

IMMUNO-ONCOLOGY IL-21 AGONIST mAb

A novel and highly differentiated immunomodulatory therapeutic based on Interleukin-21 (IL-21) activation. Our monoclonal antibody binds to and enhances IL-21, safely activating the immune system to treat cancer and chronic viral infections.

- 'Best in Class' IL-21 agonist mAb
- **Benefits over rIL-21: efficacy, safety profile, dosing regimen, duration of response**
- **Clinically validated mechanism of action**
- **Potential combination with checkpoint inhibitors and other immunotherapies**

THE CHALLENGE

IL-21 is a potent regulator of the immune system. It enhances the activity of CD8+ cytotoxic T and NK cells. Expression of IL-21 in several tumours has been linked to improved patient outcomes.

There is a significant push towards developing immuno-oncology therapies, both as single agents and in combination with existing therapies. Recombinant IL-21 (rIL-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 immuno-oncology approach.

Clinical trials combining rIL-21 with checkpoint inhibitors such as Yervoy (anti-CTLA-4) or Nivolumab (anti-PD-1) have been reported, as well as preclinical studies showing enhanced efficacy in combination with checkpoint inhibitors across a range of tumour models.

However, there are limitations to rIL-21 therapy. These include a short $t_{1/2}$ requiring a frequent dosing that is not aligned with combination mAb therapies and large bolus systemic dosing, which risks overstimulating the immune system, potentially increasing adverse events.

We have developed a unique approach to selective agonism of endogenous IL-21 that offers an improved therapeutic window over rIL-21.

THE TECHNOLOGY

Researchers from Monash University's Biomedicine Discovery Institute, led by Prof. Charles Mackay and A/Prof. Di Yu have developed a humanized monoclonal antibody (2P2) that is an agonist of hIL-2. 2P2 binds with high affinity to IL-21 to enhance its agonistic effect and has been shown to stimulate B cell proliferation and CD8+ T cell cytotoxicity *in vitro*.

2P2 increases the activity of endogenous IL-21 by ~20-fold and significantly prolongs its $t_{1/2}$ *in vivo* by ~50-fold (Fig. 1). The crystal structure of 2P2 and further modelling of the 2P2/IL-21 binding suggest a favourable conformational position that improves IL-21 half-life (Fig. 1).

Studies using human IL-21/IL-21R knock-in mice reveal that 2P2 enhances the cytotoxicity of CD8+ T cells (increases the CD8/Treg and CD8/CD4 ratios in TILs and lymph nodes, increases CD8 activation, infiltration in tumour and CD8 proliferation (Fig. 2) and reduce tumour burden compared to IL-21. Current experiments show that 2P2 alone can act on endogenous IL-21 to produce the same effects. In addition, 2P2 alone reduces T cell exhaustion and viral load in an LCMV model of chronic viral infection. Taken together, these data support the notion that 2P2 activates endogenous IL-21 to mount an effective immune response.

Our 2P2 agonist mAb opportunity provides an improved IL-21 agonist approach acting on endogenous IL-21 (safety), having longer duration of action, a more convenient dosing schedule and in alignment with co-therapeutics that can act synergistically (i.e. checkpoint inhibitors).

THE OPPORTUNITY

We seek a partnership to progress 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 hIL-21 and hIL-21R knock-in mice models.

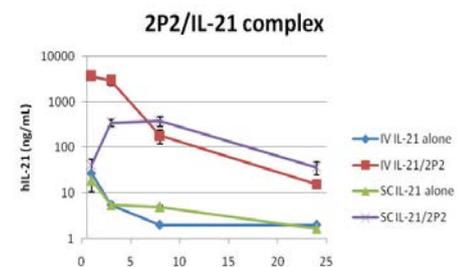


Figure 1: Administration (i.v. or s.c.) of mAb 2P2 prolongs the half-life of hIL-21 *in vivo* compared to hIL-21 alone.

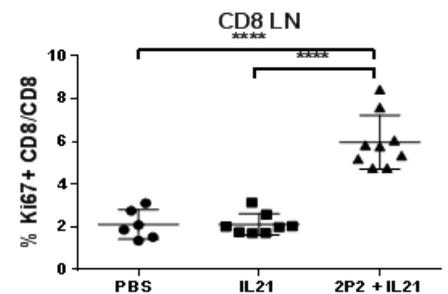


Figure 2: 2P2 increases CD8 proliferation in lymph nodes in the presence of recombinant IL-21.

mAb 2P2 offers advantages over rIL-21

- 2P2 targets endogenous IL-21 at site of IL-21 production
- 2P2 increases immune activity of endogenous IL-21
- 2P2 prolongs half-life of endogenous IL-21
- Improved safety and efficacy compared to systemic administration recombinant IL-21

Intellectual property: (i) National phase applications (US, AU, EP, CN, JA, CA) for PCT/AU2014/000673; and (ii) PCT/AU2015/050814 "Superagonist monoclonal antibody to human IL-21."

CONTACT US

Monash Innovation
T: +61 3 9905 9910
E: innovation@monash.edu