

Vascular Pharmacology at the Baker Heart Research Institute

The focus of the lab is on translational research addressing questions of significance in the prediction, diagnosis and treatment of cardiovascular diseases. Atherosclerosis remains the major underlying aetiology for cardiovascular disease. Our work in atherosclerosis is directed at the emerging areas of inflammation, immunology and cell adhesion. Other studies investigate the development and consequence of new vessel growth within atherosclerotic plaques. A new area of interest is the dependence on the presence of circulating endothelial progenitor cells as well as putative differences between diabetic and non-diabetic states. Recent studies have revealed a role for circulating adhesion molecules and the importance of these will be examined in human vessels. Lipids, hypertension and diabetes remain central to the development of clinical atherosclerosis. Our clinical lipid studies focus on HDL cholesterol and the anti-inflammatory effect of HDL on monocytes. Peripheral artery disease (PVD) presents a considerable clinical burden and also the opportunity to pursue mechanistic studies in a less precarious environment than in the coronary circulation. Current studies are involved in examining therapeutic options and the role of adhesion molecules in PVD. Other projects include studies on the role of arginine where we are examining possible mechanisms by which intracellular levels of L-arginine may be affected by competing catabolic pathways. Arginase, which catabolises L-arginine to form ornithine and urea, is one such pathway and has been shown to contribute to endothelial dysfunction in hypertension and aging blood vessels. Our current studies demonstrate that arginase inhibition conserves intracellular L-arginine stores, not only preserving endothelium nitric oxide responses in healthy vessels but preventing nitrate tolerance possibly through reducing eNOS uncoupling and regulating superoxide production. We propose to extend these investigations by deciphering the role of each arginase isoform using isoform specific knockout mice and isoform specific in vivo adenoviral transfection studies. Our preliminary data suggests a novel arginase II- RhoK pathway which may underlie the enzymes anti-hypertensive properties. Finally we have a substantial program on correcting the haemodynamic abnormalities in patients with liver cirrhosis. Current studies include the use of probiotics as a therapeutic intervention; extending our previous work on antibiotics in this patient population.



(from L to R: April Toh, Laura Willems, Emma Jones, Ann-Maree Jefferis, Ngan Huynh, Rajesh Nair, Jaye Chin-Dusting, Andrew Murphy, Margaret Vincent, Nathan Connelly, Kevin Woollard)

Recent Publications

1. Boak L, Dart A, Duffy S and Chin-Dusting. Neither responses to endogenous nor exogenous endothelin-1 are altered in patients with hypercholesterolemia. *Journal Lipid Research*, 46; 2667-2672, 2005.
2. Chin-Dusting J, Mizrahi J, Jennings G, Fitzgerald D. Outlook: finding improved medicines: the role of academic-industrial collaboration. *Nature Reviews Drug Discovery*, 4:891-7, 2005.
3. Woollard KJ, Kling D, Kulkarni S, Dart A, Jackson S and Chin-Dusting J. Raised plasma soluble P-selection in peripheral arterial occlusive disease enhances leukocyte adhesion. *Circulation Research*; 98: 149-56, 2006.
4. Chin-Dusting JPF, Shennan J, Jones E, Williams C, Kingwell B and Dart A. Effect of Dietary Beta Casein A1 or A2 on Surrogate Markers of Disease Development in Persons at High Risk of Cardiovascular Disease, *British Journal of Nutrition*, 95; 136-144, 2006.
5. Sviridov D, Chin-Dusting J, Nestel P, Kingwell B, Olchawa B, Hoang A, Starr J & Dart A. Elevated HDL Cholesterol is Functionally Ineffective in Cardiac Transplant Recipients: Evidence for Impaired Reverse Cholesterol Transport. *Transplantation* 2006;81(3):361-6, 2006.

Cardiac Hypertrophy Laboratory: Dr Julie McMullen

Julie obtained her PhD at the University of NSW and completed a postdoctoral research fellowship at Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, USA before joining the Baker early in 2005.



The lab focuses on understanding heart enlargement, cardiac hypertrophy, through comparisons between models of health and disease: examining the enlarged athletic heart in comparison to heart enlargement associated with disease.

It is well understood that the hearts of athletes grow: the super fit have a heart size greater than the average person. This enlargement is of benefit to them in their training and works to enable them to continue their level of exercise and fitness. When they stop training that healthy heart growth stops and the heart returns to a normal size. Conversely, heart failure patients commonly experience heart growth but this change is devastating, wreaking havoc and usually impossible to reverse.

From this observation, Julie's research has focused on understanding the changes in the athlete's heart that might benefit people with heart disease, whose heart growth might be caused by hypertension and/or heart failure.



Julie's studies demonstrate there are changes in genes that occur in people with cardiac hypertrophy associated with heart failure that do not occur in the athlete's heart: she has established that even though there are comparable increases in heart size, there are clear molecular and histological changes between the two.

The lab is working to identify genes causing heart enlargement that are good for the heart, as opposed to those genes causing heart enlargement with detrimental effects. In doing so she hopes to reproduce the work of the "good genes" in the failing heart.

The research area is novel in its suggestion that it is possible to promote and activate "good" genes in the heart as opposed to just inhibiting "bad" genes that cause the growth of the diseased heart. Julie's research involves genetically modified mouse models of heart failure. By over expressing a gene involved in the growth of the athlete's heart in a mouse model with heart failure, she hopes to understand whether this gene might be of use to patients with heart disease, and whether its promotion and growth can negate the effects of the "bad" growth genes.

Recent Publications

1. McMullen JR, Sadoshima J, Izumo S. Physiological versus pathological cardiac hypertrophy. In: *Molecular Mechanisms of Cardiac Hypertrophy and Failure*, edited by Walsh RA. London: Taylor & Francis, 2005, p. 117-136.
2. Luo J*, McMullen JR*, Sobkiw CL, Zhang L, Dorfman AL, Sherwood MC, Logsdon NM, Horner JW, DePinho RA, Izumo S and Cantley LC. Class IA Phosphoinositide 3-Kinase Regulates Heart Size and Physiological Cardiac Hypertrophy. *Mol Cell Biol* 25: 9491-9502, 2005.
*The first two authors should be regarded as joint first authors.
3. McMullen JR, Shioi T, Zhang L, Tarnavski O, Sherwood MC, Dorfman AL, Longnus S, Pende M, Martin KA, Blenis J, Thomas G and Izumo S. Deletion of ribosomal S6 kinases does not attenuate pathological, physiological or IGF1R-PI3K induced-cardiac hypertrophy. *Mol Cell Biol*. 24: 6231-6240, 2004.
4. McMullen JR, Sherwood MC, Tarnavski O, Zhang L, Dorfman AL, Shioi T, and Izumo S. Inhibition of mTOR signaling with rapamycin regresses established cardiac hypertrophy induced by pressure overload. *Circulation* 109: 3050-3055, 2004.