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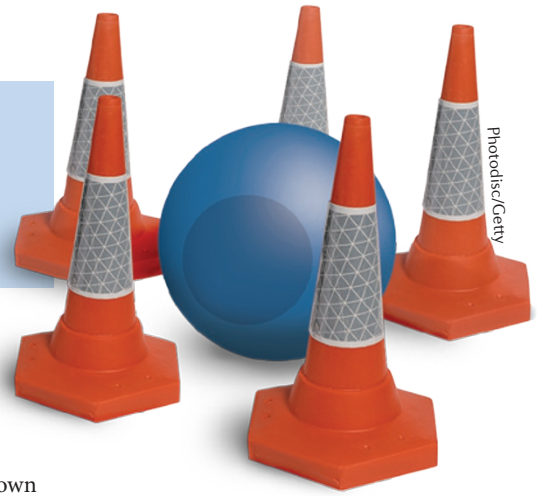
IMMUNOTHERAPY

Isolation of T_{CM} cells for tumour immunotherapy



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Reporting in *Science Translational Medicine*, Wang *et al.* describe a method to prospectively identify rare human melanoma-specific $CD8^+$ central memory T cells (T_{CM} cells) based on cytokine production.

Animal studies have suggested that T_{CM} cells can survive long-term after adoptive transfer. Human T_{CM} cells have been reported to produce more interleukin-2 (IL-2) and less interferon-γ (IFNγ) than effector memory T cells (T_{EM} cells), and therefore the authors hypothesized that these cell populations could be identified based on their relative production of these cytokines. Indeed, a high *IL2*/*IFNG* mRNA ratio in peripheral blood cells following short-term T cell stimulation correlated with the T_{CM} cell phenotype.

Using a previously described high-throughput method to screen for tumour-specific $CD8^+$ T cells, rare tumour-specific T_{CM} cells were isolated from patients with melanoma based on their high *IL2*/*IFNG* mRNA ratio. Effector T cell clones generated from tumour-specific T_{EM} cells (which have a low *IL2*/*IFNG* mRNA ratio) or T_{CM} cells had similar cytolytic activities, but T_{CM} cell-derived T cell clones had a distinct gene expression profile associated with cell survival.

> “a method to identify and isolate rare tumour-specific T_{CM} cells that can persist following … adoptive transfer”

In a pilot clinical trial, T_{CM} cells specific for gp100 (also known as PMEL) were isolated from five patients with metastatic melanoma. Effector T cell clones were then derived from these cells and adoptively transferred back into the same patients. Five days after infusion, the effector T cells were found to be targeting gp100-expressing melanocytes, resulting in the induction of autoimmune dermatitis. These data indicate that the transferred T cells were functional *in vivo*.

Importantly, the transferred cells were present in the blood at considerable frequencies in four of the five patients 1 month after transfer, and beyond 100 days in the one patient who was assessed for this time period. Furthermore, a subset of the persisting clones had regained a T_{CM} cell phenotype and the ability to produce IL-2. However, no tumour regression was observed in these patients. This may have been due to the high expression levels of negative regulatory molecules (namely CTLA4, PD1 and TIM3) on the effector T cell clones.

So, this study describes a method to identify and isolate rare tumour-specific T_{CM} cells that can persist following the adoptive transfer of the derived T cell clones. But, further work is needed to improve their antitumour efficacy, which may be achieved by combining this approach with drugs that block the negative regulatory molecules or by modulating the immunosuppressive tumour microenvironment.

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ORIGINAL RESEARCH PAPER Wang, A. *et al.* The stoichiometric production of IL-2 and IFN-γ mRNA defines memory T cells that can self-renew after adoptive transfer in humans. *Sci. Transl. Med.* **4**, 149ra120 (2012)

FURTHER READING Restifo, N. P., Dudley, M. E. & Rosenberg, S. A. Adoptive immunotherapy for cancer: harnessing the T cell response. *Nature Rev. Immunol.* **12**, 269–281 (2012)