Monash University researchers have developed a novel and 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 immune system for the destruction of cancerous cells.

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

Background
Harnessing the immune system to combat tumours has led to the development of a highly efficacious new class of oncology drugs. This class is led by Ipilimumab (Yervoy), an FDA approved monoclonal antibody developed by Bristol-Myers Squibb (BMS). Immunomodulatory monoclonal antibodies are well placed to transform the treatment of human cancers.

Interleukin-21 (IL-21) is a pluripotent cytokine with potent regulatory effects on cells of the immune system and is produced primarily by activated CD4+ T cells and natural killer T (NKT) cells. Its broad immunostimulatory functions include the enhancement of CD8+ T-cell and natural killer (NK) cell activity, a key component for the destruction of virally infected or cancerous cells.

In addition, IL-21 may also contribute to the mechanism by which CD4+ T helper cells orchestrate the immune system response to chronic viral infections, and the proliferation and differentiation of antibody producing B cells during antibody affinity maturation.

These mechanism have implications for enhancing the immunogenicity of protective vaccines.

Importantly, recombinant IL-21 has been tested in phase 1 and 2 clinical trials for cancer, both as a single agent and in combination with Sorafenib or Rituximab (Zymogenetics/Bristol-Meyers Squibb). These studies have shown promising efficacy and safety data.

Together, these data suggest that agonism of IL-21 signalling is a promising therapeutic approach in the immunotherapy/ immunomodulation field.

The opportunity
Monash University’s Immunology, Inflammation and Therapeutic Antibodies Laboratory, led by Professor Charles Mackay, and Laboratory for Molecular Immunomodulation, led by Dr Di Yu, have developed a monoclonal antibody (mAb 2P2) that is a ‘Superagonist’ of the IL-21 ligand. mAb 2P2 binds endogenous IL-21 to enhance its agonistic effect, most likely via stabilisation of its half-life, and has been shown to stimulate B cell proliferation and CD8+ lymphocyte cytotoxicity in vitro specifically through activation of IL-21R (Refer Figure 1).

Based on the commercial and clinical success of Yervoy and the clinical success of the PD-1 (Programmed Cell Death 1 receptor) inhibitor class of immuno modulation drugs, there is a significant focus on the development of this class of therapy both as single agents and in combination.

At ASCO 2013, BMS widely reported remarkable outcomes for a combination of Yervoy with its PD-1 inhibitor monoclonal antibody (nivolumab) in treating melanoma. At the same meeting, BMS also disclosed that it had initiated clinical trials combining rIL-21 with Yervoy or nivolumab based on successful pre-clinical studies in various tumour models, where combination treatments produced enhanced anti-tumour activity when compared to monotherapy.

The Monash Researchers have significant experience in the development of therapeutic antibodies and are developing numerous tools to facilitate the complete in vivo analysis of mAb 2P2 including the generation of human IL-21 and human IL-21R knock-in mice. It is expected that mAb 2P2 will offer enhanced PK, safety and efficacy to be a ‘Best in Class’ medicament in the IL-21 receptor agonism class.

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.

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5 meetinglibrary.asco.org/content/115394-132

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