MONASH University

MONASH INNOVATION

IMPROVED CAR T CELL THERAPY: Enhanced CD8+T cell formation and function

We have identified two novel targets (PTPN2, and undisclosed) for enhancing the generation and function of CAR T cells and expanding their utility to treating solid tumours.

- **Enhance existing cell therapy platforms**
- **'Proof of Mechanism' *in vivo* efficacy**
- **Inhibition of PTPN2 (and/or 'undisclosed') enhances CAR T cell generation and function, independent of IL-2 *in vivo***

THE CHALLENGE

Chimeric antigen receptor (CAR) T cell therapy has emerged as an exciting immunotherapy approach for cancer that does not require pre-existing anti-tumour immunity. CAR T cells are autologous T cells engineered to express a CAR specific for a defined tumour antigen that signals via canonical T cell receptor (TCR) signaling pathways, to promote T cell expansion and activation. CAR T cells targeting the B cell transmembrane protein CD19 have revolutionized the treatment of acute lymphoblastic leukemia (ALL), with clinical response rates of up to 90% in pediatric B cell ALL (B-ALL) patients. However, the **high cost** and **limited effectiveness in solid tumours** are two key limitations that prohibit the widespread use of CAR T cells for cancer treatment.

We have developed an approach that enhances the generation and increases the efficacy of CAR T cells against solid tumours, which may have a significant impact on the utility of CAR T cell therapy.

THE TECHNOLOGY

The Monash University research team led by Prof. Tony Tiganis, have identified PTPN2 as a negative regulator of TCR signaling. PTPN2 dephosphorylates LCK, the most proximal protein tyrosine kinase (PTK) in the TCR cascade. In addition, PTPN2 antagonizes cytokine signaling required for T cell function and homeostasis. In activated and memory T cells, PTPN2-deficiency promotes IL-2 and IL-15 induced STAT5 signaling respectively.

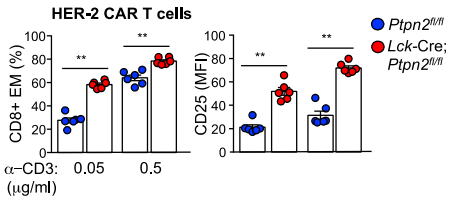

Figure 1. PTPN2-deficiency enhances CAR T cell generation.Her-2-specific control versus Her-2-specific PTPN2-deficient CD8+ CAR T cells were cultured with TCR crosslinking antibodies (CD3/CD28) and cytokines (IL-2 and IL-7) to promote T cell activation/expansion with a CAR consisting of an extracellular scFv-α-human HER-2 domain fused via a transmembrane region to the signaling domains of CD28 and CD3ζ.

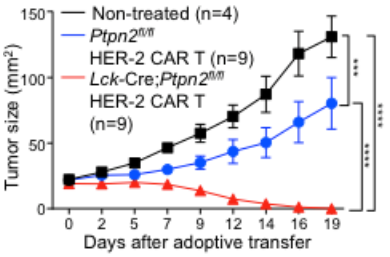

Figure 2: PTPN2-deficiency enhances CAR-T efficacy *in vivo*. A single dose of purified Her-2-specific control versus Her-2-specific PTPN2-deficient CD8+ CAR T cells were administered into sublethally-irradiated congenic recipients expressing human HER-2 (and thus tolerant to HER-2) and bearing 20-30 mm HER-2-expressing E0771 (HER-2- E0771) syngeneic mammary tumours.

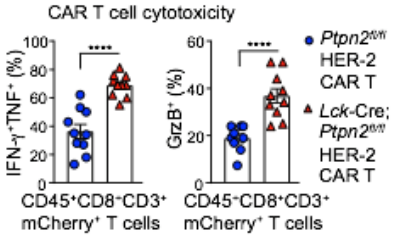

Figure 3: Enhanced cytotoxicity of PTPN2-deficient CD8+ CAR T cells. Tumour infiltrates (CD45+CD8+CD3+) were assessed for IFNγ, TNF and GzB expression.

Summary of research to date
PTPN2-deficient CD8+ T cells have enhanced cytotoxic function *ex vivo*
PTPN2-deficient CAR-T cells extend survival in a xenograft model (**independently of IL-2**)
PTPN2-deficiency enhanced the generation of long lasting central memory T cells (T_{CM}) and the tumor-killing effector T cells (T_{EM})
Pharmacological inhibition of PTPN2 enhanced the cytotoxic function of human CD8+ T cells *ex vivo*
PTPN2 deficient CAR-T cells do not persist longer than wild-type counterparts *in vivo*

The team has generated data supporting PTPN2 inhibition as an approach to enhancing CAR T cell formation and function. First, genetic deficiency of PTPN2 enhanced the generation of CAR T cells (Fig 1.). Second, PTPN2-deficient CD8+ CAR T cells prevented growth and led to eradication of solid tumours (Fig 2.). Third, CAR T cell infiltrates in tumours displayed an increase in markers of cytotoxicity (Fig 3.).

Current experiments are aimed at exploring methods of inhibiting PTPN2 and the undisclosed target, and using CAR-T cells specific for HER2, both *in vitro* and *in vivo* and in combination studies with anti-PD1 or anti-CTLA4 inhibitors.

Intellectual property: National phase applications filed (US, EP, JA, AU) for PCT/AU2015/050318.

THE OPPORTUNITY

Monash University seeks a commercial partner to develop its technology within a CAR T cell platform. The method(s) have the potential to greatly improve CAR T cell therapy.

CONTACT US

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

GROUP OF EIGHT AUSTRALIA

CRICOS provider: Monash University 00008C
Produced by Monash Innovation: May 2018