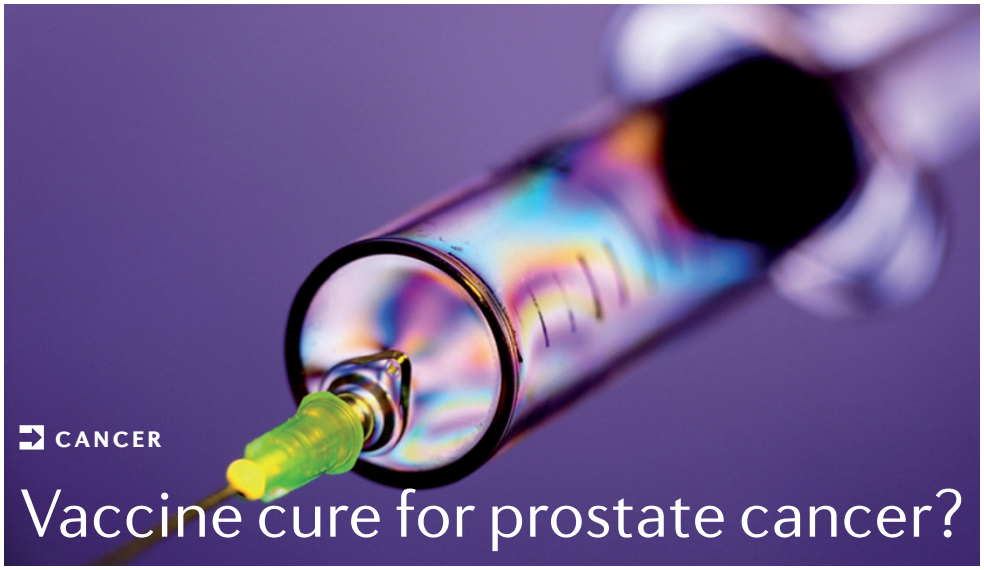

CANCER

Vaccine cure for prostate cancer?

Immunotherapeutic and virus-based anticancer strategies have attracted increasing interest in recent years, and oncolytic virus-based vaccine therapies have reached late-stage clinical trials. Now, reporting in *Nature Medicine*, the group of Richard Vile present a virus-based anticancer strategy that works predominantly by an immune-enhancing rather than an oncolytic mechanism. By cloning a cDNA library derived from normal prostate into the vesicular stomatitis virus (VSV), cure rates of up to 80% were achieved in mouse models of prostate cancer.

The biggest obstacle in the design of cancer immunotherapies is the scarcity of identified tumour-associated antigens (TAAs) for the immune system to target. The authors used a different approach: by cloning a library of human prostate-derived cDNA — termed an altered self antigen and epitope library (ASEL) — into VSV, they aimed for presentation of a broad repertoire of low-affinity antigens, rather than targeting one cancer-specific TAA. Interestingly, this did not induce autoimmunity; mice that were injected with ASEL directly into their prostate experienced an immune reaction, but after initially swelling and then shrinking, their prostates were back to normal after 60 days in terms of weight and histology.

To investigate its anticancer effects, ASEL was first tested in a mouse model of prostate cancer induced by the injection of mouse prostate tumour TC2 cells. Prostate-specific ASEL treatment of mice with 7-day-old TC2 tumours significantly enhanced survival compared to treatment with VSV–green fluorescent protein (GFP), and intravenous (i.v.) injection of ASEL proved to be more efficient than intratumoural injection. However, the treatment was not effective against the growth of melanoma cells. Conversely, VSV expressing a cDNA library derived from melanoma cells slowed the growth of tumours in mouse models of melanoma, but was ineffective against prostate TC2 tumours.

After nine i.v. injections of ASEL into mice with TC2 tumours, a cure rate of 80% was achieved. Three i.v. injections typically induced tumour regression but with aggressive recurrence, which prompted an investigation into whether vaccination with a library derived from the recurrent tumour cells (TC2Rs), termed immune-escape epitope libraries (IEELs), was effective in this setting. To avoid neutralization of virus particles in mice that were previously immunized with ASEL, the IEEL-containing virus was pre-loaded into $CD8^+$ T cells (T(IEEL)). Indeed, a sequential treatment with ASEL and T(IEEL) delayed or prevented the development of recurrences, thus demonstrating that tumours that evade the initial immune response can be re-targeted.

The authors further examined the nature of the immune responses initiated, and found that the induction of a $CD4^+$ T helper 17 (T_H17) cell response was crucial for the response against TC2 cells following the initial ASEL treatment. However, the sequential response to TC2R tumours was dependent on a T_H1-like interferon-γ response mediated by $CD8^+$ cells. They also found that responses against the xenogeneic (human) 'altered' self antigens were more potent than treatment with VSV carrying a cDNA library derived from mouse prostate.

These experiments demonstrate that cDNA libraries cloned into VSV can be used to induce antigen-specific immune responses against established tumours without eliciting autoimmunity. The authors further point out that the cDNA libraries can be readily constructed for off-the-shelf use and can be easily and systemically delivered via vectors that are amenable to production at a clinical grade.

Alexandra Flemming

ORIGINAL RESEARCH PAPER Kottke, T. *et al.* Broad antigenic coverage induced by vaccination with virus-based cDNA libraries cures established tumours. *Nature Med.* **17**, 854–859 (2011)