KEY FACTS

Team
Researchers: 6
Technicians: 2
PhD students: 1
Postdoc fellows: 1

Translation
Industry partners: 1

Links
India, United States

Keywords
Diabetic complications
Diabetes-associated atherosclerosis
Diabetic nephropathy
Diabetic retinopathy
Oxidative stress
Antioxidant defence
Reactive oxygen species
Glutathione peroxidase
Inflammation
Knockout mouse models

Bio-resources
GPx1 knockout mice
ApoE/GPx1 double knockout mice
Chemically-induced models of type 1 diabetes
Type 2 models of diabetes

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OXIDATIVE STRESS

Our team investigates the use of novel antioxidant strategies, to protect against diabetic complications. Our pre-clinical studies have focussed on the GPx1 mimetic, ebselen, novel activators of transcription factor, Nrf2, and peptide mimetics to improve NO bioavailability.

Research Brief

Diabetes with its associated complications will affect approximately 3.3 million Australians in less than 20 years with an alarming 275 Australians developing diabetes every day. Cardiovascular and renal diseases are major complications of diabetes. Despite intensive metabolic control and other interventions, diabetic complications continue to plague diabetic patients. Oxidative stress is increasingly being appreciated as an important contributor to diabetic vascular and renal injury. The work being conducted in the OSL aims at exploring both the mechanisms involved in diabetes-mediated oxidant-driven vascular and renal injury, as well as potential sites for therapeutic intervention through the use of novel antioxidants. Strategies being explored include the use of compounds such as activators of the transcriptional regulator Nrf2 that boost the body's natural antioxidant defences or synthetic mimetics of naturally occurring antioxidant enzymes. In addition, we are exploring the use of novel peptides to improve NO bioavailability. We view our approach of targeted antioxidant strategies as more likely to produce clinically relevant reductions in CVD outcomes than the current use of non-selective vitamins such as Vitamins E and C. The potential of our approach will be to improve the lives of patients living with diabetes and its complications.

Methodologies

- Murine models of diabetes-associated atherosclerosis; includes en face and aortic sinus evaluation of lesions
- Murine models of diabetic nephropathy and retinopathy
- Analysis of molecular pathways of inflammation (Western blotting, siRNA)
- Use of cultured cells to explore involvement of ROS/RNS (HEACs, NRK cells etc)

Selected Publications

- De Haan J.B. Nrf2 activators as attractive therapeutics for diabetic nephropathy. Diabetes 60: 2683-84, 2011.
- Chew P, Yuen DYC, Stefanovic N, Pete J, Coughlan MT, Jandeleit-Dahm KA, Thomas MC, Rosenfeldt F, Cooper ME and De Haan J.B. Anti-atherosclerotic and renoprotective effects of Ebselen in the diabetic Apolipoprotein E/GPx1-double knockout mouse. Diabetes 59(12):3198-207, 2010.
- Chew P, Yuen DY, Koh P, Stefanovic N, Febbraio MA, Kola I, Cooper ME, De Haan JB. Site-specific antiatherogenic effect of the antioxidant ebselen in the diabetic apolipoprotein E-deficient mouse. Arterioscler Thromb Vasc Biol. 29(6):823-830, 2009.
- Lewis, P., Stefanovic N, Pete J, Calkin AC, Giunti S, Thallas-Bonke V, Jandeleit-Dahm KA, Allen TJ, Kola I, Cooper ME, De Haan JB. Lack of the antioxidant enzyme glutathione peroxidase-1 accelerates atherosclerosis in diabetic apolipoprotein E-deficient mice. Circulation 115, 2178-2187, 2007.
- De Haan J.B., Bladier C., Griffiths P., Kelner M., O'Shea R.D., Cheung N.S.,Bronson R.T., Silvestro M.J., Wild S., Zheng S.S., Beart P.M., Hertzog P.J., and Kola I. Mice with a homozygous null mutation for the most abundant glutathione peroxidase GPx1, show increased susceptibility to the oxidative stress-inducing agents paraquat and hydrogen peroxide. J. Biol. Chem. 273: 22528-22536, 1998.

Glutathione Peroxidase-1, A Major Antioxidant Enzyme, Confers Protection Against Diabetes-Associated Atherosclerosis

Figure 1

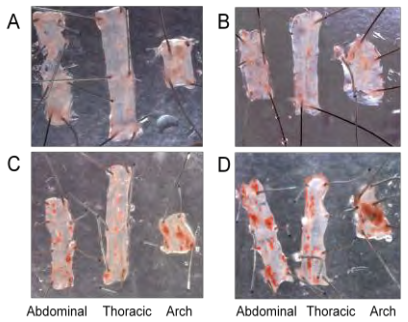
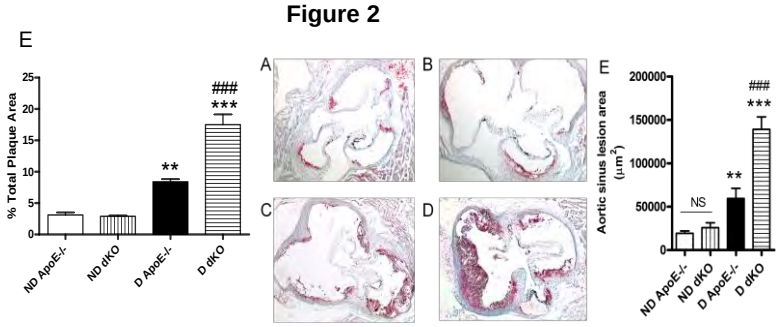
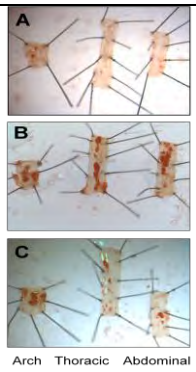


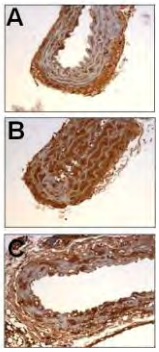
Figure 2

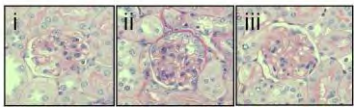


Lack of the antioxidant enzyme GPx1 in ApoE/GPx1 double knockout (dKO) mice results in significantly enhanced atherosclerotic lesions throughout the aortic tree (Figure 1) and within the sinus region of the mouse aorta (Figure 2), after 20 weeks of diabetes (D). A= Non-diabetic (ND) ApoE knockout controls, B= Non-diabetic ApoE/GPX1 double knockout controls, C= diabetic ApoE knockout mice, D=diabetic ApoE/GPx1 double knockout mice. Quantitative analysis of lesions throughout the aortic tress is shown in Fig. 1E. Quantitative analysis of lesions within the aortic sinus region is shown in Fig. 2E.

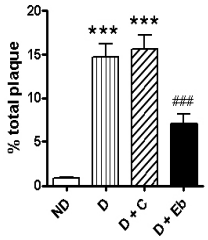
Ebselen, A GPX1 Mimetic, Protects Against Oxidative Stress, Diabetes-Associated Atherosclerosis And Diabetic Nephropathy

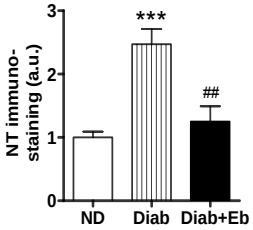


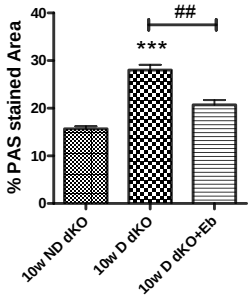




ABOVE: Mesangial expansion of glomeruli within diabetic kidneys (ii) is prevented by ebselen (iii). Control glomurulus is shown in (i).







ABOVE: En face aortas stained for lipids.
A= ApoE-/- aortas
B= Diabetic ApoE-/- aortas
C= Diabetic ApoE-/- aortas after 20 weeks of ebselen treatment.

ABOVE: Vessel walls stained for Nitrotyrosine- a marker of oxidative stress. A, B, C as before

ABOVE: Quantitation of ~20 gloms/kidney and 8 mice/group showing that ebselen significantly reduces glomerular injury in diabetic kidneys.