ENHANCED CYTOTOXIC CD8+ T-CELLS FOR ADOPTIVE CELL THERAPY

A method for enhanced ex vivo stimulation of cytotoxic CD8+ T lymphocytes (CTL), independent of CD4+ T helper cells, for improved Adoptive Cell Therapy (ACT). Inhibiting tyrosine phosphatase PTPN2 achieves greatly enhanced T-cell stimulation, compatible with the challenging ex vivo activation of tumor infiltrating lymphocytes.

- Method to stimulate ex vivo CTL populations for ACT in a T-helper cell independent manner
- Compatible with the ex vivo reinvigoration of ‘tolerised’ T-cells or tumour antigen specific CAR-T cells
- ‘Proof of Mechanism’ in vivo efficacy
- Potential use in single agent and combination therapy applications

THE CHALLENGE

Recent advances in cancer immunotherapy involve engineering a patient’s own immune cells to target tumours. This revolutionary approach, termed Adoptive Cell Transfer (ACT), uses T-cells that have a natural or genetically engineered reactivity to the patient’s cancer.

Tumour Infiltrating Lymphocytes (TILs) can be isolated from resected patient tumours, and are naturally reactive to tumour antigens. Alternatively, T-cells can be isolated from the patient and genetically modified to express chimeric antigen receptors (CARs) on their cell surface, combining the exquisite specificity of a monoclonal antibody fragment for a tumour-associated target, with T-cell receptor activation.

An underlying feature of ACT is that T-cells are expanded and stimulated ex vivo before being transferred back into the patient. This re-invigorates or generates Cytotoxic CD8+ T-Lymphocytes (CTLs) that will specifically attack the tumour, with the rationale the higher the number of CTLs administered to the patient, the greater the tumour killing effect.

While ACT has tremendous promise, complete tumour regression is rare, in part due to inhibitory signals limiting T-cell activation.

THE TECHNOLOGY

Monash University researchers have identified PTPN2 as a key negative regulator of T-cell receptor signalling, tuning CD8+ T-cells to prevent excessive responses to self-antigens. By inhibiting PTPN2, CD8+ T-cells acquire CTL activity, independent of CD4+ T-helper cells.

The researchers have generated a large body of data supporting PTPN2 inhibition as an approach to enhancing CTL formation and function ex vivo and in vivo post adoptive transfer (Fig. 1). PTPN2-deficiency enhances the tumour-specific activity of Her-2 specific CAR-T cells in the context of adoptive immunotherapy and prolongs the survival of xenografted mice.

Expanding on this, current experiments are aimed at validating the stimulation method, using CAR-T cells specific for HER2/ERBB2, both in vitro and in vivo and in combination studies with anti-PD-1 or anti-CTLA4 inhibitors.


THE OPPORTUNITY

Monash University seeks a partner to commercially develop its technology within an ACT platform. The method has the potential to greatly improve CTL production, and consequently, ACT therapy success.

Figure 1: Target-inhibition enhances naive CD8+ T-cell differentiation in vivo and in vitro.

A. Naive CD8+ T-cells from treated and control mice were adoptively transferred into hosts. Harvested CD8+ donor T-cells were restimulated; IFN-γ and Granzyme B (Grz B) expression analysed by flow cytometry.

B. Naive CD8+ T-cells from Treated and Control mice were stimulated with anti-CD3/anti-CD28 then IL-2 and processed for flow cytometry to monitor the generation of CD44hi-CD62Llo effector/memory T-cells.

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