Nature Reviews Urology | Published online 23 Jan 2018; doi:10.1038/nrurol.2018.4

PROSTATE CANCER

Developing CAR T cell therapy

A new study reports the development of prostate cancer immunotherapy on the basis of chimeric antigen receptor (CAR) T cells. Injection of patient-derived $CD8^+$ T cells that had been engineered to be specific for prostate-specific membrane antigen (PSMA) and insensitive to transforming growth factor-ß (TGFß) into PSMA-expressing PC3 tumours in mice resulted in suppressed growth, as well as widespread apoptosis and T cell infiltration of tumours.

Current treatments for prostate cancer intended to elicit antitumour immune responses have limited efficacy. Now, researchers have created prostate-tumour-specific CAR T cells by infecting $CD8^+$ T cells from patients with metastatic disease with a retroviral construct. The construct carried an anti-PSMA chimeric immunoglobulin T cell receptor(ζ) gene, conferring T cell specificity, and a dominant negative TGFß type II receptor gene, which provides resistance to TGFß-mediated suppression of cytotoxic T cell function. The cells also expressed HSV1 thymidine kinase, enabling cell killing through ganciclovir treatment as a safety mechanism.

The CAR T cells could be expanded 23.4-fold in 21 days, which was not suppressed by TGFß, but ganciclovir decreased survival to 1.3% in 5 days. In a mouse xenograft model, two injections of the CAR T cells reduced the total burden of PSMA-expressing PC3 tumours by >82%, but not that of normal PC3 tumours. PC3-PSMA tumours showed evidence of nuclear fusion, fragmentation, necrosis, and apoptosis, as well as $CD8^+$ T cell infiltration into the tumour parenchyma. In addition, mice that had received the PSMA-specific, TGFß-insensitive CAR T cells had increased serum IFNγ and IL-2 levels in compared with animals that received naive $CD8^+$ T cells, suggesting activation of local and systemic antitumour immunity.

This proof of principle study indicates this treatment as a potential new approach for men with metastatic prostate cancer.

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ORIGINAL ARTICLE Zhang, Q. *et al.* Efficacy against human prostate cancer by prostate-specific membrane antigen-specific, transforming growth factor-β insensitive genetically targeted $CD8^+$ T-cells derived from patients with metastatic castrate-resistant disease. *Eur. Urol.* https://doi.org/10.1016/j.eururo.2017.12.008 (2017)