IMMUNOLOGY

St. Vincent's Immunology Research Centre is formed from a multidisciplinary team working on the cutting edge in xenotransplantation, transplantation immunology, innate immunity and vascular biology.

About us

The major goal of the Immunology Research Centre has been to develop genetically modified pigs for use as organ and tissue donors for human recipients (xenotransplantation). Complementing this strategy our research has grown to include investigations in allotransplantation, ischemia reperfusion injury, regulatory T cells, transplant tolerance, models of innate immunity, islet graft revascularisation, and closer study of the links between thrombosis and inflammation.

Our genetic strategy is to add 'rejection-inhibiting' human genes, encoding for CD55 and CD59 (regulators of complement); CD39, thrombomodulin and EPCR (regulators of coagulation-thrombosis-inflammation); and CTLA4-Ig and anti-CD40 ('local' immunosuppression of the human cognate immune response), while removing 'rejection-promoting' pig genes such as Gal, which encodes the major xenoantigen. This has seen us develop a long-term collaborative network of national and international researchers, all making significant progress toward our goal of using xenotransplantation to alleviate the burden of disease in the community. Our network includes researchers from the University of Adelaide (Assoc Prof Mark Nottle – transgenic and knockout pig production), Westmead Hospital (Prof Philip O'Connell – pancreatic islet transplantation), the Walter and Eliza Hall Institute (Assoc Prof Andrew Lew – immunosuppression by transplanted tissues) and Harvard University (Prof Simon Robson – world's leading authority on CD39).

By combining this network with our expertise in molecular and cellular biology, transplantation immunobiology, transgenesis, and the control of thrombosis and inflammation, the Immunology Research Centre is recognised as a leader in the field of xenotransplantation.

Projects in progress or completed

- Development of Gal knockout pigs expressing human proteins (CD39, CD55, CD59, thrombomodulin, CTLA4-Ig) to delay xenograft rejection.
- Transplantation of pig kidneys to treat renal failure.
- Transplantation of pig pancreatic islets to treat Type I diabetes.
- Investigation of molecular incompatibilities between human coagulants and pig anticoagulants.
- Investigation of the role of CD39 in immune function and NKT cell development.
- Investigation of the role of CD39 in the onset and progression of diabetes.
- Investigation of the role of CD39 in the onset and progression of pre-eclampsia.
- Development of a soluble CD39 fusion protein with anti-platelet and anti-inflammatory effects.
- Development and application of mouse models of renal and hepatic ischemia reperfusion injury and transplantation.
- Discovery of novel anti-inflammatory actions of the lectin-like domain of thrombomodulin.
- Overexpression of EPCR to block coagulation, inflammation and apoptosis.
- Investigation of pathways of innate immunity using a novel rejection model.
- Development of strategies to accelerate islet graft revascularisation.
- Refinement of strategies to achieve multiple transgene expression from a single transcriptional unit.
- Investigation of antiphospholipid syndrome using a mouse model.

The team

Prof Anthony John d'Apice; Assoc Prof Harshal Nandurkar, Medical Clinician; Julie Brown, Laboratory Assistant; Joanne Chia, Student; Prof Peter John Cowan, Principle Scientist; Tanya Craig, Student; Dr Sandra Crikis, Medical Clinician; Dr Shala Dezfouli, Research Officer – Senior; Dr Karen Maree Dwyer, Medical Clinician; Sebastiana Fisicaro, Research Assistant; Dr Hilton Gock, Medical Clinician; Elizabeth Lea Kennedy, Research Assistant; Eddy Lee, Student; Dr Bo Lu, Senior Research Officer; Dr Mark Lust, Medical Clinician; Dr Jennifer Louise McRae, Research Officer – Senior; Dr Greg Moore, Medical Clinician; Lisa Jane Murray-Segal, Research Assistant; Tharun Mysore, Student; Sandra Pommey, Student; Dr Siddharth Rajakumar, Research – Medical Clinician; Evelyn Joanne Salvaris, Research Officer; Anushka Samudra, Student; Carly Selan, Research Assistant; Anup Sharma, Student; Neil Wilson, Laboratory Manager; Dr Adam Winterhalter, Research Assistant; Dr Xiang-Ming Zhang, Research Fellow

Highlights

Prof Peter John Cowan

– Professorial Fellow, Department of Medicine, University of Melbourne

Eddy Lee

– Junior Investigator Prize, St. Vincent's Research Week 2008
– Young Investigator Award, Transplantation Society of Australia and New Zealand, 2008

Sandra Pommey

– Young Investigator Award, Transplantation Society of Australia and New Zealand, 2008

Higher degrees conferred in 2008

– Tanya Craig, BSc(Hons), University of Melbourne
– Sandra Crikis, PhD, University of Melbourne
– Mark Lust, PhD, University of Melbourne
– Adam Winterhalter, PhD, University of Melbourne

Grants

Cowan PJ, Lew A

Protecting islet allografts from innate and cognate immunity. International Sources – JDRF, (2007-2009), $300,000

Cowan PJ, d'Apice AJ

A genetic strategy to accelerate revascularisation of islet xenografts. Roche Organ Transplantation Research Foundation, (2005-2008), (CHF)300,000

d'Apice AJ, Cowan PJ, Nandurkar H, Nottle M

Towards pig to human transplantation. Commonwealth Government – NHMRC, (2006-2008), $1,165,500

d'Apice AJ, Cowan PJ, Lew A, O'Connell P, Robson S, Nottle M, Dwyer KM, Sutherland R, Allen R, Hawthorne W, Enjyoji K, Usheva-Simidjiyska A, Beebe L, Harrison S

Which transgenic pig will be used for islet transplantation in humans? Commonwealth Government – NHMRC, International Sources – JDRF, (2008-2012), $3,000,000

Dwyer KM, d'Apice AJ, Cowan PJ, Nandurkar H

CD39 protects against renal ischaemic reperfusion injury. Commonwealth Government – NHMRC, (2007-2009), $391,875

Dwyer KM, d'Apice AJ, Cowan PJ

CD39 expression prevents auto-immune destruction of beta cells. International Sources – JDRF, (2008-2010), $299,416

Dwyer KM

The role of CD39 in islet transplantation. St. Vincent's Research Endowment Fund, (2008), $70,000

Genzyme Renal Innovations Program, (2007-2009), $150,000

Hartland E, d'Apice AJ, Cowan PJ

A novel CD39-like ecto-NTPDase of Legionella pneumophilia. Commonwealth Government – NHMRC, (2007-2009), $276,750

Nandurkar H, Mitchell C

Regulation of myotubularin function by the novel 3-phosphatase. Commonwealth Government – NHMRC, (2006-2008), $477,750

Nandurkar H, Robson S, d'Apice AJ, Cowan PJ

A novel approach to target inflammation and thrombosis. International Sources – NIH, (2004-2008), $1,120,000

Nandurkar H

Delineating the role of CD39 (NTPDase1) polymorphisms in cardiovascular disease. St. Vincent's Research Endowment Fund, (2008), $28,000

Rajakumar S

CD39 protects in renal ischaemia reperfusion injury. St. Vincent's Research Endowment Fund, (2008-2011), $5,000

Jacquot Research Entry Scholarship. Royal Australasian College Physicians, (2008-2009), $29,000

Robson S, d'Apice AJ, Sachs D

Thromboregulatory strategies to prolong xenograft survival. International Sources – NIH (d'Apice, Anthony John (1124963) portion of funding only reported here), (2005-2010), USD$184,000

Sachs D, Sykes M, Robson S, Fishman J, Yamada K

A tolerance approach to xenotransplantation. International Sources – NIH

(Only subcontract to d'Apice, Anthony John (1124963) reported), (2005-2010), USD$375,000

Zhang X

Postdoctoral Fellowship #PF 07M 3291. National Research Foundations – National Heart Foundation, (2008-2009), $147,000

Selected presentations

Chia J

– Speaker, *'Susceptibility of islets to inflammation in a mouse model of diabetes is influenced by the level of expression of CD39'*, The XXIII International Congress of The Transplantation Society, Sydney, Australia, August 2008

Cowan PJ

– Invited speaker, *'Engineering of the porcine genome for xenotransplantation studies in primates'*, Padua University-Hospital, Padua, Italy

– Invited speaker, *'Genetic modification techniques for discovery and therapy'* and *'State-of-the-art role of complement and thromboregulation in xenotransplantation'*, The XXIII International Congress of The Transplantation Society, Sydney, Australia, August 2008

Gock H

– Speaker, *'Innate immunity in transplantation'*, The XXIII International Congress of The Transplantation Society, Sydney, Australia, August 2008

Gock H, Murray-Segal LJ, Moore G, Cowan PJ, d'Apice AJ

– Speaker, *'NK cell and T-cell deletion can achieve tolerance to the innate and cognateImmune response to HTF transgenic skin grafts'*, The XXIII International Congress of The Transplantation Society, Sydney, Australia, August 2008

Lee E

– Speaker, *'Transgenic over expression of human EPCR confers protection against inflammation and coagulation'*, The XXIII International Congress of The Transplantation Society, Sydney, Australia, August 2008

Lee E, Lu B, d'Apice AJ, Cowan PJ, Gock H

– Speaker, *'Endothelial protein C receptor over-expression protects against renal ischemia reperfusion injury'*, 41st American Society of Nephrology Annual Scientific Meeting, Philadelphia, United States of America, November 2008

Pommey S

– Speaker, *'Over-expression of CD39 in transgenic mice affects Nkt cell development and function – implications for liver xenotransplantation'*, The XXIII International Congress of The Transplantation Society, Sydney, Australia, August 2008

Salvaris EJ

– Speaker, *'Cytokine-mediated upregulation of transgene expression in transgenic pig endothelial cells'*, The XXIII International Congress of The Transplantation Society, Sydney, Australia, August 2008

Publications

Cowan PJ, d'Apice AJ 2008, 'The coagulation barrier in xenotransplantation: incompatibilities and strategies to overcome them', ***Curr Opin Organ Transplant***, 13, 2, 178-83

d'Apice AJ, Cowan PJ 2008, 'Gene-modified pigs', ***Xenotransplantation***, 15, 2, 87-90

d'Apice AJ, Cowan PJ 2008, 'Xenotransplantation: the next generation of engineered animals', ***Transpl Immunol*** **In press, corrected proof**

Gock H 2008, ***'Small animal models of Gal-mediated and xenograft rejection: deciphering the immunology of cross-species tissue transplantation'***, VDM Verlag Dr. Müller Aktiengesellschaft and Co. KG, Saarbrucken, Germany ISBN-10: 3639030575

Lee E, Salvaris EJ, Roussel J, Robson SC, d'Apice AJ, Cowan PJ 2008, 'Recombinant pig TFPI efficiently regulates human tissue factor pathways', ***Xenotransplantation***, 15, 3, 191-7

Lu B, Rajakumar SV, Robson SC, Lee EK, Crikis S, d'Apice AJ, Cowan PJ, Dwyer KM 2008, 'The impact of purinergic signalling on renal ischemia reperfusion injury', ***Transplantation***, 86, 12, 1707-12

Moore GT, Brown SJ, Winterhalter AC, Lust M, Salvaris EJ, Selan C, Nandurkar HH, Desmond PV, Cowan PJ, d'Apice AJ 2008, 'Glycosylation changes in hFUT1 transgenic mice increase TCR signalling and apoptosis resulting in thymocyte maturation arrest', ***Mol Immunol***, 45, 8, 2401-10

Murray-Segal L, Gock H, Cowan PJ, d'Apice AJ 2008, 'Anti-Gal antibody-mediated skin graft rejection requires a threshold level of Gal expression', ***Xenotransplantation***, 15, 1, 20-6

Roussel JC, Moran CJ, Salvaris EJ, Nandurkar HH, d'Apice AJ, Cowan PJ 2008, 'Pig thrombomodulin binds human thrombin but is a poor cofactor for activation of human protein C and TAFI', ***Am J Transplant***, 8, 6, 1101-12

Sansom FM, Riedmaier P, Newton HJ, Dunstone MA, Muller CE, Stephan H, Byres E, Beddoe T, Rossjohn J, Cowan PJ, d'Apice AJ, Robson SC, Hartland EL 2008, 'Enzymatic properties of an ecto-nucleoside triphosphate diphosphohydrolase from Legionella pneumophila: substrate specificity and requirement for virulence', ***J Biol Chem***, 283, 19, 12909-18