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RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		The influence of multistrain cytomegalovirus infections on the immune repertoire: implications for organ transplantation
Name		Dr Aron Chakera
Award Received		2014 RACP Jacquot Research Establishment
Report Date		1 June 2015
Chief Investigator / Supervisor		Dr Aron Chakera
Administering Institution		University of Western Australia
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PROJECT SUMMARY

It has become increasingly apparent that most infections are polyclonal in nature, with multiple distinct strains detectable in affected individuals. A potential consequence of multistrain infection may be modulation of a range of pathogen traits including virulence, transmission, strain selection postvaccination and the acquisition of drug resistance. Despite obvious clinical importance, multi-strain infection remains poorly studied and understood.

Cytomegaloviruses (CMV) are one of the largest and most complex viruses infecting humans. A large number of genetically distinct strains have been identified and in preclinical models this variation can lead to inter-strain competition and preferential replication and transmission of more virulent viral strains. CMV is the most common viral infection in transplant recipients, and is a major cause of morbidity as well as being associated with increased mortality. Even subclinical reactivation is associated with adverse outcomes. Infection with multiple strains of CMV has been documented in transplant recipients and leads to an increased risk of symptomatic disease. Understanding how multi-strain infection alters host responses and disease outcomes will advance our knowledge of host-pathogen interactions and may improve our ability to target therapeutic interventions

PROJECT AIMS / OBJECTIVES

Hypothesis

The overarching hypothesis for this research is that the nature of the initial host response to CMV shapes the capacity of the immune system to negotiate re-infection such that multi-strain infections can compromise the host's capacity to control infection.

Specific aims of this study are:

Aim 1. Analyse the effects of multi-strain CMV infection in renal transplant recipients through profiling of T and NK cell subsets.

Aim 2. Identify the common strains of CMV present in the transplant population

Aim 1 involved detailed phenotyping of the immune response in renal transplant patients. Renal transplant recipients represent an ideal cohort for assessing the effects of multi-strain infection as they are a high risk group, and the process of transplantation provides a defined time at which patients will acquire or re-acquire infection. Central to this work is the comparison of responses between donor and recipient pairs with differing serostatus (i.e. whether the donor and/or recipient has evidence of prior exposure to CMV). Aims 2 is being performed in collaboration with A/Prof Alec Redwood, who has published seminal studies on multistrain CMV infection in mice, and Prof Andrew Davison (Glasgow), who is assisting with whole (CMV) genome sequencing.

SIGNIFICANCE AND OUTCOMES

Our studies of KIR and HLA in the setting of CMV multistrain infection are likely to identify phenotype genotype correlations that may influence disease development and provide a more accurate risk of individual risk of infection/reactivation in the setting of immunosuppression.

As we continue to define the ecology of CMV in Western Australia we hope to identify particular strains that are common in the community and to determine whether selection pressures exist, based on HLA

Collectively, the data that has been generated, as a result of the Jacquot funding, has resulted in sufficient preliminary data which has been used for an NHMRC submission this year

PUBLICATIONS / PRESENTATIONS

Abstracts have been presented locally at CMV and infection and immunity meetings. Draft manuscripts are currently being prepared