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FINAL REPORT

Project Title		Extended immunological risk profile: The key to improve kidney transplant outcomes
Name		Clinical Associate Professor Wai Lim
Award Received		2017 Don and Lorraine Jacquot Career Development Fellowship
Report Date		6 March 2018
Chief Investigator / Supervisor		Clinical Associate Professor Wai Lim
Administering Institution		The University of Western Australia
Funding Period	Start Date:	1 January 2017
	Finish Date:	31 December 2017

PROJECT SUMMARY

Kidney transplantation is the treatment of choice for people with end stage kidney disease (ESKD), providing a substantial survival advantage compared to treatment with dialysis. In Australia, the allocation of donor kidneys to people with ESKD is primarily dependent on genetic compatibility because the closer the genetic compatibility, the better the outcome of the transplanted kidney. Following failure of the transplanted kidney, people with ESKD often face a lengthy time waiting for the next kidney because they develop multiple antibodies directed against a system of donor genes from the prior kidney transplant and they are also likely to experience a higher risk of death when waiting for the next transplant. With the advancement of novel laboratory techniques that are able to examine in greater details the degree of genetic incompatibility between donors and patients, we are now able to use this information to improve the prediction of adverse kidney transplant outcomes and also enable clinicians and patients to make a better informed decision regarding the selection of the most appropriate compatible donor kidneys for transplantation, particularly in younger people who are likely to require more than one kidney transplant during their lifetime.

PROJECT AIMS / OBJECTIVES

The first aim of the study was to examine the association between extended immunological risk profiling and allograft outcomes. An abstract from our group examining the association between eplet mismatches and mismatched epitopes and development of de novo donor specific antihuman leukocyte antigen (HLA) antibodies and acute rejection using New South Wales data have been accepted for presentation in both the national and international meetings. We are about to validate these findings using a cohort of kidney transplant recipients from Western Australia. The second aim was to determine the incremental benefits and costs of an alternative

allocation algorithm based on extended immunological profile. This continues to be a work in progress with the first manuscript examining the incremental benefits and costs of an alternative algorithm based on donor and recipient survival and age matching been accepted for publication (please see below). The next analysis will be incorporating immunological profile into this alternative allocation algorithm using the same cohort and statistical technique.

SIGNIFICANCE AND OUTCOMES

A greater understanding of the association between extended immunological risk profile (e.g. eplet mismatches) and allograft outcomes is critically important to improve the understanding of why certain donor kidneys are more susceptible to acute rejection, which then result in premature allograft failure. Our findings are likely to lead to an improvement in the selection of immunologically compatible donor kidneys to patients with end stage kidney disease, therefore potentially resulting in a reduction in the risk of rejection and premature allograft failure after kidney transplantation. Future projects include the identification of the type of eplet mismatches that are immunogenic and therefore may be associated with greater clinical relevance compared to non-immunogenic eplet mismatches, which may further improve the risk stratification of adverse allograft outcomes post-transplant. With these preliminary data generated from this grant, I have been successful in securing further funding from the Telethon trust (Department of Health, Western Australia 2018-2019, $240,000) in investigating the association between immunogenic and non-immunogenic eplet mismatches and allograft outcomes in paediatric and adolescent kidney transplant recipients.

PUBLICATIONS / PRESENTATIONS

1) Fidler S, D'Orsogna L, Irish AB, Lewis JR, Wong G, Lim WH. Correlation and agreement between eplet mismatches calculated using serological, low intermediate and high resolution molecular human leukocyte antigen typing methods. Oncotarget (Immunology) 2018; 9:13116-13124.

2) Calisa V, Craig J, Howard K, Howell M, Alexander S, Chadban S, Clayton P, Lim WH, Kanellis J, Wyburn K, Johnson D, McDonald SP, Opdam H, Yang J, Chapman JR, Wong G. Survival and quality of life impact of a risk based allocation algorithm for deceased donor kidney transplantation. Transplantation in press 2018.

3) Sharma A, Lewis JR, Lim WH, Palmer S, Strippoli G, Chapman JR, Alexander SI, Craig JC, Wong G. Graft and recipient outcomes associated with the development of de novo donor specific anti human leukocyte antigen antibodies following kidney transplantation: a systematic review. Nephrology Dialysis Transplantation 2018 Apr 11 [Epub ahead of print]. 4) Do Nguyen H, Wong G, Chapman JR, McDonald SP, Coates PT, Watson N, Russ GR, D'Orsogna L, Lim WH. The Association Between Broad Antigen HLA Mismatches, Eplet HLA Mismatches and Acute Rejection After Kidney Transplantation. Transplantation Direct. 2016;2(12):e120. 5) Coorey C, Sharma A, Taverniti A, Nankivell B, Chapman J, Craig J, O'Connell P, Pleass H, Lim WH, Yang J, Wong G. Machine learning prediction for de novo donor specific antibodies (dnDSA) and graft loss in simultaneous kidney pancreas transplant (SPK) recipients. Abstract: Transplantation Society of Australia and New Zealand 2018.