EBVIRUMAB: A NOVEL HUMAN ANTIBODY TO TREAT ACUTE EPSTEIN-BARR VIRUS INFECTION AND PREVENT ITS ASSOCIATED DISEASES

Kristine Hua[1], Shane Horsefield[1], Kirrilee Beckett[1], Corey Smith[1], Martina Jones[2], Bostjan Kobe[3] and Rajiv Khanna[1]

[1]QIMR Centre for Immunotherapy and Vaccine Development, QIMR Berghofer Medical Research Institute, Brisbane, Australia; [2]Australian Institute for Bioengineering and Nanotechnology, University of Queensland, Brisbane, Australia, [3]School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, Australia;

kristine.hua@qimrberghofer.edu.au

Epstein-Barr virus (EBV) is a human herpes virus that infects more than 90% of the world's population. While the infection is benign and asymptomatic for the most part, it can result in many non-malignant and malignant diseases of lymphoid and epithelial origin [1]. Previous studies have suggested that acute EBV infection is associated with poor neutralising antibody responses against the EBV membrane antigen, glycoprotein (gp) 350, which correlated with impaired memory B cell response in patients with acute IM [2]. Promoting EBV control via the enhancement of viral neutralisation, could therefore provide a mechanism to control disease. Using human antibody phage display, we generated the first fully functional human monoclonal antibodies (mAbs) against gp350-specific EBV. In vitro studies demonstrated neutralising capacity of these antibodies against EBV infection of B cells. These findings directly correlated to binding kinetic studies, where we used single cycle kinetics to determine the dissociation constants. Antibodies with reduced dissociation constants resulted in increased stability of antigen-antibody interactions, thus increasing neutralising capacity. Using state-of-the-art structural biology techniques we are characterising antibody binding and solving atomic structures of antibody:gp350 complexes, including cryogenic electron microscopy (cryoEM) and X-ray crystallography, which will give a greater understanding of the neutralising activity of the antibodies and help guide the affinity maturation process.In vivo studies of these mAbs in EBV infected humanised mice, showed therapeutic potential exhibiting reduced viral loads in the blood and spleen, as well as inhibition of EBV positive tumour growth. These findings on the neutralising human mAbs, provide a therapeutic tool for future clinical studies to potentially treat primary infection of EBV and reduce the risk of developing EBV associated diseases.

[1] Khanna, R., S.R. Burrows, and D.J. Moss, *Immune regulation in Epstein-Barr virus-associated diseases.* Microbiol Rev, 1995. **59**(3): p. 387-405.
[2] Panikkar, A., Khanna, R, *Cytokine-Mediated Loss of Blood Dendritic Cells During Epstein-Barr Virus-Associated Acute Infectious Mononucleosis: Implications for Immune Dysregulation*. J Infect Dis, 2015. **212**(12): p1957-61.