A novel and highly differentiated immunomodulatory therapeutic based on Interleukin-21 (IL-21) activation. Our monoclonal antibody binds to and enhances endogenous IL-21 signalling conferring “superagonism” and immune cell activation that can be used to harness the patient’s immune system to target cancer cells.

- ‘First in Class’ Superagonist of endogenous IL-21
- Reduced risk of side effects; sustained effect
- Clinically validated mechanism of action
- Potential combination with checkpoint inhibitors and other immunotherapies

THE CHALLENGE

The emergence of immuno-oncology has revolutionised cancer treatment. Harnessing the immune system to combat tumours has led to the development of new classes of highly efficacious oncology medications.

Among these, interleukin-21 (IL-21) is a pluripotent cytokine and potent regulator of the immune system. IL-21 is produced primarily by CD4+ T and natural killer (NK) T cells. IL-21 enhances the activity of CD8+ cytotoxic T and NK cells, a key process in the destruction of virally infected and cancerous cells.

In addition, IL-21 likely contributes to the CD4+ T helper cell response to chronic viral infections, and in the proliferation and differentiation of antibody-producing B cells, during antibody affinity maturation. These IL-21 functions may enhance the immunogenicity of protective vaccines.

Based on the success of checkpoint inhibitors, there is a significant push towards developing additional immune-oncology therapies, both as single agents and in combination with existing drugs. Recombinant IL-21 has been tested in phase I and II clinical trials for cancer, both as a single agent and in combination with Sorafenib or Rituximab. These rIL-21 clinical studies have reported positive efficacy and safety data that supports agonism of IL-21 signalling as a promising immune-oncology approach.

Clinical trials combining rIL-21 with Yervoy (anti-CTLA-4) or Nivolumab (anti-PD-1) are in progress, based on successful studies in various tumour models and other combination clinical strategies.

However, there are limitations to rIL-21 therapy. These include a short t1/2 requiring a frequent dosing that is not aligned with combination mAb therapies and large bolus dosing, which risks overstimulating the immune system, potentially increasing adverse events.

There is a need to develop an approach to IL-21 agonism that is more sustained and with an improved therapeutic window over rIL-21.

THE TECHNOLOGY

Researchers from Monash University’s Biomedicine Discovery Institute, led by Dr Di Yu and Prof. Charles Mackay, have developed a monoclonal antibody (mAb 2P2) that is a ‘Superagonist’ of hIL-21. mAb 2P2 binds with high affinity to IL-21 to enhance its agonistic effect and has been shown to stimulate B cell proliferation and CD8+ lymphocyte cytotoxicity in vitro, specifically through activation of the IL-21R (Fig. 1).

mAb 2P2 increases the activity of endogenous IL-21 by ~20-fold and significantly prolongs its t1/2 in vivo by ~50-fold (Fig. 2). The crystal structure of mAb 2P2 and further modelling in complex with IL-21 reveals a favourable conformational change that positions IL-21 for receptor binding.

We are currently advancing to proof of concept, testing mAb 2P2 in a xenograft model using homozygous KI mice.

Intellectual property: (i) National filings based on PCT/AU2014/000673 in Australia, Canada, China, Japan, Europe and the USA; and (ii) PCT/AU2015/050814 “Superagonist monoclonal antibody to human IL-21.”

THE OPPORTUNITY

We seek a partnership to progress mAb 2P2 development, by testing efficacy in a range of experimental models (single agent and in combination with checkpoint inhibitors) and conducting formal preclinical and CMC studies. Monash Researchers have significant experience in the development of therapeutic antibodies and have generated hIL-21 and hIL-21R knock-in mice models.

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: Administration (i.v. or s.c.) of mAb 2P2 prolongs the half-life of hIL-21 in vivo compared to hIL-21 alone.

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