

JULY FEATURE ARTICLE

Hypertension Research at Monash Pharmacology in 2005

This month's Hypertension feature article focuses on hypertension-related research carried out within the Department of Pharmacology at Monash University that is performed by four main groups. In addition to the cardiovascular research, as featured in this article, the department performs research on a number of fronts including G-protein coupled receptors and relaxin (Professor Roger Summers), confocal microscopy and placental function (Associate Professor Roger King), Australasian venom research (Associate Professor Wayne Hodgson), neuropharmacology and neurodegeneration (Dr Richard Loiacono) and methods of pharmacological teaching (Dr Elizabeth Davis).

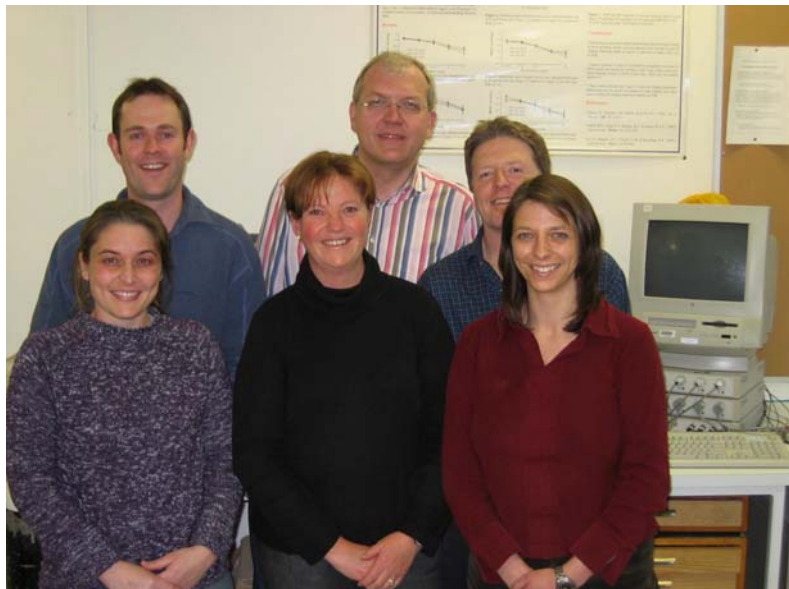


PHOTO: Hypertension Researchers at Monash Pharmacology.
Back row- Grant Drummond, Harald Schmidt, Robert Widdop
Front row- Emma Jones, Tracey Gaspari, Barbara Kemp-Harper.

In 2005, Professor Harald Schmidt was appointed Head of Pharmacology, which complemented existing research within the department. Professor Schmidt was previously Head of the Department of Pharmacology at the Justus-Liebig-University in Giessen, Germany, and his research interests are nitric oxide, cyclic GMP and reactive oxygen species in vascular biology and disease. Professor Schmidt brings a molecular and biochemical focus and an ideal fit to the classical pharmacological approaches that are already well-established at Monash for studying *in vitro* and *in*

vivo cardiovascular function. He will be joined by several German fellows moving with him from Gießen, Frankfurt and Magdeburg. As a former co-head of a Vascular Centre of Excellence at his home university and a Max-Planck-Institute, he is working on setting up several European-Australian research links, including postgraduate research training programs and program grants.

This newly formed international team of vascular pharmacologists at Monash aims at establishing a Centre for Vascular Biology and Medicine in Melbourne, with a distinct focus on vascular disease mechanisms, early diagnostics and innovative mechanism-based therapeutic approaches. Such research endeavours will be headed by the Department of Pharmacology at Monash and its international and Industry links and shall include other high-profile cardiovascular groups within Monash University (notably groups within the Department of Physiology, Biochemistry and Clinical Departments) as well as Greater Melbourne researchers from other workplaces with a similar research focus. Intense collaborations of this Centre with Australian groups and related Centres is also encouraged in order to help making Australian high blood pressure research in general a big player in the world-wide scene. As a first initiative, the Departments of Pharmacology and Physiology will be hosting a meeting entitled 'Frontiers in Vascular Medicine' which will bring together a range of outstanding international and national speakers on August 26-28, 2005. For more details or to register for this event. Please see the following website:

<http://www.conferences.monash.org/fvm>

Free Radical signalling Laboratory

Professor Schmidt heads this laboratory which consists of 4 post doctoral fellows who will be arriving at the end of 2005, and he is expecting to develop an active postgraduate student base as

well as international exchange programs and bi-national and international program grants. Projects include genetic models of vascular signalling enzymes, subcellular protein-protein interaction and protein trafficking, target validation in vascular oxidative stress, modulators of cGMP and early diagnostics. In all these projects, tight links with clinical scientists are essential in order to validate findings in a medical relevant setting.

Vascular Pharmacology Laboratory

Dr Barbara Kemp-Harper and Dr Joanne Favaloro head this laboratory. Dr Kemp-Harper's research focuses on the control of vascular tone by the nitric oxide/soluble guanylate cyclase (NO/sGC) signalling pathway under physiological and pathophysiological conditions. She is particularly interested in the function of resistance vessels and oxidative modification of sGC under disease conditions such as hypertension. Recent studies in the laboratory have examined the role of different redox species of NO in the modulation of vascular smooth muscle function. Together with Dr Joanne Favaloro, she identified for the first time an ability of the nitroxyl anion (NO⁻) to modulate vascular tone via mechanisms distinct to those of the uncharged form of NO (NO[•]). Dr Joanne Favaloro combines her expertise in small vessel myography and electrophysiological techniques to explore the ability of NO to regulate vascular function via sGC-independent pathways such as the activation of K⁺ channels.

The laboratory currently comprises a PhD student, **Ms Jennifer Irvine**, and several Honours students who are investigating the role of endogenously and exogenously generated NO⁻ in the control of vascular function both *in vitro* and *in vivo*.

The laboratory has collaborative links with Professor Chris Triggle, Dr Karen Andrews and Mr Mike Hashem at RMIT University, studying the endogenous production of distinct redox forms of NO in the resistance vasculature and alterations in vascular function in diabetes.

Vascular Oxidant Mechanisms Laboratory

Dr Grant Drummond heads this laboratory that consists of a postdoctoral fellow, **Dr Courtney Judkins**, and several Honours students. Dr Drummond is a newly-appointed Monash University Fellow who has NHMRC funding with both Dr Chris Sobey in the Department of Pharmacology, University of Melbourne, and Associate Professor Greg Dusting at the Bernard O'Brien Institute of Microsurgery, as well as commercial funding via his role as Senior Scientist and stake holder in the start-up company, Radical Biotechnology. Dr Drummond's research is focussed on identifying the major sources of reactive oxygen species (ROS) in the vasculature, not only during disease states (e.g. hypertension, atherosclerosis) where excessive production of these molecules leads to oxidative stress, but also during normal physiology, when tightly controlled production and removal of ROS allows them to be utilised as important signalling molecules. To this end, Dr Drummond's team has recently identified a family of enzymes called NADPH oxidases (Nox) as major contributors to vascular oxyradical production. The team is now attempting to determine which isoforms of Nox (Nox1, Nox2 or Nox4) are most important for physiological (i.e. beneficial) ROS production, and which are responsible for the excessive ROS production that occurs in pathophysiological settings. The ultimate goal of these studies is to identify a drug target for therapeutics aimed at preventing oxidative stress and the ensuing vascular remodelling and inflammation associated with diseases like hypertension, diabetes and atherosclerosis.

Integrative Cardiovascular Pharmacology Laboratory

Associate Professor Robert Widdop heads this NHMRC-funded laboratory that consists of two postdoctoral fellows (Gaspari & Jones), a research assistant, **Iresha Weungoda**, and several PhD and Honours students.

Associate Professor Widdop's research is focused on the functional roles of angiotensin (Ang) receptor subtypes in normal and pathophysiological settings such as hypertension, atherosclerosis, stroke and aging. In particular, the potential role of the AT₂ receptor subtype as a novel target in its own right is being studied, as well as its complementary role in the actions of 'sartan' compounds. As part of this research, the physiological effects of a number of Ang peptide fragments, including Ang-(1-7), Ang III and Ang IV, are also being examined as they appear to contribute to some of the counter-regulatory mechanisms that oppose the effects of the classical effector peptide, Ang II. A variety of *in vivo* (regional haemodynamics, telemetry in rats and mice), *in vitro* (vascular reactivity) and *ex vivo* (hypertrophy, fibrosis, histology) techniques are used.



PHOTO: 'Hypertensive' PhD and Honours Students. Backrow- Chan Chew, Janahan Dharmarajah, Sonja Tesanovic, Jennifer Irvine. Front row- Claudia McCarthy, DamiePhua, Ravina Ravi

Dr Tracey Gaspari has been studying the role of the renin angiotensin system (RAS) in the development and progression of atherosclerosis. Atherosclerosis is a multifactorial disease in which one of the earliest symptoms to become apparent is that of endothelial dysfunction. Ang II has a number of pro-atherogenic actions. Clinically AT₁ receptor antagonists and ACE inhibitors have been found to significantly lower total mortality and incidence of stroke in patients with high risk for cardiovascular disease. Importantly, the 'mix' of Ang peptides may change substantially during chronic RAS inhibition, therefore the focus of this research is to delineate the roles the various angiotensin peptide fragments and receptors. Currently, a PhD student,

Antony (Bill) Vinh, is investigating the role of Ang IV in the prevention of endothelial dysfunction and on the development of atherosclerotic lesions in the apolipoprotein E-deficient mouse model of atherosclerosis. With **Dr Anthony Dear** at AMREP, we are also examining novel treatments for abdominal aortic aneurysms in the Ang II-infused apolipoprotein E-deficient mouse model.

Dr Emma Jones has been studying the role of the AT₂ receptor during chronic AT₁ receptor blockade in aged rats. It is hypothesised that stimulation of unblocked AT₂ receptors by raised levels of endogenous Ang II, during AT₁ receptor blockade, may contribute to some of the beneficial effects of sartans. Indeed, this appears to be the case in aged normotensive rats since the AT₂ receptor antagonist PD123319 could reverse the beneficial remodelling (anti-hypertrophic and antifibrotic effects in heart and vasculature) effects of sartans. Future studies will be performed on an aged hypertensive cohort. In addition, a PhD student, **Claudia McCarthy**, is examining analogous functional interactions between AT₁ and AT₂ receptors in an experimental model of stroke, in collaboration with **Dr Jenny Callaway** at the Howard Florey Institute.

Associate Professor Widdop has a number of overseas and local collaborations, including role of AT₂ receptors in the renal medullary circulation (NHF-funded, **Dr Roger Evans** et al, Dept Physiology Monash University) and human arteries obtained at coronary artery bypass grafting (NHF-funded, Associate **Professor David Hare**, **Dr Anthony Zulli** et al, Austin Repat Hospitals).

