

Current Research

Research Report Update - 2009

The Respiratory Medicine Group Research Report (95kb)

Research Report Update - July 2007

Report on Research on Lung Transplantation

Human lung transplantation now has a history dating back 40 years. It is now 26 years since the first lung transplant procedure with long term survival. There has been dramatically improved assessment, surgical management and post operative management of lung transplant recipients to the point that it is anticipated that 90-95% of patients will leave hospital alive and well.

The key problems persist which restrict the number of long term survivors with a high quality of life following lung transplantation include: donor shortages, chronic rejection in the form of bronchiolitis obliterans, renal function impairment due to drug toxicity and recurrent infections in the lung transplant.

In 2006 the Alfred Hospital's Lung Transplant Service performed 49 lung transplants. Now in its seventeenth year, The Alfred Heart Lung Transplant Service is one of the largest clinical programs in lung transplantation in the world. They have developed an active research program focusing these key issues with the objective of increasing survival and long term quality of life in those referred for lung transplantation.

Immunopathology of Chronic Lung Transplant Rejection

Chronic lung transplant rejection in the form of the bronchiolitis obliterans syndrome is associated with progressive scarring and narrowing of small airways in the transplanted lung. Factors such as viral infections, fungal infections and gastro-oesophageal reflux are potentially important as either contributory or triggering factors to the chronic lung injury. Our research group have been one of the international leaders in defining the changes that occur in the airway leading to this condition. We were the first to describe an increase in scarring in small airways, changes in blood vessels and also the nature of airway inflammation in patients with established bronchiolitis obliterans syndrome. We continue to explore the sequence of events that occur very early on in the development of BOS.

We have now managed to establish a group of transplant recipients whom we are following with airway biopsies on a

regular basis to try and determine the process by which the immune system can scar and narrow airways. Despite appearing clinically stable in long term transplant, we believe that the immune system is actually activated, leading to the production of chemical signals, which leads to stimulation of myofibroblasts, ultimately scarring and narrowing of small airways. As a result of these studies we have been able to show (part of Dr Tanya McWilliams PhD thesis) that the levels of an important chemical signaller-TGF beta are increased in the wall of airways well before there is a measurable effect on lung function.

The Margaret Pratt Foundation has also provided substantial financial support for our Research Laboratory Manager, Dr Ling Zheng to analyse a large number of specimens, both in patients who remain stable without chronic rejection and in those patients before, during and after the development of chronic rejection in the form of bronchiolitis obliterans syndrome. Without this support these important studies would not have occurred. The preliminary data has allowed us to gain external funding through an international Actelion Endothelin Research Award. We are particularly interested to see if the ‘down stream’ effects of TGF-beta are mediated by endothelin 1 through its relevant receptors. If it is then a rationale for a potential therapeutic strategy (endothelin blockade) is confirmed.

Investigators, Associate Professor Greg Snell, Associate Professor Trevor Williams, Dr Tom Kotsimbos, Dr Ling Zheng, Ms Bronwyn Levvey, Dr. Tanya McWilliams and Dr Helen Whitford. The Alfred Hospital, Melbourne.

Recent publications:

Snell, G. I., B. J. Levvey, L. Zheng, M. Bailey, B. Orsida, L. Law, H. M. Whitford, T. C. Kotsimbos, T. J. Williams. 2005. Everolimus alters the bronchoalveolar lavage and endobronchial biopsy immunologic profile post-human lung transplantation. *American Journal of Transplantation* 5:1446-1451. (I.F. 6.002)

Zheng, L., B. Orsida, H. Whitford, B. Levvey, C. Ward, E. H. Walters, T. J. Williams, G. I. Snell. 2005. Longitudinal comparisons of lymphocytes and subtypes between airway wall and bronchoalveolar lavage after human lung transplantation. *Transplantation* 80:185-192. (I.F. 3.879)

Button, B. M., S. Roberts, T. C. Kotsimbos, B. J. Levvey, T. J. Williams, M. Bailey, G. I. Snell, J. W. Wilson. 2005. Gastroesophageal reflux (symptomatic and silent): a potentially significant problem in patients with cystic fibrosis before and after lung transplantation. *Journal of Heart & Lung Transplantation* 24:1522-1529. (I.F. 2.992)

Langenbach, S. Y., L. Zheng, T. McWilliams, B. Levvey, B. Orsida, M. Bailey, T. J. Williams, G. I. Snell. 2005. Airway vascular changes after lung transplant: potential contribution to the pathophysiology of bronchiolitis obliterans syndrome. *Journal of Heart & Lung Transplantation* 24:1550-1556. (I.F. 2.992)

Law, L., L. Zheng, B. Orsida, B. Levvey, T. Oto, A. T. Kotsimbos, G. I. Snell, T. J. Williams. 2005. Early changes in basement membrane thickness in airway walls post-lung transplantation. *Journal of Heart & Lung Transplantation* 24:1571-1576. (I.F. 2.992)

Zheng, L., H. M. Whitford, B. Orsida, B. J. Levvey, M. Bailey, E. H. Walters, T. J. Williams, T. Kotsimbos, G. I. Snell. 2006. The dynamics and associations of airway neutrophilia post lung transplantation. *American Journal of Transplantation* 6:599-608. (I.F. 6.002)

Donor shortages

Presently only a small proportion of those who may benefit from a lung transplant will actually be transplanted. Estimates in Australia put this at approximately 1 lung transplant in 15 people with severe lung disease (aged under 65y). Two broad strategies have been developed first try to find alternatives to lung transplantation and second work to increase the donor pool.

1. Lung Transplant alternatives

(a). New therapies for Pulmonary Hypertension. In partnership with the pharmaceutical industry we have been evaluation in clinical studies new drug therapies for what had previously been rapidly fatal diseases unless lung transplantation was

available. Based on the results of these (and other) studies over

the last 3 years 4 specific therapies are now available on the PBS system and we continue to explore newer options. Fewer patients have needed to be listed for lung transplantation and the outlook of these diseases has improved dramatically.

Investigators; A/Prof Trevor Williams, Dr Helen Whitford, A/Prof Greg Snell, Ms Angela Nichols and Ms Cristianne Manterfield. The Alfred Hospital, Melbourne.

Recent publications:

Keogh, A. M., K. D. McNeil, J. Wlodarczyk, E. Gabbay, T. J. Williams. 2007. Quality of life in pulmonary arterial hypertension: improvement and maintenance with bosentan. *Journal of Heart & Lung Transplantation* 26:181-187. (I.F. 2.992)

Gabbay, E., A. Reed, T.J. Williams. 2007. Assessment and treatment of pulmonary arterial hypertension: an Australian perspective in 2006. *Internal Medicine Journal* 37: 38-48. (I.F. 1.518)

Wlodarczyk, J. H., L. G. Cleland, A. M. Keogh, K. D. McNeil, K. Perl, R. G. Weintraub, T. J. Williams. 2006. Public funding of bosentan for the treatment of pulmonary artery hypertension in Australia: cost effectiveness and risk sharing. *Pharmacoeconomics* 24:903-915. (I.F. 2.198)

(b).Bronchoscopic Lung Volume reduction for severe emphysema.

Severe emphysema represents a frequent referral for lung transplantation. The Alfred Hospital performed Australia's first lung volume reduction procedures in 1996 and have the greatest experience in Australia with this type of surgery. This surgery whilst in selected cases can be very successful, carries substantial risk both of a complicated hospital stay but also of procedure related death. In the last 5 years we have been, with US venture capital partners, investigating new minimally invasive approaches. We have performed very early (first in man) studies that give considerable optimism that we can improve the lung efficiency in many with severe emphysema. We believe the parallel development of precise imaging to target such procedures plus the development of new devices and procedures will reduce the need to perform lung transplantation for emphysema.

Investigators; A/Prof Greg Snell, A/Prof Trevor Williams, Dr. Glen Westall, Lynda Holdsworth, Sue Fowler and Dr Helen Whitford . The Alfred Hospital, Melbourne.

Recent Publications

Wan, I. Y., T. P. Toma, D. M. Geddes, G. Snell, T. Williams, F. Venuta, A. P. Yim. 2006. Bronchoscopic lung volume reduction for end-stage emphysema: report on the first 98 patients. *Chest* 129:518-526. (I.F. 4.008)

Higuchi, T., A. Reed, T. Oto, L. Holdsworth, S. Ellis, M. J. Bailey, T. J. Williams, G. I. Snell. 2006. Relation of interlobar collaterals to radiological heterogeneity in severe emphysema. *Thorax* 61:409-413. (I.F. 6.150)

2. Expanding the donor pool

(a). The Use of Marginal donors

Over several years The Alfred Hospital Lung Transplant Program have progressively widened the acceptance criteria for organ donation. Our current practice is to use almost 50% of all multi organ donors for lung transplantation in humans. We have repeatedly evaluated our methods and results and published in international peer review journals. Interestingly the organ procurement agency of California adopted our approach and this has resulted recently in a doubling of the lung donation utilisation in California in the United States.

We continue to conduct studies that determine the extent to which multi-organ donors can be used for Lung Transplantation.

Investigators; A/Prof Greg Snell, A/Prof Trevor Williams, Dr. T Otto, Ms Bronwyn Levvey. The Alfred Hospital, Melbourne.

Recent Publications

Oto, T., B. J. Levvey, H. Whitford, A. P. Griffiths, T. Kotsimbos, T. J. Williams, G. I. Snell. 2007. Feasibility and utility of a lung donor score: correlation with early post-transplant outcomes. *Annals of Thoracic Surgery* 83:257-263. (I.F. 2.229)

Oto, T., M. Rabinov, A. P. Griffiths, H. Whitford, B. J. Levvey, D. S. Esmore, T. J. Williams, G. I. Snell. 2005. Unexpected donor pulmonary embolism affects early outcomes after lung transplantation: a major mechanism of primary graft failure? *Journal of Thoracic & Cardiovascular Surgery* 130:1446.

Oto, T., M. Rabinov, A. P. Griffiths, H. Whitford, B. J. Levvey, D. S. Esmore, T. J. Williams, G. I. Snell. 2005. Unexpected donor pulmonary embolism affects early outcomes after lung transplantation: a major mechanism of primary graft failure? *Journal of Thoracic & Cardiovascular Surgery* 130:1446.

Pilcher, D. V., G. I. Snell, C. D. Scheinkestel, M. J. Bailey, T. J. Williams. 2005. High donor age, low donor oxygenation, and high recipient inotrope requirements predict early graft dysfunction in lung transplant recipients. *Journal of Heart & Lung Transplantation* 24:1814-1820.

Reed, A., G. I. Snell, C. McLean, T. J. Williams. 2006. Outcomes of patients with interstitial lung disease referred for lung transplant assessment. *Internal Medicine Journal* 36:423-430. (I.F. 1.518)

Oto, T., A. P. Griffiths, B. J. Levvey, D. V. Pilcher, T. J. Williams, G. I. Snell. 2006. Definitions of primary graft dysfunction after lung transplantation: differences between bilateral and single lung transplantation. *Journal of Thoracic & Cardiovascular Surgery* 132:140-147. (I.F. 3.727)

(b). Donation after cardiac death (DCD)

At present the vast majority of donors used in lung transplantation have suffered a catastrophic neurological event resulting in complete cessation of blood flow to the brain of the potential donor. This is so called brain death.

A report by Dr Steen et al from Sweden and a visit by one of his senior collaborators (Dr. L Eriksson) alerted us to the feasibility of using donors where there has been complete cessation of heart function for more than an hour (cardiac death) as a viable source for organ donation.

A seeding grant from The Alfred Foundation allowed us to set up animal modelling experiments to develop these techniques in Australia. A large effort, particularly by Bronwyn Levvey and Greg Snell has led to the development of approved protocols and information material at the Alfred Hospital. Detailed education program for health care professionals as well as a large public education program has been undertaken. In the last 12 month 5 successful lung transplants from DCD donors at the Alfred (Australia's first) have brought this to clinical fruition and have led to

the first “true” increase in donor numbers.

Present research focuses on the feasibility of multi-organ procurement from DCD donors (kidney, liver and perhaps even heart). Further work is ongoing on the rollout across Australia . We believe that if successful we could increase the number of available donor organs by 50-75%.

Investigators; A/Prof Greg Snell, A/Prof Trevor Williams, Dr Leif Eriksson, A/Prof Frank Rosenfeldt, Ms Bronwyn Lewey. Alfred Hospital, Melbourne.

Recent Publications:

Snell, G. I., T. Oto, B. Levvey, R. McEgan, M. Mennan, T. Higuchi, L. Eriksson, T. J. Williams, F. Rosenfeldt. 2006. Evaluation of techniques for lung transplantation following donation after cardiac death. *Annals of Thoracic Surgery* 81:2014-2019. (I.F. 2.229)

Oto, T., B. Levvey, R. McEgan, A. Davies, D. Pilcher, T. Williams, S. Marasco, F. Rosenfeldt, G. Snell. 2007. A practical approach to clinical lung transplantation from a Maastricht Category III donor with cardiac death. *Journal of Heart & Lung Transplantation* 26:196-199. (I.F. 2.992)

Viral Infections and Immune Activation

When the human immune system sees foreign tissue it mounts a very specific attack through the adaptive immune system. In more technical terms, our main research focus is to investigate the central role of adaptive immune mechanisms in both driving allograft injury and protecting against common infections such as DNA virus reactivation in lung transplant recipients (LTR). In particular, we are interested in (i) quantitative and qualitative measurement of specific cell populations involved in cellular-mediated immunity and (ii) to determine either the destructive or suppressive effects of these cell populations in relation to post-transplant outcomes. There are four key inter-related areas of active research: (i) Alloreactivity or the immune attack on the foreign graft, ii) DNA virus reactivation and specific CD8 T cell immunity (iii) Regulatory T cell associated immune regulation, and (iv) Collaborative research programs incorporating Dendritic cell (DC) chimerism, CD34 cell associated tissue repair and more sensitive physiological markers of persistent airway damage.

Firstly, the vast majority of lung transplants proceeds with a high degree of HLA mismatching and as a direct result LTR generate allo-specific T cells, which recognize the graft as being foreign. Utilizing a novel approach for detection and measurement of these allo-specific T cells we are able to monitor the magnitude of alloreactivity generated to each mismatched alloantigen at various time points post-transplant. Secondly, DNA virus reactivation and specific CD8 T cell immunity (especially against HCMV – the major infectious disease pathogen post transplantation) are being measured in parallel in both the blood and lung allograft to dissect out the pathobiology of HCMV associated rejection syndromes. Thirdly regulatory T cells (Tregs) play an important role in immune regulation through suppression of alloreactivity and/or pathogenic attack. Both systemic (cells in peripheral blood) and local (cells within the allograft) Treg measurement enables us to track dynamic changes occurring following lung transplantation and to correlate such changes with concurrent immunological responses and/or clinical outcomes.

Finally, collaborative research projects are aimed at the investigating the downstream effects of excessive immunopathology in LTR. This work includes a)investigating the role of donor-derived DC to determine whether donor-derived DC persistence or “chimerism” relates to either a good or adverse clinical outcome in LTR; b)measurement of early lineage CD34 cells (as a surrogate marker of active repair processes) and correlation CD34 enumeration at various time points post-transplantation with histopathological (acute rejection grade, apoptotic and proliferation signals) and clinical outcomes in LTR; and c)correlating the above immunological/inflammatory/tissue repair signals with more sensitive tests of small airways disease in the lung allograft(multiple breath nitrogen washout, high resolution CT scanning & He*-MRI scanning).

We believe that these investigations will enable us to build individual LTR immunological and physiological profiles that can then be used to optimize immunosuppressive and anti-viral strategies, with the ultimate goal being to improve long term health outcomes. The support given by the Margaret Pratt foundation has already allowed us to secure further funding from the NH&MRC both as project grants and PhD scholarships. Dr. Mifsud has been a recent recipient of a prestigious NHMRC Doherty Fellowship.

Investigators; A/Prof. T. Kotsimbos, Dr Nicole Mifsud,, Dr Glen Westall, Ms Oanh Nguyen, Ms Alex Michaelides, Mr Joel Van Der Meulen, Ms Diahn Abud, Ms Rowena Meani, A/Prof Greg Snell and A/Prof Trevor Williams. The Alfred Hospital and Monash University, Melbourne.

Recent publications

Westall G, Brooks A, Kotsimbos T. CMV-specific CD8 T-cell dynamics in the blood and the lung allograft reflect viral reactivation following lung transplantation. *Am J Transplant.* 2006 Mar;6(3):577-84.

Snell G, Kotsimbos T, Williams TJ. Lung transplantation in Australia: barriers to translating new evidence into clinical practice. Evidence "beyond reasonable doubt" may never be achievable for low-volume drugs. *Med J Aust* 2006 May 1;184(9):428-9.

Oto T, Levvey BJ, Whitford H, Griffiths AP, Kotsimbos T, Williams TJ, Snell GI. Feasibility and utility of a lung donor score: correlation with early post-transplant outcomes. *Ann Thorac Surg.* 2007 Jan;83(1):257-63.

Kotsimbos T, McCormack J. Respiratory infectious disease: complacency with empiricism in the age of molecular science. We can do better! *Intern Med J.* 2007 Jul;37(7):432-5.

Snell GI, Levvey BJ, Zheng L, Bailey M, Orsida B, Williams TJ, Kotsimbos TC. Interleukin-17 and airway inflammation: a longitudinal airway biopsy study after lung transplantation. *J Heart Lung Transplant.* 2007 Jul;26(7):669-74.

Chaves NJ, Kotsimbos TC, Warren MA, McLean CA, Spelman DW, Williams TJ, Snell GI, Westall GP.. Cranial leiomyosarcoma in an Epstein-Barr virus (EBV)-mismatched lung transplant recipient. *J Heart Lung Transplant.* 2007 Jul;26(7):753-5.