Immuo-Oncology: Novel ‘Cytokine Release Syndrome’ Therapeutic

A team of world leading researchers, including structural biologists from Monash University, have identified novel target residues for point mutations in a key cytokine. These mutations alter the cytokine’s biological properties and promote an unexpected and potent anti-inflammatory response in vitro, ex vivo (human PBMCs) and in vivo (rodent). The team has elucidated the Mechanism of Action (MoA), which results in the down-regulation of numerous inflammatory markers including IL-6: a target of incumbent ‘Cytokine Release Syndrome’ (CRS) therapies. This molecule could form the basis of a therapeutic composition to accurately modulate the level of CRS responses in patients undergoing Chimeric Antigen Receptor T cell (CAR-T) therapy and/or in other forms of severe inflammation.

Benefits over existing therapies:

- Differentiated MoA from the incumbent IL-6 specific inhibitors.
- Pleiotropic nature of immunosuppressant response offers widespread and potent inhibition of CRS drivers.
- Novel biologic well suited to intravenous delivery in an in-patient/ICU setting to precisely modulate the level of patient CRS response during CAR-T therapy.
- Potential to dramatically broaden the pool of viable CAR-T cell therapy patients.

Background

Recent advances in cancer immunotherapy involve the engineering of a patient’s own immune cells to recognise and attack tumours. The most high profile focus of this work has been on T cells that can be isolated from the patient and genetically modified to express chimeric antigen receptors (CARs) on their cell surface. CARs combine the exquisite specificity of a monoclonal antibody fragment (scFv) for a tumour associated target with the T-cell receptor activation.

The clinical use of CAR-T cells has generated some amazing results in early trials and has dramatically expanded the viable pool of CAR-T therapy patients.

Such exquisite control on CRS could be maintained but also effectively controlled. This would allow more patients to benefit from these breakthrough medications.

The opportunity

A team of world leading researchers, including structural biologists from Monash University, have identified novel target residues for point mutations in a key cytokine. These mutations alter the cytokine’s biological properties. The new molecule promotes an unexpected and potent anti-inflammatory response in vitro and in vivo, which can be measured through reduction of IL-6 expression. Importantly, the compound shows identical results in human PBMCs ex vivo (Figure 1).

The team has elucidated the Mechanism of Action, which results in the down-regulation of numerous inflammatory markers including Tumor Necrosis Factor (TNF) and IL-6; the latter being the target of incumbent CRS ‘therapies’ that support CAR-T cell treatment.

This potent biologic molecule, with a relatively short half-life (2-4 hours) - could be dosed appropriately to CAR-T patients, receiving intravenous fluids in an in-patient setting, to apply exquisite control on the level of CRS (unlike dosing with immunosuppressant mAbs like tocilizumab with half-lives measured in weeks). This would allow patients to retain CRS at levels that support CAR-T related efficacy but prevents deleterious or dangerous side effects.

Such exquisite control on CRS could dramatically expand the viable pool of CAR-T therapy patients.

Figure 1. THP-1 macrophages were transfected with the indicated variants of the cytokine followed by differentiation of the cells with PMA and subsequent stimulation with LPS (250 ng/ml) or vehicle. Supernatants were collected 24 h later and assayed for IL-1β by ELISA. Graph shows IL-1β protein abundance ± SEM.


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