A novel, highly differentiated immunomodulatory monoclonal antibody to the human Interleukin-21 (IL-21) cytokine that acts as a ‘Superagonist’. This antibody enhances endogenous IL-21 signalling and could be used to harness the patient’s immune system for the elimination of chronic viral infections, such as HIV.

- ‘First in Class’ ligand Superagonist
- ‘Best in Class’ medicament in the IL-21 receptor (IL-21R) agonism class
- Clinically de-risked Mechanism of Action
- Potential single agent and combination therapy

THE CHALLENGE
Interleukin-21 (IL-21) is a pluripotent cytokine and potent regulator of the immune system. It is produced primarily by activated CD4+ T-cells and natural killer (NK) T-cells. IL-21’s broad immuno-stimulatory functions include enhancement of CD8+ cytotoxic T-cell and NK T-cell activity - a key mechanism contributing to the destruction of virally infected and cancerous cells.

Recent data suggest that IL-21 agonists could be useful in combination with anti-HIV therapeutics. High levels of IL-21 improve HIV-specific cytotoxic T and NK T-cell function in vivo. In vitro stimulation of CD8+ and NK T-cells with IL-21 inhibits the viral replication rate of HIV.

Similar to oncology, targeting negative regulation - or the so-called ‘brakes’ - of the immune system to fight chronic viral infections is a growing area of drug research. Anti-PD-1 antibodies have shown efficacy in Hepatitis C infection models. Furthermore, there are case reports of PD-1 and CTLA-4 being upregulated on the T-cells of chronically infected Hepatitis B patients.

Human rIL-21 is in clinical development for oncology (both as a single agent and in combination) with the immuno-oncology check point inhibitors that present tumour-driven negative immune regulation.

IL-21 agonists should combine well with checkpoint inhibitors (and/or existing anti-viral medicaments) in treating chronic viral infections.

Agonism of IL-21 signalling is a promising therapeutic approach. However, rIL-21 treatment necessitates administration of high levels of an exogenous and short acting cytokine, requiring frequent dosing and risks overstimulating the immune system, so improved IL-21 agonists are needed.

THE TECHNOLOGY
Monash University researchers Professor Charles Mackay and Dr Di Yu have developed a monoclonal ‘Superagonist’ antibody (mAb 2P2) that binds with high affinity to IL-21, dramatically enhancing its agonistic effect.

The team has demonstrated mAb 2P2:
- increases IL-21 activation of human B and CD8+ T-cells (Fig.1)
- increases the activity of endogenous IL-21 by ~20-fold
- prolongs the t1/2 of human IL-21 in vivo by ~50-fold
- stimulates the immune cells of HIV-infected patients (mAb 2P2 promotes the cytotoxicity of NK and CD8+ T-cells from HIV-infected patients)
- enhances CD8+ T-cell cytotoxicity and reduces viral loads in knock in mice (hIL-21/IL-21R) infected with LCMV (Fig.2)

mAb 2P2 offers prolonged enhancement of endogenous IL-21 activity, targeting only those tissues where IL-21 is already expressed.

Intelectual property: National filings based on PCT/AU2014/000673 in Australia, Canada, China, Japan, Europe and the United States; and PCT/AU2015/050814, “Superagonist monoclonal antibody to human IL-21”.

The Monash team has significant experience in IL-21 biology, therapeutic antibody development and has generated numerous tools to facilitate the complete in vivo analysis of mAb 2P2 including hIL-21/IL-21R double knock-in mice.

THE OPPORTUNITY
We seek a partnership to progress mAb 2P2 development including pre-clinical toxicity and safety studies, and GMP mAb production.

Figure 1: mAb 2P2 increases hIL-21-mediated activation of human CD8+ T-cells to express cytotoxic molecules including granzyme B and perforin, which are important for anti-virus and anti-tumour immunity.

Figure 2: mAb 2P2 decreases viral load in hIL-21/IL-21R knock-in mice infected with LCMV to establish infection.

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