



RACP Foundation Research Awards

PROGRESS REPORT

| | | |
|--|--|------------------|
| Project / Program Title | The impact of de novo donor specific antibodies and eplet matching in kidney transplantation | |
| Name | Dr Ankit Sharma | |
| Award Received | 2018 Jacquot Research Entry Scholarship in Nephrology | |
| Report Date | 13 July 2018 | |
| Chief Investigator / Supervisor | A/Prof Germaine Wong | |
| Administering Institution | The University of Sydney | |
| Funding Period | Start Date: | 1 January 2018 |
| | Finish Date: | 31 December 2018 |

PROJECT SUMMARY

Recipients who develop antibodies directed against the donor kidney after kidney transplantation experience an increased risk of rejection and subsequent graft loss, with 25% losing their graft within 3 years. Improving immunological matching of kidney transplant recipients and donors decreases the risk of antibody production.

Thus far we have shown that novel eplet based matching techniques provide better discrimination for adverse kidney transplantation outcomes such as antibody production and acute rejection when compared to conventional broad antigen HLA matching. Further work aims to define which particular eplet mismatches may predict these outcomes and determine the utility of incorporating them into the organ allocation algorithm.

PROJECT AIMS / OBJECTIVES

1. To determine the relationship between de novo donor specific antibodies (dnDSA) development and graft outcomes, including acute cellular rejection, acute and chronic antibody mediated rejection (AMR) and graft loss.
2. To determine the impacts of dnDSA development on paediatric transplant recipients.
3. To determine the impact of eplet mismatches on clinical outcomes including acute rejection and graft loss after paediatric kidney transplantation.
4. To identify novel HLA alleles in Indigenous Australians and incorporate these alleles into HLA-Matchmaker.
5. To determine the association between specific location of eplet mismatches at transplantation and dnDSA production and acute rejection.

6. To determine the utility of incorporating eplet matching in the deceased allocation algorithm for high risk transplant candidates, including Indigenous Australians and paediatric recipients.

SIGNIFICANCE AND OUTCOMES

Despite advances in immunosuppressive therapy targeting acute cellular rejection, the long-term outcomes after kidney transplantation remain poor due to the critical role of dnDSA and AMR. After development of dnDSA, 24% of patients will progress to graft loss within 3 years due to development of antibody mediated rejection. Currently, the evidence pertaining to the clinical significance of dnDSA are sparse and inconclusive. The prognostic significance of the types, class and load of these antibodies, and whether these antibodies are truly noxious to the graft are unclear. My research proposal is conceptually and technically innovative. First, the integrated approach of incorporating clinical and molecular data in probabilistic modelling is intended to be clinically applicable and relevant for clinicians, policy-makers and patients. Second, the use of machine learning methodologies enables identification of patterns of risk associated with individual eplet mismatches, thus being able to identify those eplets with the greatest risk of antibody production and rejection (immunogenic eplets). Third, the knowledge of novel alleles in Indigenous transplant recipients and the immunogenicity of mismatched HLA antigens between donors and recipients will provide the definitive answer as to whether eplet-matching could replace or complement broad HLA-antigen matching in stratifying immunological risk amongst high-risk kidney transplant candidates. Therefore, outcomes of my research proposal will address the critical uncertainties in current transplant practice and has the ability to transform the current organ allocation algorithm and the routine care of kidney transplant recipients. It also has the potential to provide greater equity to Indigenous Australian and paediatric transplant recipients who remain disadvantaged under current organ allocation procedures.

PUBLICATIONS / PRESENTATIONS

Publications:

1. Renal transplant outcomes and de novo donor-specific ant-human leukocyte antigen antibodies: a systematic review. A Sharma, JR Lewis, W Lim, S Palmer, G Strippoli, JR Chapman, SI Alexander, JC Craig, G Wong. Published in 'Nephrology Dialysis Transplantation' (April 2018, online ahead of print).
2. Desensitisation strategies in high-risk children before kidney transplantation. A Sharma, A Durkan. Published in 'Paediatric Nephrology' (January 2018, online ahead of print).
3. Systematic reviews and meta-analyses in transplantation: challenges and pitfalls. G Wong, A Sharma, A Teixeira-Pinto, M Howell. Accepted for publication in Transplantation (May 2018).

Abstracts:

1. Machine learning prediction for de novo donor specific antibodies and graft loss in simultaneous kidney pancreas transplant recipients. A Sharma*, C Coorey*, A Taverniti, B Nankivell, JR Chapman, J Craig, P O'Connell, H Pleass, W Lim, J Yang, G Wong. *Co-first author. TSANZ ASM 2018.
2. Association between location of eplet mismatches, de novo donor specific antibodies and acute rejection in simultaneous pancreas-kidney transplant recipients. A Sharma*, C Coorey*, A Taverniti, B Nankivell, JR Chapman, J Craig, P O'Connell, H Pleass, W Lim, J Yang, G Wong. *Co-first author. American Society of Nephrology Kidney Week 2018 and ANZSN ASM 2018 (submitted).

3. Prognostic value of abdominal aortic calcification: A systematic review and meta-analysis of observational studies. K Leow*, P Szulc*, J Schousboe, D Kiel, A Teixeira-Pinto, H Shaikh, A Sharma, M Sawang, P Thompson, R Prince, J Craig, W Lim, G Wong, J Lewis. Manuscript in preparation for submission.
4. Novel HLA alleles and eplet mismatches in Indigenous renal transplant recipients. A Sharma, A Taverniti, HTD Nguyen, RJ Duquesnoy, JR Lewis, A Irish, L D'Orsorgna, J Craig, G Wong, W Lim. ANZSN ASM 2017.
5. Incidence, types and predictors of acute rejection in Indigenous kidney transplant recipients in Western Australia. P Howson, A Irish, G Perry, A Sharma, G Wong, W Lim. ANZSN ASM 2017.