

Cardiovascular Research in the Department of Physiology at Melbourne University



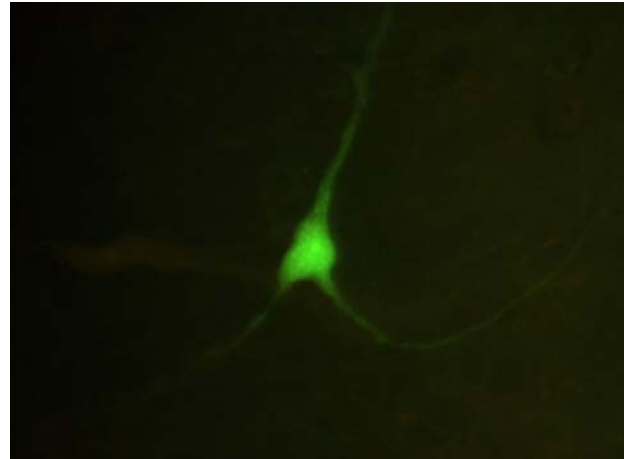
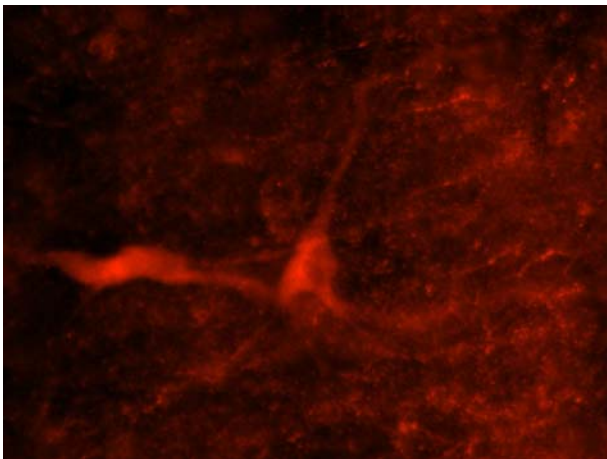
Physiology at Melbourne has always had a strong commitment to cardiovascular research with names such as Trefor Morgan and the late Sandy Skinner just 2 outstanding examples. Today, **Cardiovascular Health** is one of 3 Research Clusters in Physiology (the others being Neurophysiology and Muscle & Exercise). The Cardiovascular Health cluster is characterised by the diversity of research across molecular genetics, cardiomyocyte electrophysiology, central cardiovascular regulation, perinatal origins of adult disease and clinical trials. This diversity facilitates active collaborations here and abroad and provides a strong foundation for competitive funding and research training. The following paragraphs and photographs briefly describe the details of cardiovascular research in Melbourne Physiology. You can learn more about the Department and its research at

<http://www.physiology.unimelb.edu.au>. This edition we highlight 2 laboratories and

will complete the set next time. Happy reading, **Stephen Harrap**.

Central Cardiovascular Regulation: Dr Andrew Allen

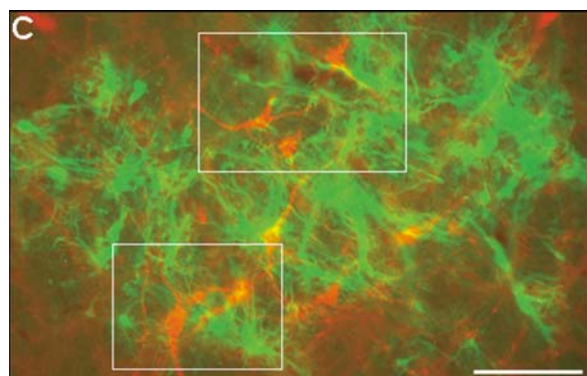
The group has an overarching interest in how the central nervous system modulates cardiovascular function via the autonomic nervous system. This encompasses an interest in neuroscience, particularly how neural groups interact *in vivo* to generate specific motor patterns (in this case sympathetic activity to vascular smooth muscle), as well as the cardiovascular physiology.



Juxtacellular-labelling, with Neurobiotin, of an electrophysiologically characterized RVLM neuron (green). Subsequent immunohistochemistry demonstrates that this is a catecholaminergic neuron (red = tyrosine hydroxylase).

The specific research questions being addressed: How does the renin-angiotensin system in the brain function? Is upregulation of this system in the brain involved in the generation or maintenance of cardiovascular diseases? What are the neural mechanisms involved in the generation of sympathetic nerve activity to the cardiovascular system? Is increased sympathetic vasomotor activity sufficient to induce an increase in blood pressure?

These specific research questions are being addressed by recordings of neuronal activity *in vivo* and *in vitro*, measurement of gene and protein expression from defined brain regions, measurement of cardiovascular parameters using radiotelemetry *in vivo* and viral transduction approaches to modulate gene expression *in vivo*.



Green fluorescent protein expression in astrocytes (green) in the region of RVLM presympathetic neurons (red) following adenoviral microinjection in vivo.

Staff and students

Dr Andrew Allen (Head of Laboratory), Jaspreet Dosanjh (Research Assistant), Lisa Hazelwood (Research Assistant), Charles Seigny (PhD Student), Erin O'Callaghan (B.Biomed.Sci.(Hons) student).

Collaborators

Dr W.G. Thomas (Baker Heart Research Institute), Prof. B.J. Oldfield (Department of Physiology, Monash University), Prof. I. Llewellyn-Smith (Department of Medicine, Flinders Medical Centre), D. J. Phillips (Department of Health Science, Murdoch University), Prof. M.J. McKinley (Howard Florey Institute), Prof. R.A.L. Dampney (Department of Physiology, University of Sydney), Dr. T. Le and Prof. T. Coffman (Department of Medicine, Duke University, North Carolina, USA), Associate Prof. S. Kasparov and Prof. J.F.R. Paton (Department of Physiology, University of Bristol, UK).

Recent publications

Montanaro M, Allen AM, Oldfield BJ. Structural and functional evidence supporting a role for leptin in central neural pathways influencing blood pressure. *Experimental Physiology* 2005; 90:689-696.

McAllen RM, Allen AM, Bratton BO. A neglected 'accessory' vasomotor pathway: implications for blood pressure control. *Clin. Exper. Pharmacol. Physiol.* 2005; 32: 473-477.

Richardson RJ, Grkovic I, Allen AM, Anderson CR. Separate neurochemical classes of sympathetic postganglionic neurons project to the ventricle of the rat heart. *Cell Tissue Res.* 2006; 324: 9-16.

Allen AM, Dosanjh J, Dassanayake S, Tan G, Thomas WG. Baroreceptor reflex stimulation does not induce cytomegalovirus promoter-driven transgene expression in the ventrolateral medulla in vivo. *Auton. Neurosci.* 2006; 126: 150-155.

Allen AM, Dosanjh J, Erac M, Dassanayake S, Hannan RD, Thomas WG. Expression of constitutively active angiotensin receptors in the rostral ventrolateral medulla increases blood pressure. *Hypertension* 2006; 47: 1054-1061.

Steinberg GR, Watt MJ, Fam BC, Prietto J, Andrikopoulos S, Allen AM, Febbraio MA, Kemp BE. Ciliary neurotrophic factor suppresses hypothalamic AMP-kinase signaling in leptin resistant obese mice. *Endocrinology* 2006; 147: 3906-3914.

Cardiac Phenomics Laboratory: Associate Professor Lea Delbridge

Our goal is to understand how genes and environmental factors interact to shape heart growth and function. We use unique genetic models of hypertrophic cardiac disease to probe the molecular and cellular abnormalities associated with hormonal disturbances (eg diabetes, renin-angiotensin system dysfunction, estrogen withdrawal). We investigate how pharmacological and dietary interventions can both exacerbate and alleviate cardiomyopathic conditions. In pursuing these studies, we have developed and patented novel microscopic techniques for measuring myocyte morphology and growth responses.



Recently we have demonstrated that elevated production of angiotensin II in the heart, even when systemic hormone levels and blood pressure are normal, can induce growth and excitation-contraction coupling abnormalities. At a cellular level we have characterized the links between abnormal growth and defective

cellular Ca²⁺ flux. Our studies of the effects of omega-3 dietary interventions have revealed a beneficial influence of these lipids in suppressing excessive heart growth and arrhythmogenesis. The role of reactive oxygen species in mediating abnormal cardiomyocyte growth responses in insulin resistant hearts is emerging as an important theme in our research. We have characterized the extent to which the heart relies differentially on glycolytic and oxidative energy supplies in a compromised metabolic environment.



Staff and students

A/Prof Lea Delbridge (Head of Laboratory), Dr Claire Curl (Post Doctoral Fellow), Ms Kate Huggins (PhD Student), Mr Enzo Porrello (PhD Student), Ms Ruchi Patel (PhD Student), Ms Wendy Ip (Honours Student), Ms Sarah Miller (MSc Student), Ms Belinda Howard (Honours Student), Ms Kim Mellor (Honours Student), Ms Beata Zoltkowski (Research Assistant), Mr Bill Meeker (Research Assistant), Ms Greta Meredith (Research Assistant)

Collaborators

Associate Professor Igor Wendt (Department of Physiology, Monash University), Dr Salvatore Pepe (Baker Heart Research Institute), Dr Rebecca Ritchie (Baker Heart Research Institute), Dr Walter Thomas (Baker Heart Research Institute), Professor Joe Proietto (Austin Repatriation Hospital), Dr Gordon Smyth (Walter and Eliza Hall Institute), Associate Professor Thierry Pedrazzini (University of Lausanne), Associate Professor Peter McLennan (University of Wollongong), Associate Professor Robert Widdop (Department of Pharmacology, Monash University), Professor Keith Nugent (School of Physics, University of Melbourne), Associate Professor Ann Roberts (School of Physics, University of Melbourne), Associate Professor Michell Gee (Department of Chemistry, University of Melbourne), Professor Peter Harris (University of Melbourne), Dr Brendan Allman (Iatvia Ltd, Australia), Associate Professor Alastair Stewart (Department of Pharmacology, University of Melbourne), Professor Margaret Morris (Department of Pharmacology & Physiology, University of New South Wales)

Recent publications

Ritchie RH & Delbridge LMD. Cardiac hypertrophy, substrate utilization and metabolic remodeling: cause or effect? *Clin Exp Pharmacol Physiol* 33:171-178, 2006.

Curl CL, Bellair CJ, Harris PJ, Allman BE, Roberts A, Nugent KA, Delbridge LM. Single cell volume measurement by quantitative phase microscopy (QPM): a case of erythrocyte morphology. *Cell Physiol Biochem*. 2006; 17: 193-200.

Domenighetti AA, Wang Q, Egger M, Richards SM, Pedrazzini T, Delbridge LMD. Angiotensin II-mediated phenotypic cardiomyocyte remodeling leads to age-dependent cardiac dysfunction and failure. *Hypertension*. 2005 Aug;46(2):426-32.

Curl CL, Bellair CJ, Harris T, Allman BE, Harris PJ, Stewart AG, Roberts A, Nugent KA & Delbridge LMD. Refractive index measurement in viable cells using quantitative phase-amplitude microscopy and confocal microscopy. *Cytometry* 65A:88-92, 2005.

Cardiovascular Research in the Department of Physiology at Melbourne University (Part 2)

Fetal, Postnatal & Adult Physiology and Disease: Associate Professor Mary Wlodek and Dr Andrew Siebe

Recent human studies have confirmed that being born small is associated with the increased risk of developing adult diseases including cardiovascular disease and hypertension. Growing evidence suggests that the nutrition provided to the baby via the mother's milk during lactation, and rapid growth of the baby after birth, are both critical factors influencing the programming of adult disease. Our laboratory has made novel and significant contributions to understanding the importance of the nutritional environment provided by the placenta to the baby before birth and that of the mother's milk after birth in the programming of adult diseases. We are the first to demonstrate that placental compromise in rats, which causes slow fetal growth, also adversely affects breast development, milk quality and supply, which further impair growth after birth.

We are exploring how a reduction in the number of functioning units (nephrons) of the kidney, alterations in key genes involved in kidney and heart development and function as well as changes in blood vessel reactivity are associated with rat offspring born small developing hypertension and cardiovascular disease. We are able to manipulate nutrition for a rat pup born small after birth by altering the quality and quantity of nutrition they consume after birth (by cross-fostering) and subsequently explore disease consequences. We aim to identify developmental stages during which nutritional or other interventions may have beneficial consequences. These studies will enable us to identify individuals at increased risk of developing later diseases and provide the scientific basis for the design and testing of appropriately targeted early life interventions.



Staff and students

Assoc Prof Mary Wlodek (Head of Laboratory), Dr Andrew Siebel (NH&MRC Peter Doherty Research Fellow), Kerry Westcott (Senior Research Officer), Rachael O'Dowd (PhD Student), Amy Mibus (MSc Student), Nicole Reti (PhD Student), Lenka Vodstrcil (PhD Student), Marc Mazzuca (PhD Student)

Collaborators

Prof Julie Owens (Obstetrics and Gynaecology, University of Adelaide), Dr Karen Moritz (Anatomy & Cell Biology, Monash University) and Dr Marianne Tare & A/Prof Helena Parkington (Physiology, Monash University)

Genes and Environment in Cardiovascular Risk

At the interface of genomics and physiology, our research group deals with the genetic and environmental determinants of cardiovascular risk, such as blood pressure, body mass index, cholesterol, cardiac hypertrophy, socio-economic status, dietary preferences, pregnancy and male pattern baldness (baldness by the way has been associated with increased cardiovascular risk in a variety of independent studies).

The research is both human and experimental.

The human studies are based around large epidemiological surveys such as the Victorian Family Heart

Study (VFHS), clinical trials such as PROGRESS and ANBP2 and specific samples such as those defined by conditions such as pregnancy and baldness.

Established in 1990, the VFHS is a population sample of approximately 800 volunteer adult families, enriched by families with twins. Our biometric and molecular studies have led to successful identification of genes for blood pressure, male pattern baldness and height.

Such projects require a team comprising expert biostatisticians (Katrina Scurrah, Sophie Zaloumis) working closely with molecular biologists (Justine Ellis, Cara Büssst, Joanna Cobb, Anna Duncan, Angela Lamantia). Having confirmed evidence of familial genetic and environmental effects through variance component analyses, our goal is to then find the gene and DNA variant. The next important step is to discover the way in which the variant perturbs normal physiological function and how this interacts with environmental factors such as socio-economic status. Many of our projects are just starting to translate from the molecular to the physiological, yet there are still many biometric and molecular questions to be answered.

Complementing our population-based genomic physiological studies, clinical trials provide a more medical perspective. Our involvement has been as the Regional Coordinating Centres (with responsibilities across Australasia, SE Asia & India) for the PROGRESS Study of stroke prevention and the ADVANCE Study of cardiovascular prevention in type 2 diabetes (Ravathi Subramaniam, Bianca Chan & Shan Chan). In these studies we are also undertaking genetic analyses.

The more specific clinical studies include those of the cardiovascular physiology of pregnancy (Dominica Zentner), female pattern baldness (Leona Yip) and taste preferences for salt, sugar and alcohol (Rob Di Nicolantonio). These studies provide fundamental perspectives on novel cardiovascular risk factors.

Our experimental research is largely dependent on rat breeding experiments to dissect the traits such as cardiac hypertrophy, blood pressure and behaviour. Indeed, we have discovered mutations that have led to human studies in ANBP2 to determine the presence of like DNA variation in cardiac hypertrophy (which after age, is the single most important predictor of death from cardiovascular disease).

The multi-faceted nature of our research provides a rich environment for collaborative experiments to bring novel approaches to cardiovascular research that we hope will contribute meaningfully for many years to come.

Staff and students

Prof Stephen Harrap (Head of Group), Dr Robert Di Nicolantonio (Head of Experimental Laboratory), Dr Justine Ellis (Research Fellow and Head of Molecular Laboratory), Dr Katrina Scurrah (Chief Genetic Biostatistician), Cara Büssst (PhD Student), Joanna Cobb (PhD Student), Leona Yip (PhD Student), Dr Dominica Zentner (PhD Student), Anna Duncan (Research Assistant), Angela Lamantia (Research Assistant), Sophie Zaloumis (Research Assistant), Ravathi Subramaniam (ADVANCE Regional Study Manager), Bianca Chan (ADVANCE Regional Study Associate Manager), Shan Chan (ADVANCE Regional Study Associate Manager).

Collaborators

Prof Graham Watt (Department of General Practice, Glasgow University), Prof Vernon Oh (Department of Medicine, National University of Singapore), Prof Colin Nichols (Washington University, St Louis, USA), Prof Tien Wong (Department of Ophthalmology, University of Melbourne), Dr Paul Baird (Centre for Eye Research), Prof Rod Sinclair (Department of Dermatology), Prof John Hopper (MEGA Centre, University of Melbourne), Dr Graham Byrnes (MEGA Centre, University of Melbourne), Prof John Chalmers (George Institute), Prof Stephen MacMahon (George Institute), Prof Lindon Wing (Flinders University), Prof Garry Jennings (Baker Heart Research Institute), Dr Walter Thomas (Baker Heart Research Institute), Dr Steve Petrou (Howard Florey Institute), Dr Lyle Gurrin (MEGA Centre, University of Melbourne), Dr Melanie Matheson (MEGA Centre, University of Melbourne), Prof Graham Giles (Cancer Council Victoria), Dr Gianluca Severi, (Cancer Council Victoria), Prof Lyle Palmer (University of WA), Dr Andrew Robinson (Dept of Mathematics and Statistics), Dr Anne Kavanagh (Key Centre for Women's Health in Society), Prof Shaun Brenneke (Dept of Obstetrics & Gynaecology), Dr Leeanne Grigg (Dept of Cardiology, Royal Melbourne Hospital), Dr James Wong (Dept of Cardiology, Royal Melbourne Hospital), Prof Sam Berkovic (Department of Medicine, Austin Hospital), Associate Prof Lea Delbridge (Dept of Physiology), Dr Jeremy Jowett (International Diabetes Institute), Dr Michal Pravene (Institute of Physiology, Czech Republic)

Recent Publications

Di Nicolantonio, R. Why does the SHR have an exaggerated preference for sweet and salty solutions? An hypothesis. *J Hypertens*. 2004;22:1649-1654.

Di Nicolantonio R, Kostka V, Kwitek A, Jacob H, Thomas WG, Harrap SB. Fine mapping of *Lvm1*: A quantitative trait locus controlling heart size independently of blood pressure. *Pulmon Pharmacol Therap*. 2006;19:70-73

Buresova M, Zidek V, Musilova A, Simakova M, Fucikova A, Bila V, Kren V, Kazdova L, Di Nicolantonio R and Pravenec M. Genetic relationship between placental and fetal weights and markers of the metabolic syndrome in rat recombinant inbred strains. *Physiol Genomics* 2006;26:226-231.

Ellis JA, Panagiotopoulos S, Akdeniz A, Jerums G, Harrap SB: Androgenic correlates of genetic variation in the gene encoding 5 α -reductase type 1. *Journal of Human Genetics* 2005; 50:534-537

Ellis JA, Scurrah KJ, Cobb JE, Zaloumis SG, Duncan AE, Harrap SB: Baldness and the Androgen Receptor: The AR polyglycine repeat polymorphism does not confer susceptibility to androgenetic alopecia. *Human Genetics* In Press

Ellis JA, KJ Scurrah, AE Duncan, A Lamantia, GB Byrnes, SB Harrap: Comprehensive multi-stage linkage analyses identify a locus for adult height on chromosome 3p in a healthy Caucasian population. *Human Genetics* In Press

Harrap SB, Wong ZYH, Scurrah KJ, Lamantia A. Genome wide analysis of population variation in HDL cholesterol. *Human Genetics* 2006;119:541-546

Scurrah KJ, Byrnes GB, Hopper JL, Harrap SB. Sex differences in genetic and environmental determinants of pulse pressure. *Genet Epidemiol*. 2006 30:397-408

Ellis JA, Panagiotopoulos S, Akdeniz A, Jerums G, Harrap SB: Androgenic correlates of genetic variation in the gene encoding 5 α -reductase type 1. *Journal of Human Genetics* 2005; 50:534-537

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