities of a school principal's day".

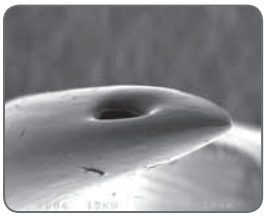
GA Anderson (Lung Disease Laboratory) & MJ Morris (University of New South Wales) had extensive news coverage of their paper: Hui Chen, Michelle Joan Hansen, Jessica E Jones, Ross Vlahos, Gary Anderson, and Margaret J Morris, Detrimental metabolic effects of combining long term cigarette smoke exposure and high-fat diet in mice, in the American Journal of Physiology and Endocrinology and Metabolism (October 16, 2007). The article was featured on National Nine News; The Sydney Morning Herald "Smoking doesn't keep fat off: study" October 29, 2007 - 9:16AM; The Age. "Smoking burns muscle not fat," November 6, 2007 - 9:49AM, News.com.au "Smoking does not keep you slim – study" October 23, 2007 and FoxNews.com "Study: Smoking does not aid weight loss."

Dr Joakim Ek Research Fellow, (Developmental Neuroscience lab) was awarded the Solander Fellowship to work in Lund (Lund University) during 2007.

Pharmacology staff were again recognised by their peers with the following awards:

Dr Jane Ward was awarded Best Oral Presentation in the Interstitial Lung Disease Assembly from the meeting of the Asia Pacific Society of Respirology.

Mr Ran Li, AMS student from AVRU lab won 3rd prize in Anatomy "Under the coverslip" for his image "Holey Apparition".



Holey Apparition Ran Li

Dr James Ziogas led a team of 10 academics from around the country that was awarded a Carrick (Now Australian Teaching & Learning Council) Discipline-Based Investigation entitled "Ensuring Quality Graduates in Pharmacology." The aim of the project will be to undertake a national survey of pharmacology teaching in Australia to provide an overview of teaching in this discipline area. The project will also undertake a needs analysis of identified stakeholders with respect to the teaching of pharmacology.

The survey results will be used to develop the discipline of Pharmacology and enhance student learning outcomes by:

-identification of good pharmacology learning & teaching practices;
-comparison and benchmarking of pharmacology courses nationally and internationally;
-determining how the discipline in this region is addressing international trends and issues in pharmacology education.

In addition the group will work closely with the ASCEPT Education special interest group to establish an Australian Pharmacology & Therapeutics Education Network (APTEN) to foster a supportive environment that will improve the efficiency and effectiveness of teaching and the quality of the student learning experience. Specifically APTEN will provide the opportunity to:

-Share teaching resources and expertise;
-Encourage professional development;
-Promote good teaching practice;
-Improve the scholarship of teaching through research and evaluation.

Pharmacology seminar series 2007

A/Prof. Simon Cowell
Nuclear Medicine
School of Medical Sciences, RMIT
What microSPECT/CT animal imaging can do for pharmacology?

Dr James Bailey
Department of Computer Science
The University of Melbourne
Data mining and its possible uses in pharmacological data analysis

Dr Mark Connor
University of Sydney
Direct cannabinoid modulation of sensory neuron ion channels

Prof Mike Hubbard
Department of Pharmacology
A proteomics voyage from teeth to new drug targets

Prof Geoff Head
Baker Heart Research Institute
Does the sympathetic nervous system contribute to angiotensin dependent hypertension?

Dr Simon Bailey
Faculty of Veterinary Science
University of Melbourne
The effects of cooling on cutaneous blood vessels: role of the alpha2C adrenoceptor

Prof Luke O'Neill
Head, School of Biochemistry & Immunology
Trinity College, Dublin, Ireland
Toll-like receptor signalling in inflammatory and infectious diseases

Dr Larbi Gallagha
AMBION
siRNA and miRNA: Current research uses and potential downstream applications

Dr Samantha Richardson
School of Medical Sciences, RMIT
From transthyretin evolution to spinal cord regeneration: adventures with marsupials

Dr Alice Pebay
Centre for Neuroscience & Department of Pharmacology
University of Melbourne
Maintenance of pluripotency of human embryonic stem cells (hESC) by sphingosine-1-phosphat (S1P) and platelet-derived growth factor (PDGF): regulation by intracellular signalling pathways

Prof Dick Cotton
Genomic Disorders Research Centre
University of Melbourne
Human Variome Project

Dr Benjamine Kile
WEHI
The molecular control of platelet life span

Prof Mal Horne
Howard Florey Institute
Regeneration of nigral neurons

Special Seminars:

Emeritus Professor Geoff Burnstock
Autonomic Neuroscience Centre
Royal Free and University College Medical School
Rowland Hill Street, London UK.
Autonomic Neurotransmission: 60 years since Sir Henry Dale

Dr Stuart Hirst
Reader in Respiratory Cell Pharmacology
King's College London School of Medicine
MRC & Asthma UK Centre in Allergic Mechanisms of Asthma
UK
Synthetic responses of airway smooth muscle in asthma - The London Experience

Professor Roy Jackson
Monash University
Chemists interacting with Pharmacologists,
Some Examples and a Search for Future Collaboration

Special Lecture:

Prof Newman Stephens
Professor of Physiology & Program Director
Smooth Muscle Research, University of Manitoba
Smooth muscle cell differentiation.

Newman Stephens is Professor of Physiology and Program Director, Smooth Muscle Research at the University of Manitoba.
He has made many seminal contributions to smooth muscle physiology and cell biology over a long and distinguished career. His recent interests include identification of asthma-related changes in gene expression and function in airway smooth muscle. This work and new studies in pulmonary hypertension are using state of the art techniques to probe cross-bridge cycling.
Prof Stephens has received many honours and distinctions over his career spanning more than 50 years, and in 2005 received the Joseph Rodarte Award for lifetime contribution to the American Thoracic Society.

Workshop & Special Lecture

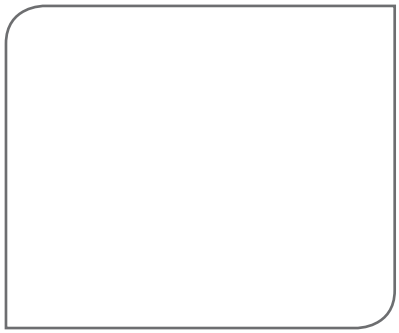
In conjunction with: The Walter and Eliza Hall Institute of Medical Research

Mina J Bissel, PhD
Distinguished Scientist, Life Sciences Division
Faculty, Comparative Biochemistry, UC Berkeley
Ernest Orlando Lawrence Berkeley National Laboratory
Berkeley, California, U.S.A.

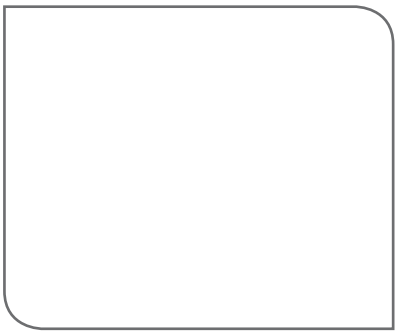
From 3D models to therapy: Putting the mammary gland and breast cancer in context

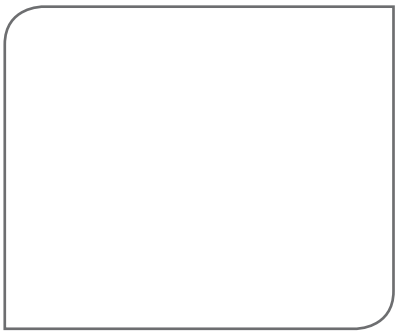
Dr Bissell is a pioneer in the area of the role of extracellular matrix (ECM) and microenvironment in regulation of tissue-specific function with special emphasis in breast cancer, where she has changed some established paradigms. She earned an A.B. with honors in chemistry from Harvard/Radcliffe College and a PhD in bacterial genetics from Harvard University. She joined the Lawrence Berkeley National Laboratory in 1972, became Director of Cell & Molecular Biology in 1988, and was appointed Director of all of Life Sciences in 1992.
Upon stepping down as the Life Sciences Division Director, she was named Distinguished Scientist. She is also the OBER/DOE Distinguished Scientist Fellow in Life Sciences. Dr Bissell has authored more than 280 publications, is member of 5 international scientific boards, and is on the editorial board of a dozen scientific journals, including Science magazine. She has given more than 80 'named and distinguished' lectures. Her awards include the Lawrence Award and Medal, the Mellon Award from the University of Pittsburgh, the Eli Lilly/Clowes Award from AACR, the first "Innovator Award" of the US DOD, the Brinker Award from Komen Foundation, the Discovery Health Channel Medical Honor and Medal, the H. Lee Moffitt Cancer Center Ted Couch Lectureship and Award, the Pezcoller Foundation–AACR International Award for Cancer Research, and she has been awarded the 2008 Excellence in Science Award from FASEB. Dr Bissell was elected as a Fellow of AAAS, the Institute of Medicine of the National Academies, the American Academy of Arts and Sciences, and the American Philosophical Society. She served as President of the American Society of Cell Biology and the International Society of Differentiation. She has received honorary doctorates from Pierre & Marie Curie University in Paris and the University of Copenhagen.

Lecture also included a workshop:
Workshop with Dr Mina Bissell
Extracellular matrix and phenotype in development and pathophysiology
Co-conveners, Prof Alastair Stewart and Dr James Ziogas organised a workshop with special guest Dr Mina Bissell - a leading international cell biologist in matrix and phenotype regulation. This workshop seeked to generate an increased awareness of common interests in matrix and phenotype regulation amongst diverse research groups. Workshop participants were encouraged to make brief, informal presentations to stimulate discussion.
Topics discussed included:
1. Epithelial mesenchymal transition;
2. Estrogen and breast tumour epithelial cell function;
3. Matrix degradation and invasion.



Research Laboratories





Anaesthesia & Pain Management Unit

The Anaesthesia and Pain Management Research Unit (AMPRU) is a new unit located within the department of Pharmacology to represent the teaching and research interests of the disciplines of anaesthesia and pain management within the University of Melbourne.

A/Prof Colin Royse

Director

A/Prof Colin Royse, MBBS, MD (Melb), FANZCA
Contact: colin.royse@unimelb.edu.au
www.heartweb.com.au

University of Melbourne affiliated institutions:

The following departments of anaesthesia and pain management are affiliated with the University of Melbourne
Austin and Repatriation General Hospitals
Ballarat Hospital
Barwon Health
Goldburn Health
Mercy Hospital
Northern Hospital
Royal Children's Hospital
Royal Melbourne Hospital
Royal Victorian Eye and Ear Hospital
Royal Women's Hospital
St Vincent's Hospital
Wangaratta Hospital
Western Hospital

Honorary Appointments to Department of Pharmacology

Dr David Andrews
Dr Ioana Arhangelschi
Dr Andrew Bjorksten
A/Prof Duncan Blake
Dr Christopher Bolton
Dr Malcolm Brown
A/Prof David Crankshaw
Clin A/Prof Andrew Davidson
A/Prof Michael Davies
Dr Alicia Dennis
Dr Garry Donnan
Dr John Faris
Dr Geoffrey Frawley
Dr Roman Kluger
Dr Ajay Kumar
A/Prof Kate Leslie
Dr James Love
Dr Desmond McGlade
Dr Andrew Nash
Dr Ni Rhuizi (visiting academic)
A/Prof David Scott
Dr David Sidebotham
Clin A/Prof Scott Simmons
Dr Paul Soeding
A/Prof David Story
Dr Michael Veltman
Dr Konstantin Yastrebov
Dr Garry Donnan

Honorary appointments aims

The aim of AMPRU is to facilitate teaching and research efforts for the discipline of anaesthesia and incorporating pain medicine and perioperative medicine.

Evolution of group

The structure of the group and the teaching and research sub-committees are in evolution. Honorary appointments to the unit are encouraged from anaesthetists wishing to contribute to the University teaching and research efforts.

Website

www.pharmacology.unimelb.edu.au

Australian Venom Research Unit

Research Laboratories

Website
www.avru.org

Collaborators

Prof Joan Ozanne-Smith, Monash University
Prof Lohi Matainaho, University of PNG
A/Prof James Harrison, Flinders University
A/Prof Wayne Hodgson, Monash University
A/Prof Peter Fenner, James Cook University
Dr Angel Yanighara, University of Hawaii
Dr Lisa-ann Gershwin, Marine Stinger Advisory Services
Dr Vincent Atua, Modilon Hospital, Madang, PNG
Dr Kevin Markwell, University of Newcastle
Capt Al Cruz, Miami Dade County Fire Rescue, Florida, USA
Mr Tim Carroll and Rachel Jensen, CSL Limited
Mr Lex Lucas, Australian College of Rural and Remote Medicine
Mr Martyn Kirk, OzFoodNetwork, Australian Government
Mr Russell Hore, Quicksilver Connections, Port Douglas

Funding/Awards

Commonwealth Department of Health and Ageing
Australia Pacific Science Foundation
University of Melbourne Collaborative Grant Scheme
Snowy Nominees

Key References

- Hobbins, P.G., & Winkel, K.D. (2007) 'The forgotten successes and sacrifices of Charles Kellaway, Director of the Walter and Eliza Hall Institute, 1923–1944.' Med. J. Aust. 187: 645–648.
- Nair, D.G., Fry, B.G., Alewood, P., Kumar, P.P., Kini, R.M. (2007) 'Antimicrobial activity of Omwaprin, a new member of Waprin family of snake venom proteins.' Biochem. J. , 402: 93-104.
- Nimorakiotakis, V. (2007) 'How to treat: snakebite – part one' Rural Doctor, November.
- Steuten, J., Winkel, K., Carroll, T., Williamson, N.A., Ignjatovic, V., Fung, K., Purcell, A.W. & Fry, B.G. (2007) 'The molecular basis of cross-reactivity in the Australian Snake Venom Detection Kit (SVDK).' Toxicon 50: 1041-52.
- Williams, D.J., Jensen, S.D., Nimorakiotakis, B., Muller, R. and Winkel, K.D. (2007) 'Antivenom use, premedication and early adverse reactions in the management of snake bites in rural Papua New Guinea.' Toxicon 49: 780-92.

2007 was year of transition for the Australian Venom Research Unit (AVRU) as we faced staff changes and a review of our major funding by the Australian Government. Firstly, concerning staff changes, Dr Bryan Grieg Fry left the Unit to commence his QEII Fellowship at Bio21, and Dr Roger Lowe replaced him as Deputy Director (Research). We look forward to Roger's new foray into terrestrial invertebrate venoms as well as continuing his leadership of knowledge transfer activities. Our team received a boost in mid-year with three University of Melbourne AMS students joining us to tackle various venom research projects. During the year, one of these AMS students, Ran Li was awarded third place in the Faculty student photography contest. Ran also organised a successful jellyfish collecting expedition to northern Australia late in the year. His project, in collaboration with the Wright/Angus laboratory, was assisted by a very generous donation from a benefactor with a strong interest in the Irukandji syndrome. A second AMS student, Patricia Ky, reinvigorated our venom bioinformatics collaboration with Professor Vladimir Brusic, now at the Dana Farber Cancer Institute in Boston. Patricia spent the last few months of 2007 in Boston working on this important project. Our third AMS student, En'en Tong initiated a project on Australian scorpion toxins.

Another great personal achievement was the promotion, late in 2007, of Dr Bill Nimorakiotakis (Deputy Director Clinical) to become Deputy Director of the Epworth Hospital Emergency Department. Bill was also appointed as a consultant to Care Flight (Queensland), strengthening our links with Queensland Health. Bill continued our collaboration with the Australian College of Rural and Remote Medicine (ACRRM), convening the second AVRU Australian toxinology course in April 2007 and continuing the development of ACRRM's TeleTox on-line distance education module. In July, at the Annual Scientific Conference of the Australasian College of Tropical Medicine (ACTM) in Townsville, AVRU and Nossal Institute PhD Scholar, David Williams, was awarded the prize for the best student presentation. At that same meeting AVRU Director Dr Ken Winkel was awarded the ACTM Medal for Outstanding Contribution to Tropical Medicine. After being featured on '60 Minutes' in February, David expanded his educational activities during 2007 with new toxinology teaching courses being run in Milne Bay and Oro Provinces. Also in mid-year our links with the Nossal Institute were further strengthened by the award of the inaugural Melbourne Business School-Nossal Institute MBA student Internship to Ms Zeenat Patrawala. Zeenat, a Cornell University Alumni, joined us in mid-year to assist in developing a business case for the advancement of the PNG snakebite project, especially the proposed University of PNG-based National Antivenom Unit. She spent time with David in PNG and Thailand progressing various aspects of this project. Through Zeenat's work, the AVRU is providing a bridge between the Business School and the Nossal Institute, an exemplar of how global health is everyone's business.

Concerning funding, after several presentations in Canberra, we successfully reapplied for support from the Australian Government Department of Health and Ageing. Indeed, additional funding has been provided for 2007-2008 to expand AVRU personnel and activities, including a children's book – due for distribution in early 2008. Further, a new grant was obtained from the Australia Pacific Science Foundation to address snake taxonomic studies in PNG. This project achieved rapid success with a paper in press by years end concerning the origin of the PNG brown snake. Our international students, Larissa and Laura, completed their projects and were replaced by two new international students. From Krems University Austria, Bernard Radinger, undertook collaborative studies with Professor Nik Petrovsky on venom-related cytokine responses. Lilly Bellman, from Brandeis University, Boston, undertook elective research on US snake bite mortality. This work, presented by Lilly, was awarded the student poster prize at the "Venom Week" research meeting in Tucson, Arizona, in August. Late in the year, Dr Michelle Philander (Royal Melbourne Hospital) successfully completed her research training as part of the requirements of the Australian College of Emergency Medicine (ACEM). Her presentation, on brown snake fatalities, received national media coverage when presented at the ACEM summer conference. Joint AVRU-University of Sydney Masters Student, Peter Hobbins, successfully completed his thesis on Charles Kellaway, and published his first paper in the Christmas edition of the Medical Journal of Australia. Finally, in December, a very generous member of the public finalised the first bequest designed to benefit future AVRU students.

Australian Venom Research Unit

Venom Research

The AVRU undertakes basic research into venoms of importance to Australia and the region in the context of establishing and maintaining a National Reference Collection of venom toxins. In doing so we seek venoms and toxins with novel activities that may have potential for new drug discovery or as investigational tools to aid in basic and applied medical research. This complements our efforts to develop new, and improve existing, antivenoms and antitoxins in association with existing biotechnology and pharmaceutical companies.

Advisory Service and Public Health

The Unit provides advice and teaching to medical and paramedical professionals as well as to the general public on the prevention and management of bites and stings. It also carries out national and international surveillance and analysis of venomous bite and sting mortality and morbidity. This includes the analysis of the burden and determinants of severity of such injuries. This work is funded by the Commonwealth Department of Health and supported by CSL Limited.

Clinical Research

As part of its research activity, AVRU investigates the clinical presentation and management of venomous bites and stings. This work is focused on snakebite in Australia and the Asia-Pacific. The AVRU contributes to the undergraduate and postgraduate training of medical and paramedical staff in research on venomous bite and sting injuries and their management. It also aims to enhance the evidence base underlying contemporary recommendations in the prevention and treatment of venomous bite and sting injuries through direct clinical research and the analysis of appropriate animal models. The Unit also provides expert advice and diagnostic services for the investigation of ante-mortem and post-mortem cases of suspected snakebite.

Group

Dr Ken Winkel, Director
Dr Roger Lowe, Research Fellow, Deputy Director (Research)
Mr David Williams, Nossal Institute PhD Scholar
Ms Zeenat Patrawala, Master of Business Administration Student (Melbourne Business School)(from June 2007)
Ms Laura Greisman, Fulbright Scholar (Cornell University) (until July 2007)
Mr Peter Hobbins, Masters of Medical Humanities Student (Sydney University)(from July 2006)
Ms Larissa Kern, Occupational trainee (from Krems University, Austria)(until February 2007)
Ms Patricia Ky, Advanced Medical Science Student (from July 2007)
Mr Ran Li, Advanced Medical Science Student (from July 2007)
Ms En'en Tong, Advanced Medical Science Student (from July 2007)

Principal Fellows

A/Prof James Tibballs, Royal Children's Hospital
Prof P. Gopalakrishnakone, National University of Singapore
Prof David Warrell, University of Oxford, UK

Fellows

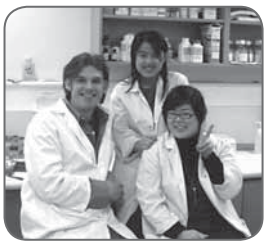
Dr Bill Nimorakiotakis, Deputy Director (Clinical), Epworth and Western Hospitals
Dr Forbes McGain, Royal Melbourne Hospital
Prof Vladimir Brusic, University of Qld and Dana Farber Cancer Institute, Boston (from July 2007)
Dr Nadine Levick, Miamonades Medical Center, NYC, USA
Dr Katia Barbaro, Institute Butantan, SP, Brazil
Dr Chris Hogan, Medical College of Virginia, USA
Dr Steven Pincus, Royal Melbourne Hospital
Dr Wolfgang Wuster, University of Wales, Bangor, UK
Dr Simon Jensen, Port Moresby General Hospital, PNG
Dr Mark O'Shea, National Institute for Research into Aquatic Habitats, UK
Dr Chris Barnes, Bundaberg Base Hospital

Anti-Allergic Therapeutics

Collaborators
Prof. Alastair Stewart
Dept. of Pharmacology, University of Melbourne
A/Prof. Margaret Hibbs
Ludwig Institute for Cancer Research, Parkville.
Prof. Mark Hogarth
Burnet Institute (Austin campus)
Dr Bruce Wines
Burnet Institute (Austin campus)
Dr Maree Powell
Burnet Institute (Austin campus)
Prof. Owen Woodman
RMIT University
Dr Andreas Lopata
RMIT University

Funding
The Asthma Foundation of Queensland- Novel anti-allergic therapies based on Fc-receptor antibodies

Projects
- Modulation of antibody Fc receptors as a strategy for anti-allergic therapy
- Negative regulators of mast cell and basophil signal transduction and degranulation
- Immunoglobulin Fc receptors on airway smooth muscle cells and fibroblasts
- Anti-allergic effects of flavonoids



Allergies and allergic disorders such as asthma are a huge health problem in Australia and the rest-of-the-world. Our laboratory aims to generate knowledge that will lead to the development of new and improved anti-allergic agents.

The antibody class immunoglobulin E (IgE) and its high-affinity receptor Fc□RI are known to be key components of the allergic process as they are able to trigger activation of potent pro-inflammatory cells called mast cells and basophils. These cells release mediators such as histamine and a variety of cytokines and lipid-derived products. The laboratory aims to develop a better understanding of the expression and regulation of Fc□RI and how to pharmacologically modulate mast cell and basophil activation.

In 2007 Connie Xia commenced her PhD project following on from a very successful honours year. Her project, jointly supervised by Prof. Alastair Stewart, aims to examine antibody Fc receptor expression on human airway smooth muscle cells and lung fibroblasts. Her work had yielded some very interesting data which demonstrates functional expression of an inhibitory IgG receptor on these cells. This finding has potential implications for the therapeutic benefit of both immunotherapy and intravenous immunoglobulin (IVIG) treatment for conditions such as asthma and we hope this knowledge may lead to more targeted treatments in the future. Connie's work was presented at a Victorian Branch meeting of the Thoracic Society of Australia and New Zealand (TSANZ). Our collaboration with the Burnet Institute has been instrumental to the success of this project.

2007 also saw collaboration with A/Prof. Margaret Hibbs and the development of new capabilities in the generation of murine bone marrow-derived mast cells (BMMCs). This project was undertaken by Honours student Suang Suang Koid and sought to unravel the interaction between the signal transduction molecules Lyn, SHIP and Dok-1 in a mast cell setting. Suang Suang had a very productive Honours year and her findings were presented at the SEAWP/ASCEPT conference in Adelaide this year where her poster was short-listed for the Whelan Prize.

The group has also recently began a more clinically focussed collaboration with Andreas Lopata at RMIT where our mast cell and basophil model systems will be used to investigate the prevalence and cross-sensitisation of seafood allergies in Australia.

Group
Graham Mackay, Lecturer & Laboratory Head
Connie Xia, PhD Student
Suang Suang Koid, Honours Student

Cardiovascular Therapeutics Unit

The Cardiovascular Therapeutics Unit has been formed by the collaboration from two laboratories – Integrated Pharmacology and Human Cardiovascular Research - which share a common focus in cardiovascular pharmacology and translation research. Although each laboratory has special interests and individual projects, the unit structure allows a project-driven approach utilising the diverse research techniques and expertise within the group. These strengths enable exciting collaborative partnerships with the pharmaceutical industry and/or contract projects with early start-up and Biotech companies eager to establish safety pharmacology and mechanism of action of novel lead compounds.

Group

A/Prof Christine E. Wright, BSc Hons, PhD, Laboratory Head
A/Prof Colin Royse, MBBS, MD, FANZCA, Laboratory Head
A/Prof Alistair Royse, MBBS, MD, FRACS, FCSANZ, Laboratory Head
Prof James A. Angus, BSc Hons, PhD, FAA, Dean, Faculty of MDHS
Ms Heather J. Daykin, BSc Hons, Research Assistant
Mrs Catherine Jones, B Appl Sci, Research Assistant (to Feb 2008)
Mr Mark Ross-Smith, BSc Hons, Research Assistant
Ms Clare Savage, BSc, Research Assistant
Ms Jenny Pang, Research Nurse
Ms Linda Cornthwaite-Duncan, Technical Officer
Ms Danielle Nicholas, BSc, Grad Dipl (Med Lab Sci), Dipl Med Ultrasound (Cardiac), Echocardiography Technologist
Mrs Marcelle Wood, Administration Officer
Mrs Kerrie Edmond, Administration Officer
Dr Paul Soeding, BSc Hons, MBBS, FANZCA, PhD student
Dr David Andrews, MBBS, FANZCA, PhD student
Dr Graeme Maclaren, MBBS, FRACP, MD student
Ms Nitya Jani, BSc (Lond), PhD student
Dr Alicia Dennis, MBBS, FANZCA, PhD student
Ms Amanda Reid, BSc Hons, MSc student (to Dec 2007)
Mr Greg Chang, AMS student (to May 2007)
Mr Ran Li, AMS student
Mr Andrew Huynh, AMS student
Dr Ni Ruizhi, B Med, M Med (Kunming, China), Honorary Fellow

Website

http://www.pharmacology.unimelb.edu.au/research/ctu.html
http://www.heartweb.com.au

Collaborators

Dr R. Newman, Western Hospital, Victoria, Australia
Dr K. Yastrebov, Mersey Community Hospital, Tasmania, Australia
Dr Kim Connelly, Sunnybrook Hospital & St Michael's Hospital, Toronto, Canada
Prof Carl Schiesser, ARC Centre of Excellence for Free Radical Chemistry and Biotechnology
Dr James Ziogas, Pharmacology
Prof Wayne A. Morrison, Bernard O'Brien Institute of Microsurgery
Dr Rod Dilley, Bernard O'Brien Institute of Microsurgery
Prof Bruce Kemp, St. Vincent's Institute of Medical Research
Prof Norman Saunders and A/Prof Kate Dziegielewska, Pharmacology
A/Prof Terry O'Brien, Dr Nigel Jones, Dr Damian Myers, Dept of Medicine
Dr Jenny Callaway, Dr Mark Habgood, Pharmacology

Funding

ARC Centre of Excellence for Free Radical Chemistry and Biotechnology
Various industry collaborations and competitive grants

Key Research Areas

Investigation of novel angiotensin II receptor antagonists for the treatment of vascular disease

A major risk factor for cardiovascular disease is atherosclerosis, which is defined by the accumulation of lipid and cholesterol deposits in the innermost layer of arteries. Atherosclerotic plaques eventually affect blood supply to the heart leading to ischaemic events such as angina and myocardial infarction. Antihypertensive drugs such as the sartan class of angiotensin AT1 receptor antagonists may also suppress atherosclerotic plaque formation. However, the association between hypertension and atherosclerosis is not fully understood and the effectiveness of the sartans may not just be due to inhibition of the renin-angiotensin system. Pathological events central to vascular disease progression include oxidative stress and subsequent inflammatory events at the site of atherosclerotic plaque formation. Over-expression of AT1 receptors contributes to the atherosclerotic process, which includes vascular remodelling in conditions of hypercholesterolaemia. In this project, within the ARC Centre of Excellence for Free Radical Chemistry and Biotechnology program, novel AT1 receptor antagonists have been modified chemically to possess additional antioxidant and cellular protection properties. These will be investigated in bioassays, in vitro and in vivo, of acute and chronic vascular disease and atherosclerosis.

Acute and chronic effects of methadone and buprenorphine on QTc prolongation and cardiac function

Methadone, generally considered a safe medication, has been used since the 1960's in the management of opioid dependence, with now over 500,000 patients treated worldwide, and over 35,000 in Australia. Although there were early reports of cardiac electrocardiogram (ECG) abnormalities amongst heroin users and methadone patients, there had been little research and no case reports of ECG abnormalities or cardiac toxicity in methadone patients until recently. Concerns regarding opioid agonists, prolonged QTc intervals and the potentially fatal ventricular arrhythmia, Torsade de Pointes (TdP), emerged following case reports of methadone patients developing TdP, as well as evidence of QTc prolongation and related cardiotoxicity. The other opioid substitution medication, buprenorphine, has also been suggested to cause adverse cardiac effects. This project is examining cardiac function (ECG and transthoracic echocardiography) and cardiovascular variables in a serial manner in methadone-, buprenorphine- or morphine-dependent experimental animals. Further experiments are being completed in isolated cardiac muscle preparations in vitro.

Cannabinoid receptor ligands in acute and neuropathic pain

Many patients with terminal cancer, other illnesses or injuries suffer chronic intractable pain. These patients may be unable to receive relief with currently available pain-relieving (anti-nociceptive) drugs, such as morphine, due to problems of dependence and tolerance. Our research is directed at the discovery of novel therapeutic agents for the treatment of chronic (neuropathic) pain. The effectiveness of novel cannabinoid CB1 and CB2 receptor ligands administered via intrathecal or peripheral routes, are being examined in the treatment of allodynia in a neuropathic pain model. Effects on acute and inflammatory pain, as well as possible cardiovascular, autonomic and/or motor coordination side effects, of these routes of administration are also being examined. In addition, current studies are investigating whether or not synergy exists between cannabinoid receptor agonists and other classes of analgesic agents – alpha2-adrenoceptor agonists and μ opioid receptor agonists. Issues of drug tolerance and cross-tolerance are being considered as well. Both peripheral and central routes of co-administration are being compared in acute and neuropathic pain in rats and mice.

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Co-Laboratroy Heads
A/Prof Colin Royse and A/Prof Alistair Royse

Key Research Areas

Our laboratory investigates cardiovascular responses to drugs in vivo using pressure-volume (PV) loops and echocardiography to obtain load-independent measurements of cardiac contractility and diastolic function. Accordingly, we are able to separate myocardial from vascular effects in vivo. Echocardiography is widely used in human clinical practice to measure cardiac function, and we have incorporated this technology to perform sophisticated measurements of cardiac function non-invasively in small animals. The current focus is on the cardiovascular and organ protection effects of anaesthetic agents using a variety of preparations, from in vitro atrial tissues (guinea pig and human), in vivo guinea pig and rat preparations and in rabbit PV loops. We aim to establish both rat and pig preparations for PV loop studies. Drugs being tested include propofol, sevoflurane, desflurane and levosimendan. As a parallel study we will study the neurocognitive effects of desflurane and propofol in a human randomised control trial (RCT) in patients undergoing cardiac surgery.

We also conduct human studies at the University of Melbourne using echocardiography in volunteers. Clinical studies focus on innovations in cardiac surgery, anaesthesia and pain management and innovations in echocardiography, which are conducted at the Royal Melbourne Hospital. Postoperative studies are examining the radial artery in asymptomatic patients. The current research projects include long term follow up of the radial artery when used for coronary artery bypass graft (CABG), using ultrasound; assessment of diastolic function post-CABG to identify if diastolic dysfunction diagnosed at the time of surgery resolves after surgery; assessment of tissue Doppler strain and tissue Doppler imaging as a measurement of left ventricular systolic and diastolic function. We have submitted grants for multicentre research (RCT) to investigate the utility of ultrasound to determine haemodynamic state in patients undergoing fractured neck of femur surgery. We will also investigate the use of ultrasound to improve safety and efficacy of regional anaesthesia.

Coagulation following cardiopulmonary bypass is a major area of interest. Following an audit project, we have submitted a grant to conduct an early intervention trial of Novoseven (activated rVIIa) to treat coagulopathy following cardiopulmonary bypass. This will be a multicentre, Level 1 RCT.

Our educational focus is in teaching echocardiography to perioperative and critical care physicians through the “Postgraduate Diploma of Perioperative and Critical Care Echocardiography”. This distance-learning course will be supplemented by hands on workshops in echocardiography for small groups with animal and human volunteer models. Faculty for the Diploma course steering committee: C. Royse, A. Royse, P. Soeding, R. Kluger, A. Kumar, M. Veltman, S. Yastrabov, D. Sidebotham, L. George and John Farris. We are also involved in both AMS (medical) and BSc Hons student research programs.

Website

http://www.heartweb.com.au

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Developmental Neuroscience

Group

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Dr Joakim Ek, Research Fellow
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Prof Klaus Unsicker, University of Heidelberg

Funding
VNI
NHMRC

Internal environment of the developing brain

This project has two main components:
Studies of transfer mechanisms into developing brain (the blood brain and blood-cerebrospinal fluid barriers) demonstrated that tight junctions at these interfaces close off the intercellular transfer even at the earliest stages of brain development. Instead, the transfer appears to be across a small proportion of choroid plexus epithelial cells with uptake into the brain from the CSF, rather than across cerebral blood vessels. Recent studies showed that protein is transferred by a different mechanism but also across a small proportion of choroid plexus cells. The next stage of the work involves molecular characterisation of these transfer mechanisms.
Effects of inflammation on brain barriers and brain development. Maternal infection during pregnancy is thought by many obstetricians and paediatricians to be a major cause of brain damage in the newborn. A mechanism of this damage has been suggested to be via an effect of increasing permeability of the blood-brain barrier. Results show that there are substantial differences in blood-brain barrier permeability following induction of an inflammatory response by lipopolysaccharide injection, at different postnatal ages. This may have important implications for brain development in the off-spring of mothers experiencing infections during pregnancy.

Mechanisms of damage and recovery after spinal cord injury

This project is a collaborative one to study the early outgrowth of nerve fibres in the immature spinal cord (opossum) following injury. Elecronmicroscopical and immunocytochemical methods are being used to define changes in the developing spinal cord that may explain the ability of the immature CNS to regenerate, a capacity that is lost later in development. Behavioural studies show correlations between the degree of functional recovery and morphological repair. State of the art molecular, proteomic and bioinformatics techniques are being used to identify genes and proteins that are involved with the promotion and inhibition of spinal cord regeneration.

Traumatic injury to the brain and spinal cord: Limiting the damage

The group is part of a consortium, the Victorian Neurotrauma Research Group, studying the inflammatory response in the early stages of brain and spinal cord injury. The aim is to develop new therapies for limiting secondary brain damage following trauma to the brain or spinal cord.

2007 Highlights

Joakim Ek was awarded the Solander Fellowship to work in Lund (Lund University) during 2007.

State of the art molecular, proteomic and bioinformatics techniques are being used to identify genes and proteins that are involved with the promotion and inhibition of spinal cord regeneration.

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The Drug Design Laboratory uses computer-aided molecular modelling techniques to drive the development of novel bioactive compounds. Following their design, candidate molecules are synthesised by members of the laboratory and evaluated in appropriate in vitro and in vivo assays. Data from these assays are then used to hone the design process, with the goal of producing more active molecules.

Mimetics of growth factors

Growth factors are naturally-occurring proteins which regulate the growth and survival of cells. Their potent biological effects make them attractive targets for the development of novel therapeutic agents for a multitude of as yet untreatable diseases. However, because of their poor pharmacokinetic properties — the physical size and chemical nature of proteins renders them highly susceptible to breakdown in the bloodstream, requires that they be injected, and limits their access to certain areas of the body — recombinant proteins themselves are unlikely to be the optimal agents for clinical use. We have developed techniques that enable us to design conformationally-constrained peptides that act as potent mimetics or inhibitors of selected growth factors. Our current projects include the inhibitors of Eph/ephrin system with potential for the treatment of spinal cord inury (in collaboration with Drs Kirsty Dixon and Dr Ann Turnley) and mimetics of the relaxin family of hormones (in collaboration with A/Prof John Wade and Dr Ross Bathgate).

Other Projects

In addition to the above projects, the Drug Design laboratory collaborates with Professor Alastair Stewart in developing three dimensional structure-activity relationships (3D-QSAR) of 2-methoxyestradiol and synthetic analogues, Professor Peter McIntyre on the synthesis of vanillotoxins and other aspects of the chemical biology of TRPV1, and Professor Owen Woodman (RMIT) and Dr Spencer Williams (Chemistry) examining structure-activity relationships of flavonols.

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Ms Thippadey Khau, PhD Student, jointly with Stewart lab
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Ms Christine Keenan, BSc Hons Student 2008
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Collaborators

A/Prof John Wade and Dr Ross Bathgate, Howard Florey Institute
Drs Kirsty Dixon and Dr Ann Turnley, Centre for Neuroscience
Prof Alastair Stewart
Prof Peter McIntyre
Prof Owen Woodman, RMIT University
Dr Spencer Williams, Department of Chemistry

Funding

Victorian Neurotrauma Initiative Project Grant: Development of EphA4 peptide inhibitors for the treatment of neurotrauma.
NHMRC Project Grant: The structural basis of the interaction of human relaxins with their receptors.
NHMRC Project Grant: The structural basis of the interaction of insulin-like peptide 3, a key regulator of fertility, with its receptor.

Ion Channel Molecular Mechanisms

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Brett A. Cromer (Heymanson Research Fellow)

Collaborators
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Prof. Graham Lamb, Latrobe University
Prof. Michael Parker, St. Vincent's Institute
Prof. James Cook, University of Wisconsin

Brief description of project/s

Ion channels have important roles in all cells but have a particularly prominent role in rapid signalling in nerves and muscle and are the targets for many clinically important drugs, including anaesthetics, anti-anxiety treatments and alcohol. We are interested in understanding the detailed molecular mechanisms underlying ion channel function, dysfunction in disease states and regulation by both physiological and pharmacological modulators. To tease apart these mechanisms and their significance we use a combination of computational molecular modelling, experimental structure-function studies of recombinantly expressed channels and animal models. Current projects include:

GABAA receptor; a) dysfunction in epilepsy, b) a target for novel steroid analgesics?

The GABAA receptor is the primary mediator of inhibitory currents in the brain that modulate neuronal activity. Mutations in GABAA receptors genes can lead to hyper-excitability and epilepsy. In collaboration with Dr Steve Petrou, we are investigating the molecular mechanisms linking the mutation to the disease. We are also investigating the molecular details of the interaction between neurosteroids and the GABAA receptor, with the goal of understanding the basis for the recently described analgesic activity of some synthetic steroids.

TRPV1 activation; a target for painful toxins?

TRPV1 was initially identified as the target for capsaicin, the "hot compound in chilies, and is important for pain-sensing, particularly sensing noxious heat. Recently, a toxin from a painful spider venom was also shown to target TRPV1. In collaboration with Peter McIntyre, we are investigating whether other painful toxins may also act on TRPV1 and their mechanism of action.

Modulation of ClC-1 by ATP; a role in fatigue?

ClC-1 has a similar role in muscle to that of the GABAA receptor in the brain, mediating inhibitory currents that modulate muscle excitability and activation. Mutations in the ClC-1 gene can lead to hyper-excitability and stiff or rigid muscles in the disease, myotonia congenita. We have shown recently that regulatory domains of ClC-1 control channel function in response to ATP (the energy currency of the cell) and acidosis, a mechanism that may be important for muscle fatigue during intense exercise. In collaboration with Graham Lamb, we are investigating further the molecular mechanism underlying this modulation and its physiological significance.

Funding
NHMRC project grant (2003-2007)
Heymanson Fellowship (2007-2010)
University of Melbourne, Early Career Researcher Grant (for 2008)

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Last 5 years:

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Immunopharmacology

Our Laboratory investigates the mechanisms and treatment of pathological tissue remodelling in asthma and other disorders. Airway smooth muscle and fibroblast growth and differentiation are central to the airway remodelling. We are also exploring new anti-inflammatory agents related to 2-methoxyestradiol (2-MEO) that also inhibit mesenchymal cell proliferation.

Airway Smooth Muscle can be stimulated to proliferate by a range of factors identified in the inflamed airways of asthmatics, including epidermal growth factor, basic fibroblast growth factor and thrombin. These growth factors increase levels of the key regulatory protein in the cell-cycle, cyclin D1, by increasing gene transcription and decreasing protein breakdown. Further definition of the pathways regulating cyclin D1 levels in airway smooth muscle may lead to identification of new pharmacological targets for regulation of excessive airway smooth muscle proliferation.

2-Methoxyestradiol is a metabolite of estradiol with low affinity for the estrogen receptor. 2-MEO is anti-angiogenic and reduces the proliferation of a number of different cell types by inhibiting the function of tubulin during formation of the mitotic spindle. 2-MEO arrests G1 progression that decreases entry of cells into S-phase of the cell cycle. Initial pre-clinical studies from other laboratories support the utility of this compound in regulating aspects of tumour growth. However, we have identified a lack of anti-tumour action in vivo in mouse models of human breast tumour, and 2-MEO has estrogenic activity that could accelerate tumour growth in some circumstances. Structure activity relationships amongst 2MEO analogues have the potential to provide new insights into the molecular targets of action of 2MEO.

Anti-remodelling activity of currently used and potential anti-asthma agents 2-adrenoceptor agonists including salbutamol inhibit DNA synthesis by arresting cell cycle progression late in G1 near the restriction point of the cell cycle, as do glucocorticoids. However, 2-agonists and other agents which increase cAMP reduce cyclin D1 protein levels by influencing its proteasome-dependent degradation, whereas glucocorticoids reduce levels by reducing mitogen-stimulated increases in cyclin D1 mRNA. Our recent work suggests that the extracellular matrix component collagen, induces resistance to some anti-remodelling actions of glucocorticoids.

Medicinal Chemistry Collaborations between our group and the Research School of Chemistry at ANU have been developed. Our goal is to develop non-steroidal nuclear hormone receptor ligands having selective and efficacy as anti-remodelling agents.

Fibrosis The extracellular matrix is expanded in fibrotic tissues. However, the ECM is not merely providing filler between cells, but also has a wide ranging impact on cell function. Our studies are examining the impact of ECM components on the efficacy of anti-remodelling agents on fibrogenic activities of fibroblasts.

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Crytopharma: Novel 2-MEO analogues

Key References

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Lung Disease

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www.pharmacology.unimelb.edu.au/research/LungDisease.html

Prizes and Awards
G.P. Anderson, Research Medal, Thoracic Society of Australia and New Zealand (TSANZ)
R. Gualano, Prize for best talk by a scientist at the annual meeting of TSANZ Victorian Branch
E.Tsantikos, Larkins Prize, University of Melbourne

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Our group is a core laboratory of the Cooperative Research Centre for Chronic Inflammatory Diseases (CRC-CID). We provide lung biology expertise. The CRC-CID (website: macrophages.com) is a national organisation of around 100 scientists focused on identifying novel therapeutic targets for chronic inflammatory disease of the lungs and joints, in partnership with AstraZeneca Pharmaceuticals. We are also supported by an NHMRC program grant on the role of innate immunity in severe persistent asthma, and three new project grants on mouse models of lung disease and its systemic comorbidities.
Our current research is centred on the macrophage biology of lung inflammation, innate immunity signalling in vivo, and mouse models of asthma and COPD including viral exacerbations of these conditions.

Research projects that are currently underway include:

Acquired somatic mutations in COPD: Not all long term smokers develop COPD. We propose that mutagens in cigarette smoke cause genetic mutations in lung epithelial progenitors that lead to tissue changes which may be a key determinant of COPD severity, exacerbation and progression.

Macrophage biology of COPD: Macrophages are the main effector cells in chronic lung inflammation but little is understood about how to limit their role in pathology without losing their essential defence capacity. Research in this area includes work on the src family kinases Hck , molecular determinants of macrophage subpopulations, differentiation and survival. The role of a variety of macrophage growth factors in the pathogenesis of COPD is also being explored.
Lyn kinase in asthma: Lyn is a src family kinase that regulates the integration and amplitude of numerous signalling pathways thought to be important in allergy and asthma.

Molecular basis of viral exacerbations of lung disease: Exacerbations of asthma and COPD are common and associated with much of the illness and costs of these diseases. They are often caused by viral lung infection but the molecular basis of this worsening is not understood.

Wasting as a COPD co-morbidity: Skeletal muscle wasting is a major COPD co-morbidity that increases suffering and reduces life expectancy but its molecular basis is not understood.
Immune subversion by cigarette smoke: although smoke causes inflammatory lung disease it also has the property of suppressing immune defences in the lung. This increases the chance of bacterial colonisation and viral infections. Research in this area is directed towards repairing the molecular defects in the lung that weaken lung defences.
Gp130 in lung fibrosis. Gp130 is a co-receptor used by a family of growth factors implicated in the development of lung inflammation and fibrosis.

The role of IL-17A in neutrophilic lung inflammation: IL-17 is a factor released from neutrophils that may have a central role in sustaining neutrophilic lung inflammation.
Proteomics of COPD: proteomic profiling methods are increasingly used to identify patterns of disease associated molecules. Work in his area includes understanding the pathways of disease exacerbations and the identification of predictive biomarkers.

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Molecular Pharmacology

The Molecular Pharmacology Laboratory was established in 2006 after Prof. McIntyre moved to the University of Melbourne from the Novartis Institutes of Biomedical Research in London. The laboratory focuses on the molecular pharmacology of receptors and ion channels involved in pain sensation. In particular, a group of thermosensitive "Transient Receptor Potential" (TRP) ion channels that help us to sense heat, cold and pain.

Hot chilies spice-up our food but they can also cause excruciating pain if they get into a cut or onto sensitive tissues. This pain is caused by the opening of the TRPV1 ion channel on the affected sensory nerves and initiating action potentials in them. TRPV1 is also activated by noxious heat and by low pH solutions and it is a marker for pain-sensing or "nociceptive" nerves. The "polymodal" activation of TRPV1 makes it a major target for drug companies trying to make new types of pain-killing drugs. Prof. McIntyre's group was the first to show that antagonists of TRPV1 are effective in reversing inflammatory and neuropathic hyperalgesia in experimental models [1]. They have since developed orally available TRPV1 antagonist which could prove to be effective in humans [2]. The TRPV1 ion channel is regulated at multiple levels. It expression on the surface of nerves is controlled by phosphorylation and probably also by interacting proteins, it ability to open in response to agonist is under feedback control by calcium-dependent mechanisms to either sensitize or desensitize the channel to activators (also involving phosphorylation). We are interested in understanding how this ion channel and its close homologue TRPV4, is trafficked to the cell surface and how phosphorylation acts as a molecular switch to sensitize and desensitize these channels to agonists. We also use species differences to dissect important functional regions of the channel [4].

Working together with the group of Ardem Patapoutian in San Diego, we identified one novel and two "orphan" TRP channels. This exercise revealed the existence of the heat –activated TRPV3 [5] and the cold-activated TRPM8 [6] and TRPA1 (formerly anktm1) [7].

We are currently studying the post-translational modification of TRP channels and the molecular mechanisms controlling sensitization of this ion channel to agonists and thermal stimulation. We are currently particularly interested in two areas: 1) desensitization and activation of the heat-activated ion channels, TRPV1 and TRPV4 and the cold-activated ion channel TRPM8 [3] and 2) Involvement of TRP ion channels in the hippocampus (with Dr D. Bowser).

The laboratory also has broad interests in ion channel expression in mammalian cell systems for analysis of multi-subunit ion channel function.

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Funding
University of Melbourne "NH&MRC near miss" grant. Faculty of Medicine, Dentistry and Health Sciences, set-up grant.

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Neuropharmacology

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Victorian Trauma Foundation
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Projects for Honours and PhD
- How a pro-oxidant state and increased reactive oxygen species affect cellular signal transduction systems.
- The role of oxidative stress in the regulation of Interleukin-6 and implications for neurological disease.
- The involvement of the Toll-Like Receptor family in the progression of neural inflammation and neural injury.
- Genomic profile of the brain after traumatic brain injury.

Oxidative stress and Neural Injury

The major focus of our laboratory are the mechanisms that underpin the progression of neural injury. The causes of neural injury are multifactorial so our laboratory's research is focused on the role that oxidative stress and reactive oxygen species (ROS) play in the predisposition and/or progression of neural injury. Rather than serving solely as harmful by-products of aerobic metabolism, it has become apparent that ROS have a much broader role in the regulation and co-ordination of cellular homeostasis. ROS are used to fine-tune cellular signaling and play an important role in the transduction of message along specific signal transduction pathways. In the event of oxidative stress, which is associated with varied human diseases including neurological disorders, the persistent inactivation of signal transduction pathways by ROS may lead to reduced or ablated, sustained or elevated cellular signaling and predispose or otherwise contribute to disease pathology. In understanding how signal transduction systems are regulated by oxidative stress and ROS we can gain a better understanding how new generation therapeutics can target these pathways in the hope to reduce and or prevent neuronal pathology.

Innate Immunity and Neural Injury

A major new area of research in our laboratory is the role that the innate immune system plays in the progression of neural injury. It is now appreciated that the central nervous system (CNS) does exhibit features of inflammation, and in response to injury, infection or disease, resident CNS cells generate inflammatory mediators, including proinflammatory cytokines, prostaglandins, free radicals and complement, which in turn induce chemokines and adhesion molecules, recruit immune cells, and activate glial cells. Cerebral ischemia triggers acute inflammation, which exacerbates primary brain damage. Activation of the innate immune system is an important component of this inflammatory response. The innate immune system uses a newly discovered family of receptors to transducer its' signal called the Toll-like receptors (TLRs). The roll that the TLR's play in the progression and response to neural in jury is an exciting and emerging field of research. The molecular mechanisms that are influenced by the TLRs comprise new targets for therapeutic intervention into acute neurological conditions such as stroke and neurotrauma and chronic neurological diseases such as multiple sclerosis and Parkinsons disease.

Stroke

Stroke is the leading cause of long-term disability in adults and ranks as the third leading cause of death after heart disease and cancer. Approximately 80% of all strokes suffered are ischemic, resulting from artery occlusion and causing absent perfusion at the core of the infarct and hypoperfusion at the margin of the blood vessels territory (penumbra). The extent of neurological damage following stroke and the severity of the neurological sequelae depend on the viability of the hypoperfused penumbra and also on whether artery occlusion is transient, resulting in reflow (reperfusion). Hypoperfusion and reperfusion is accompanied by the production of reactive oxygen species (ROS) or free radicals at an enhanced rate. In turn, ROS trigger molecular pathways that lead to necrosis, apoptosis and neuroinflammation with subsequent neuronal loss and consequent disability. The devastation of stroke could be greatly ameliorated if therapies were available to salvage these potentially viable neurons. Therefore the molecular pathways that are involved in ROS generation and neuronal cell injury following ischemia are a prime target for the development of improved therapies.

Traumatic Brain Injury

Traumatic brain injury (TBI) represents the major cause of death in young individuals in industrialised countries. Despite the improvement of neurosurgical procedures as well as critical care management, morbidity and mortality are still high and approximately 25% of these patients remain with permanent disabilities becoming a familiar, social and economic burden for society. A better understanding of events occurring in the brain after traumatic brain injury is essential to identify ways to limit the damage and ultimately improve the outcome. The advent of microarray technology has given the researcher the ability to potentially identify the regulation of thousands of genes and enables a broad assessment of gene changes after traumatic brain injury. With the backing of the Victorian Trauma Foundation we have undertaken a microarray study to determine a temporal profile of gene changes in the brain after TBI. This data is being used to understand the molecular pathways that are changed in the brain after TBI.

Paracrine Control Systems

We have developed an alternative view as to roles of protease-activated receptors (PARs), particularly those located on barrier cells of the body – the epithelial and endothelial cells – that are often faced with potentially harmful environments. We believe that PARs located on these 'frontline' cells act as sensors of inflammation and respond by activating a range of anti-inflammatory mechanisms that in concert provide an 'umbrella' of protection of both the barrier cells themselves and the underlying tissues. We have already demonstrated that airways epithelial PAR2, and to a lesser extent PAR1, are bronchoprotective. From these and other studies, we have proposed that selective activation of barrier cell PARs represent new strategies for anti-inflammatory therapies. Honours student Christine Koulis is investigating the role of PAR2 in the inflammatory skin disorders and skin grafting.

Dr Cocks and Dr Devlin are involved in a start-up company, Pargenex Pharmaceuticals Pty Ltd, operating within the Department that has developed new anti-inflammatory drugs for a variety of diseases. As well as producing structure-activity profiles on these novel synthetic PAR agonists using an assay of cell calcium mobilisation, Pargenex is also testing their therapeutic potential in mouse models of colitis, arthritis and asthma.

Ongoing techniques in our laboratories include immune cell trafficking, epithelial ion transport, smooth muscle reactivity, receptor turnover, in vivo and in vitro measurements of vascular and airways smooth muscle reactivity, confocal immunohistochemistry, enzymography and Ca2+ fluorescence imaging.

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Funding

NH&MRC: Two concurrent project grants

Funding
Melbourne Research Unit for Facial Disorders: Fellowship/RF (MH/JM); project support (FA)
NHMRC Project: Active transport of calcium across dental enamel cells – testing a new paradigm
NHMRC Project: Probing developmental causes of soft tooth enamel with novel mouse models
NIH Project: Molecular signals for trafficking surfactant protein B (subcontract)
Dentsply Project: Are antibiotics a risk factor for developmental defects of enamel?

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A. CALCIUM TRANSPORT

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B. PROTEOMICS

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C. ERp29

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Our research focuses on fundamental questions about the mechanisms used by cells to handle calcium safely, and particularly how cytotoxicity is avoided in the calcium-transporting cells that produce dental enamel. Protein chemistry and proteomics are used extensively in this work, with applications ranging from biological discovery through to elucidating the function of a novel protein (ERp29) and drug toxicology. A second role of our group is to facilitate translational research within the recently formed Melbourne Research Unit for Facial Disorders (MRUFD). Comprising a broad variety of clinicians and researchers from the Royal Children's Hospital, School of Dental Science and elsewhere, the MRUFD exists as an academic network supporting craniofacial and orodental science locally. Current MRUFD projects involving our lab are proteomics-based investigations of facial development and malformed tooth enamel.

Our three main research avenues are:

Transcellular calcium transport – a new paradigm

Transport of calcium across cell layers plays a key role in many tissues (e.g. gut, kidney, mammary, lung, oviduct, teeth and bones). Our studies of dental enamel-forming cells have contradicted the dogma of a cytosolic-ferry based mechanism and instead suggested a "calcium transcytosis" pipeline involving calcium-tolerant organelles. We are using pharmacological and genetic (knockdown, knockout) approaches to study this new idea. Many medical benefits would accrue from an improved ability to manipulate transcellular calcium transport.

ERp29 – a novel chaperone in the Endoplasmic Reticulum

We discovered ERp29 during proteomic analysis of dental enamel cells and, with others, have gone on to reveal a broad biomedical significance of this ubiquitous Endoplasmic Reticulum (ER) resident protein. Several projects underway with local and overseas collaborators are aimed at elucidating the functional activity of ERp29 and its role in various diseases. As a novel chaperone involved in producing secretory and membrane proteins, ERp29 is a potential drug target for protein-misfolding diseases (e.g. cystic fibrosis, diabetes, Alzheimer's) and cancer.

Soft tooth enamel – pursuing the causes and new modes for prevention

Defective hardening of enamel can increase the risk of dental caries and lead to major pain, disfigurement and treatment costs. Recently the incidence of such defects has increased disturbingly, possibly due to side-effects of drugs commonly given to infants. To test this and also explore ways of strengthening tooth enamel developmentally, we have developed two novel animal models for investigating the combined effects of drugs, fluoride, genotype and diet. This research could ultimately lead to diagnostics and prevention modes that benefit dental health broadly.

Group

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Dr Steve Shnyder, University of Bradford, UK
Dr Joost Hoenderop, Radboud University, Nijmegen, The Netherlands
Dr Susan Guttentag, Children's Hospital of Philadelphia, USA

Brief description of project/s

The laboratory is currently focused on investigating novel aspects of 3 distinct receptor systems. The long-standing interest in angiotensin receptor pharmacology remains a key focus of the laboratory. Antagonists of the AT1 receptor have become effective therapeutic agents in cardiovascular diseases. In collaboration with Carl Sciesser and James Angus we are investigating the potential of novel selenium containing angiotensin receptor antagonists to determine if they have an improved profile of activity in a range of cardiovascular diseases.

Investigation of the growth promoting properties of angiotensin II stimulated collaboration with Professor Alastair Stewart on the properties of an orphan G-Protein coupled receptors GPR3. This protein had 20-30% sequence homology with GPCRs for a variety of chemoattractants and peptides including the high affinity IL8 receptor and the angiotensin II AT1 receptor, however none of the known peptide ligands for these receptors showed affinity for GPR30. We are investigating the possibility that GPR30 may play a role in tissue remodelling processes and may be involved in the non-genomic actions of oestrogens.

In collaboration with Professor Peter McIntyre, we are investigating changes in the sensitivity and activation properties of the transient receptor potential (TRP) channels TRP channels are a super-family of cation selective ion channels that are involved in many sensory functions. We are focusing on the temperature-sensing TRP channels that are recognised top play an important role in pain sensation. We are interested in determining how specific post-translational modifications of the TRPV1 and TRPV4 channels modulates their structure and function.

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ARC Centre of Excellence for Free Radical Chemistry and Biotechnology

Key References

TARA E. SUTHERLAND, ROBIN L. ANDERSON, RICHARD A. HUGHES, EMILE ALTMANN, MICHAEL SCHULIGA, JAMES ZIOGAS & ALASTAIR G. STEWART. 2-Methoxyestradiol - a unique blend of activities generates a new class of anti-tumour/anti-inflammatory agents. Drug Discovery Today, (in press).

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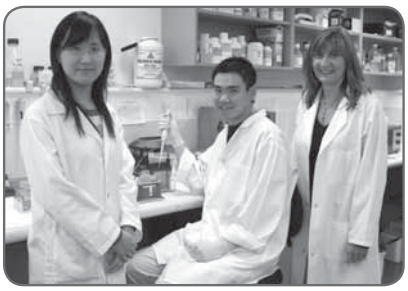
Respiratory Pharmacology



Current research focuses on the role of the peroxisome proliferator-activated receptor gamma (PPARgamma), a ligand-activated transcription factor, in the regulation of changes in lung structure and function that occur during the development of asthma and lung fibrosis (Ward and Tan, 2007). Recent publications from the group have established that the PPARgamma ligand, rosiglitazone inhibits cell proliferation and the release of mediators of inflammation from human airway smooth muscle cells (Ward et al., 2004). Significantly, rosiglitazone also reduces airways hyperresponsiveness in a mouse model of asthma (Ward et al., 2006).

Studies on the mechanism of these actions in smooth muscle, fibroblasts and epithelial cells have recently been expanded through both local and international collaborations. The Respiratory Pharmacology group has acquired the expertise to synthesise novel drugs to target PPARgamma (with Dr Hutton), to establish a murine lung slice model for studies of airway contractility and calcium signalling (Professor Sanderson), and to examine airway smooth muscle synthetic functions in the disease context (Dr Hirst). Additionally, a new project exploring the potential of airway cells to remodel the extracellular matrix, using an in vitro floating collagen gel model, forms the basis for an exciting new avenue of research.

Group

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Australian Lung Foundation
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Key References

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Stem Cell Laboratory (Centre for Neuroscience)

Major Lab Interests

•Signalling pathways involved in human embryonic stem cell maintenance of pluripotency

•Differentiation of neural stem cells derived from human embryonic stem cells

•Lysophospholipid biology

Brief description of project/s

1) Signalling pathways involved in the pluripotency of human embryonic stem cells; Involvement of lysophospholipids in stem cell biology:

The discovery of human embryonic stem cells (hESC) opened up many exciting new opportunities to further investigate the basic biology as well as the therapeutical potential of stem cells in general. The signalling pathways involved in hESC self-renewal are still poorly characterized and their understanding remains a challenge.

We previously demonstrated that the combination of sphingosine-1-phosphate (S1P) and platelet-derived growth factor (PDGF) is sufficient, in the absence of serum, to maintain hESC undifferentiated and pluripotent (Pébay et al. 2005). This discovery has allowed us to work in a chemically defined environment suitable to dissect more precisely the signalling mechanisms involved in hESC maintenance and/or differentiation, proliferation and death.

Sphingosine-1-phosphate (S1P) and lysophosphatidic acid (LPA) are bioactive lysophospholipids that are released by activated platelets and present in serum. These lysophospholipids act on a wide range of cells and regulate numerous cellular functions, including proliferation and differentiation, from the early stages of embryonic development. Most of their effects are mediated by specific G-protein-coupled receptors: S1P1-5, LPA1-5. There is now increasing evidence of their role in stem cell maintenance or differentiation. This project focuses on the understanding of the signalling pathways activated by S1P and LPA in hESC.

Differentiation of neural stem cells derived from hESC:

Neural stem cells (NSC) can be easily derived from adult and fetal tissue, as well as directly differentiated from embryonic stem cells. In the human, the signalling factors and mechanisms that regulate NSC maintenance and their further differentiation into neural and glial progenitor subtypes still remain largely unknown. The use of hESC neural derivatives may provide important breakthroughs in medical research by providing cultured human cells that can be used as in vitro models to study neurodegenerative disorders. If hESC are to be used to study of early human neural development and disease, it is essential to understand the key pathways involved that regulate hESC neuronal differentiation.

In our laboratory we have established an in vitro model of human NSC differentiation. Using a range of culture systems, we can monitor the various stages of neuronal differentiation from hESC to mature neurons and glia, which is very useful for exploring the signals involved in regulating this process. Our major aims are to 1: Direct differentiation of hESC towards specific neural lineages, including neural crest derivatives 2: Identify key factors that regulate hESC neural differentiation. For the latter aim, our focus has been on two different gene families that are both known to play important roles in neuronal differentiation: the canonical Wnt gene family and the SoxB1 gene family of transcription factors. Our studies together with past studies in mouse, have demonstrated the canonical Wnts and the SoxB1 transcription factors are significant extrinsic and intrinsic signalling factors, respectively, that regulate neural differentiation from ES cells. From these studies we can regulate hESC neural differentiation and derive specific neural cell types to be used for further research and clinical studies.

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Technique used

- Cell culture
- Neural differentiation assays
- Proliferation assays
- Apoptosis and necrosis assays
- Migration assays
- ELISA
- Immunostaining
- Western-blots
- FACS analysis
- RT-PCR
- Transfection
- Lentiviral transduction
- Chick embryo transplants

Recent publications

Pébay A* Wong R*, Koh K, Nguyen L and Pera M. (2004). Presence of Functional Gap Junctions in Human Embryonic Stem Cells. Stem Cells 22 (6), 883-889. *: equal first authors.

Pébay A* Wong R*,Pitson S, Wolvetang E, Peh G, Filipczyk A, Koh K, Tellis I, Nguyen L and Pera M. (2005). Essential roles of sphingosine-1-phosphate and platelet-derived growth factor in the maintenance of human embryonic stem cells. Stem Cells 23, 1541-1548. *: equal first authors.

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Pébay A, Bonder C and Pitson S (2007). Stem cell regulation by lysophospholipids. Prostaglandins & other lipid mediators, 84(3-4), 83-97.

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Pera M and Dottori M. Stem cells and their development potential. (2005) In: Stem Cells From Bench to Bedside. A. Bongso and EH Lee, Editors. World Scientific Press

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Dottori M and Pera M.F. Neural differentiation of human embryonic stem cells. (In Press) In: Methods in Molecular Biology, Neural Stem Cells, Second Edition. L.P.Weiner, Editor. The Humana Press Inc.

Davidson K, Dottori M and Pébay A (2008). Human embryonic stem cells: key characteristics and main applications in disease research. Cell Applications in Diseases. M. L. Sorensen Editor. Nova Science Publishers.

Wong R and Pébay A (2008). Signaling pathways involved in the maintenance of human embryonic stem cells. Leading-Edge Stem Cell Research. P. S. Koka Editor. Nova Science Publishers

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Website
www.pharmacology.unimelb.edu.au/research/TheoreticalEmpirical.html

Statistical publications

Lew, 2006. When there should be no difference – how to fail to reject the null hypothesis. Trends in Pharmacological Sciences 27: 274-278.

Software to perform the equivalence test described in the above paper can be downloaded from <http://www.pharmacology.unimelb.edu.au/statboss.html>

Lew, MJ, Good statistical practice in pharmacology. Problem 1. Br J Pharmacol. 2007 Oct;152(3):295-8.

Lew, MJ, Good statistical practice in pharmacology. Problem 2. Br J Pharmacol. 2007 Oct;152(3):299-303.

The main research focus of this small research group is advanced statistical analysis of conventional biomedical experiments. Recently I have devised a novel method of sequential analysis that offers the promise of allowing increased experimental power or a reduction in the number of experimental replicates necessary for a reliable result. Sequential analyses are fairly widely used in the analysis of clinical trials results, but my approach is novel in its simplicity and offers the substantial advantage over other approaches of being completely generalisable.

Most biomedical researchers have never even heard of sequential analyses, much less applied them, but my approach is simple to implement. It may even sound similar to the (flawed) usage of conventional analyses that some researchers use already...

Two approaches to experimental analysis

The conventional approach

1. Choose a type 1 error rate, α, that you are comfortable with. (Almost invariably people choose 0.05.)
2. Decide on an effect size that is big enough to care about, or from preliminary experiments estimate how big an effect you expect to find.
3. Estimate from preliminary experiments the degree of variability to expect in the data. Alternatively you can guess the variability on the basis of experience, historical data or simple intuition.
4. Decide on the power you want the experiment to have to detect an effect of the size that is big enough to matter to you, or that you expect to find. Usually people choose a power of 80% or more, corresponding to a type 2 error rate, β, of 20% or less.
5. Perform a power analysis to determine the number of samples, n, that you will need to satisfy the criteria set above.
6. Run the experiments and collect the specified number of samples.
7. Analyse the results and decide whether to accept or reject the null hypothesis on the basis of the P value obtained.

An alternative, sequential approach

1. Choose a type 1 error rate, α, that you are comfortable with. Almost invariably people choose 0.05.
2. Decide on the minimum number of samples that you are prepared to use, nmin, and the maximum number of samples that you are prepared to invest in, nmax.
3. Run the experiments to gather nmin samples, and analyse them to obtain P.
4. If the P value exceeds a threshold then stop the experiments and accept the null hypothesis. If the P value is less than another threshold then stop the experiments and reject the null hypothesis. Otherwise, go on to the next step.
5. Run the experiment again to obtain one more sample in each treatment group, and analyse again to obtain another P value.
6. Go back to two steps. (The protocol automatically terminates at or before nmax.)

If you are a practising laboratory researcher, it is quite likely that the conventional approach will sound only vaguely realistic. Rarely do experimenters to follow the steps in anything like the formal manner presented even though experimenters who use animals may describe the outcomes of step 5 in their ethics applications. Most often the choices of power and effect size are not declared at the design stage, and the number of samples to be obtained is decided on the basis of habit or convention. It is also quite common for experimenters to 'check out the data' with undeclared interim analyses, and to alter their experimental design in response to the interim results either by stopping the experiments early or by increasing the number of samples in an effort to 'chase' a significant outcome. Unfortunately, such adhoc interventions in the experimental design lead to inflated type 1 error rates, and can substantially reduce the quality of any scientific inference drawn from the outcomes.

In contrast to the above, the steps in the alternative approach may sound surprisingly familiar despite the fact that the method is relatively novel. The iterative cycle of adding new data and reanalysing is quite similar to the informal process described in the paragraph above, but it doesn't render the outcomes invalid by inflation of the type 1 error rate. The sequential analyses are a feature of the experimental design rather than being ad hoc interventions, because the P thresholds used in step 5 are chosen to ensure that the type 1 error rate is maintained at the nominal level. The use of pre-determined stopping rules in the sequential design prevents the accumulation of type 1 errors beyond the desired level. The number of samples that will be needed is not known exactly in advance, but it will always be between nmin and nmax.

Thus we have two contrasting approaches to experimental design—one that is conventional and valid, but tends to suffer in practice from inappropriate on the fly modifications that rob it of validity, and one where on the fly adjustment of the number of samples is essential. Which should laboratory researchers use? Should they eschew interim analyses and apply the conventional approach more rigidly or should they switch to the novel sequential analysis approach? The answers to those questions depend on the relative power or efficiencies of the two methods. Investigation using Monte Carlo simulations so far have shown that the novel approach offers improvements in analytical efficiency in the range of 10 to 40%, and so it is possible that it will be widely adopted before the end of this century.

Vascular Pharmacology

In the Vascular Pharmacology laboratory we are interested in the regulation of vascular tone, the influence of disease on vascular reactivity and potential pharmacological strategies to improve vascular function. A major focus of our work is investigation of the ability of flavonoids to induce vasodilatation and to selectively enhance nitric oxide (NO) mediated dilatation.

Flavonoids are polyphenolic compounds that are found in fruits and vegetables. In populations with a diet high in fruits and vegetables there is a lower incidence of coronary artery disease and that effect has been linked to the beneficial actions of flavonoids. We are examining the mechanism of the vasodilator actions of flavonoids and their ability to prevent ischaemia-induced vascular dysfunction. Our studies thus far suggest that flavones, flavonols and isoflavones upon acute administration are able to inhibit the utilisation of calcium leading to smooth muscle relaxation but that this occurs only at relatively high concentrations. At lower concentrations, the flavones and flavonols exert antioxidant effects that lead to enhanced NO-mediated dilatation. By contrast, chronic treatment with isoflavones may increase the activity of endothelial nitric oxide synthase (eNOS) enhancing endothelium-dependent vasodilatation.

The vascular endothelium is an important source of powerful vasodilators such as NO, endothelium-derived hyperpolarising factor (EDHF) and prostacyclin (PGI2). The relative importance of these agents in regulating blood flow to the heart and other organs may be influenced by coronary artery disease. We have demonstrated that upon reintroduction of blood flow to a vascular bed that has been ischaemic (no blood flow) for some time there is a reduction in resting blood flow, in comparison to pre-ischaemic levels, and an impaired ability of the arteries to respond to vasodilator drugs. That vessel dysfunction may be due to damage to the endothelium or accumulation of leukocytes (white blood cells) that attach to the endothelium and block blood flow. In collaboration with Drs May and Thomas at the Howard Florey Institute, we are investigating the effects of myocardial ischaemia and reperfusion on cardiac and coronary vascular function. This work has led to the establishment of the start-up company, NeuProtect Pty Ltd, with work continuing at the Department of Pharmacology, University of Melbourne and the Howard Florey Institute. Investigation into the synthesis of new flavonoids that will optomise the beneficial actions of the naturally occurring compounds is being conducted in collaboration with Dr Spencer Williams and Dr Tony Hughes.

With Dr Rebecca Ritchie (Baker Institute), isolated cardiac myocytes are being used to model the effects of ischaemia and reperfusion and hypertrophy with a view to developing novel means to reduce cardiac injury. Recent studies have demonstrated that the plant-derived polyphenol resveratrol may effectively reduce reperfusion injury.

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NeuProtect Pty Ltd
Melbourne Research Grants Scheme

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Current Projects

Bone Cell Biology- Intracellular signalling in response to thrombin treatment of osteoblasts

(In collaboration with Professor Mackie's Bone Cell Biology Laboratory)

Bone diseases such as osteoporosis result from alterations in the balance of activity of bone-forming cells (osteoblasts) and bone-resorbing cells (osteoclasts). It is therefore of critical importance to understand the factors that influence the number of osteoblasts available for bone formation, and how they can be manipulated pharmacologically.

As well as its role in haemostasis and thrombosis, thrombin acts as an agonist for a number of cellular responses. Thrombin treatment of osteoblasts has been shown to stimulate proliferation and inhibit differentiation and programmed cell death (apoptosis) of treated cells. Previously we have shown that thrombin inhibits osteoblast apoptosis by a mechanism involving the secretion of a second diffusible survival factor. Further experiments have identified prostaglandins, produced by cyclooxygenase-2 (COX-2), as candidate mediators of the effect of thrombin on osteoblast apoptosis.

Using tissue culture techniques, this project aims to characterise the sequence of events leading to prostaglandin production and its role in inhibiting osteoblast apoptosis.

Bone Cell Biology- the Role of Tenascin-C in Bone Remodelling and Repair

(In collaboration with Professor Mackie's Bone Cell Biology Laboratory)

Tenascin–C is an extra-cellular matrix protein with multiple roles in regulation of cell behaviour in a variety of tissues. It is secreted by osteoblasts and present on bone surfaces. We are studying the role of this protein in oestrogen dependent bone turn over. Histomorphometric analysis is being conducted on bone samples collected from wild type and tenascin-C null ovariectomised mice and ovariectomised mice that have received supplemental oestrogen.

Using a bone repair model developed in our laboratory, bone healing is being compared in tenascin-C null mice and their wild type littermates.

Bone Cell Biology- The direct in vitro effects of anti-epileptic drugs (AED's) on stromal osteoblasts and myoblasts. We propose that certain AED's cause a decrease in bone mass, bone mineral density and bone mineral content by altering the balance between bone formation and resorption via mechanisms involving the coupling of mesenchymal stromal osteoblasts and haemopoietic osteoclasts, which lead to an increased fracture risk. We also propose that certain AED's can alter body mass through direct actions on skeletal muscle precursor cells or myoblasts.

The general aim of this research is to assess the direct in vitro effects of AED's on stromal osteoblasts (OB) and myoblasts (MB) grown in culture.

Muscle Cell Biology- myoblast extracellular matrix and the role of osteopontin in muscle cell biology

(In collaboration with Professor Mackie and Drs White and Pagel: Muscle Cell Biology Laboratory)

Maintenance of muscle strength throughout life and regeneration after injury relies on the population of skeletal muscle specific precursor cells called myoblasts. Muscle cell repair and renewal may be limited by the capacity of these myogenic cells to differentiate or by the size of the myogenic cell population. Our laboratory is studying the role of specific extra cellular matrix proteins in myoblast survival, differentiation, migration and adhesion.

Muscle Cell Biology – the Effects of Leukaemia Inhibitory Factor (LIF) on Myogenic Cells These studies are investigating the effects of LIF on myoblasts, the myofiber forming myogenic precursor cells. More specifically aspects of proliferation, apoptosis and differentiation are being explored using numerous techniques that examine cell viability, DNA synthesis, activation of apoptotic pathways, and transcriptional regulation of genes associated with myogenesis and apoptosis.

Clinical studies of the neurosteroid anaesthetic- alfaxalone

Alfaxalone is a neurosteroid anaesthetic that is widely used for the induction of anaesthesia in dogs and cats. It has not previously been evaluated for induction and maintenance of anaesthesia by constant infusion (TIVA).

During 2006-7 we conducted a clinical trial to evaluate the efficacy and safety of alfaxalone in a TIVA protocol in dogs. Two cohorts of dogs were enrolled, one in a field setting in a remote aboriginal community, the other in a private suburban veterinary practice.

This was extended in 2007 to investigate whether alfaxalone provides a pre-emptive analgesic effect on post-operative hypersensitivity and pain in a clinical setting following ovariohysterectomy in dogs.

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This publication covers the activities of the Department through 2007.
Listed for each laboratory are current staff at December, 2007.

FRONT COVER PHOTOGRAPH CREDITS:
Roger Lowe (Research Assistant in the AVRU Unit) - Scanning Electron Microscope image of the venom injecting hole of the fang of a Huntsman spider taken at x400 magnification
Alice Pebay (Lab Head of Stem Cell Lab) - Human neurons derived from human embryonic stem cells
Shane Liddelow (PhD Student in Developmental Neuroscience Lab) - Monodelphis ribcage

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