RACP
Specialists. Together
EDUCATE ADVOCATE INNOVATE

# RACP Foundation Research Awards

# FINAL REPORT

| | | |
|---|---|---|
| **Project Title** | | The identification of key driver genes in acute renal allograft rejection |
| **Name** | | Dr Karen Keung |
| **Award Received** | | 2017 Jacquot Research Entry Scholarship |
| **Report Date** | | 13 July2018 |
| **Chief Investigator / Supervisor** | | Philip O'Connell |
| **Administering Institution** | | The University of Sydney |
| **Funding Period** | Start Date: | 1 March 2017 |
| | Finish Date: | 1 March 2018 |

## PROJECT SUMMARY


Acute rejection in transplant recipients is associated with inferior transplant outcomes. Despite modern immunosuppressive drug regimens, it still occurs in ~15% of recipients. The development of technologies for large scale gene profiling at the turn of the century, has enabled the characterisation and measurement of hundreds of genes through to the entire human genome at the same time, and has given us insight into human diseases that were previously unknown. This has allowed the comparison, for example of the changes in gene expression in kidney transplant biopsy tissue with acute rejection versus without. The advancement of computational strategies has now allowed us to identify amongst the gene expression changes, which are the key genes in major pathways that are not adequately controlled despite standard immunosuppressive drugs.

Due to the costs and time constraints of developing new drugs from scratch, there has been an increased focus in research towards drug repurposing. Drug repurposing refers to finding alternative applications for a drug that is already in clinical use for a different disease. Large scale gene profiling has provided extensive information of the gene expression changes that are a result of individual drug treatments. There are several advantages to repurposing drugs- it bypasses the significant cost and time issues associated with new drug design and development, and also given these drugs are already in clinical use, the safety and side effect profiles are already well known and understood.

If we are able to identify drugs already in existence that can target our key genes in acute rejection, then we could potentially reduce acute rejection rates further and hopefully improve transplant outcomes.

## PROJECT AIMS / OBJECTIVES

1. To identify genes that are over expressed in acute rejection from large scale gene profiling data
2. To identify the key genes amongst these
3. To apply a drug repurposing tool to identify drugs that could potentially dampen the expression of the key genes
4. To demonstrate in an animal experimental model that the selected drug can delay/prevent acute rejection

## SIGNIFICANCE AND OUTCOMES

If we are able to identify drugs already in existence that can target our key genes in acute rejection, then we could potentially reduce acute rejection rates further and hopefully improve long term transplant outcomes- currently around 50% of patients' transplants fail after ~12 years. Our research demonstrates the potential for novel drug therapies to be identified this way, and by 'repurposing' drugs it provides the opportunity to circumvent the numerous difficulties encountered when drugs are developed from scratch.

## PUBLICATIONS / PRESENTATIONS

1. Oral abstract- President's Prize winner for the Transplantation Society of Australia and New Zealand annual scientific meeting in Brisbane 2017
2. Oral abstract in the Transplantation Society world congress in Madrid Spain 2018.
3. Book Chapter 'Biomarkers of kidney transplant injury and rejection in kidney transplantation' in Kidney Transplantation 8th Edition, Ed, Peter Morris, Stuart Knechtle, Elsevier Press in press Philip J O'Connell1, Karen L Keung1, Madhav Menon2 and Barbara Murphy2