achieve this due to steric constraints. As Dennis Burton told *Nature*, "It's an ideal molecular solution to recognizing a tight cluster of repeating patterns".

Whereas the sugars on the surface of gp120 are closely clustered, on host proteins the same sugars tend to be widely spaced, so the unusual antibody structure allows the recognition of a unique feature of the virus.

Researchers can now start thinking about how to exploit this chink in the armour of HIV. The authors of the paper point out that one possibility is to engineer carbohydrate vaccines that mimic the close array of sugars on gp120.

Jennifer Bell

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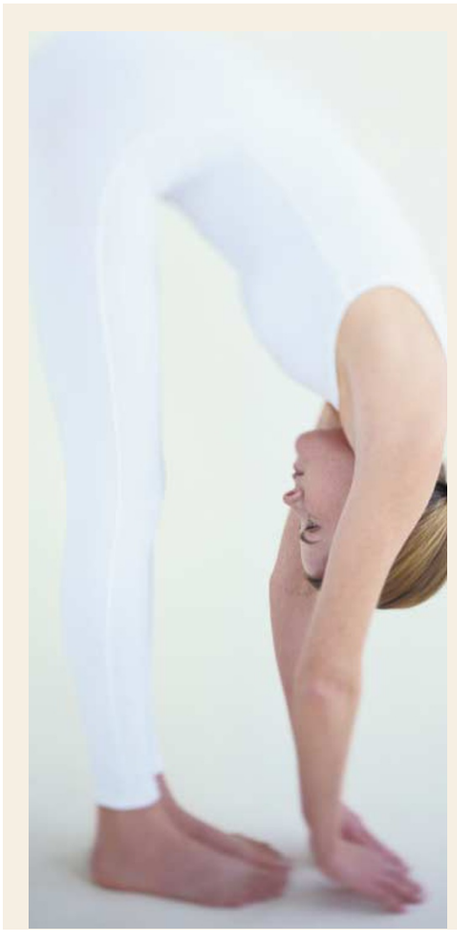
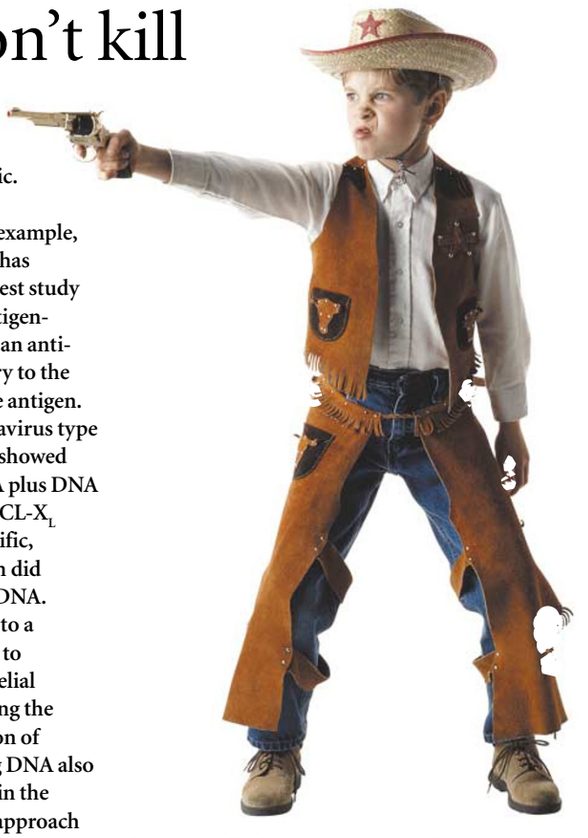


VACCINES

Shoot but don't kill



DNA vaccines are quick and easy to produce, and have few side effects, but they are often only weakly immunogenic. However, work on improving the immunogenicity of DNA vaccines (for example, through the use of cytokine adjuvants) has renewed hope in this approach. This latest study shows that the co-administration of antigen-encoding DNA with DNA that encodes an anti-apoptotic molecule by gene-gun delivery to the skin can enhance T-cell responses to the antigen.

Kim *et al.* used the human papillomavirus type 16 protein E7 as a model antigen. They showed that vaccination with E7-encoding DNA plus DNA encoding the anti-apoptotic molecule BCL-X_L resulted in a greater number of E7-specific, interferon-γ-secreting $CD8^+$ T cells than did vaccination with E7 DNA plus control DNA. This effect on T-cell number translated to a positive effect on the immune response to challenge with E7-encoding TC-1 epithelial tumour cells in mice. As well as inhibiting the formation of TC-1 tumours, the addition of BCL-X_L-encoding DNA to E7-encoding DNA also enhanced inhibition of tumour spread in the blood to the lungs, indicating that this approach has both protective and therapeutic effects.

The authors then showed that this anti-apoptotic vaccine strategy could be further enhanced by targeting antigen to the MHC class I and class II antigen-presentation pathway. They achieved this by using DNA encoding E7 antigen linked to the sorting signal of lysosome-associated membrane protein type 1 (LAMP1), which targets E7 to endosomal/lysosomal compartments. This strategy enhanced memory responses to the antigen as shown by analysing E7-specific $CD8^+$ T-cell responses 14 weeks after DNA vaccination.

By looking at the effects of minimal mutations that abrogate the anti-apoptotic activity of BCL-X_L, the enhanced immunogenicity that results from adding BCL-X_L-encoding DNA was shown to be due to these anti-apoptotic actions. Also, other anti-apoptotic proteins, such as BCL-2 and X-linked inhibitor of apoptosis protein (XIAP), and dominant-negative caspase mutants had similar, although less marked, effects.

The authors explain these results in terms of prolonging dendritic-cell (DC) survival. They suggest that gene-gun delivery to the skin can target antigen-presenting cells (APCs), known as Langerhan's cells, in the skin. Expression of BCL-X_L by these cells increases the life span over which they can express and present antigen to $CD8^+$ T cells and it might protect the APCs from killing by the T cells that they activate. This theory is supported by the observation that addition of BCL-X_L-encoding DNA increases the number of E7-expressing DCs in the lymph nodes five days after vaccination and decreases the number of apoptotic cells.

These results are in contrast to previous studies showing enhanced immunogenicity with the use of pro-apoptotic strategies such as FAS (CD95). However, these studies have mainly used intramuscular immunization, which targets DNA to non-professional APCs (myocytes), which are more susceptible than DCs to pro-apoptotic stimuli. It is probable that myocyte apoptosis enhances antigen uptake and presentation by APCs. A combination of these two approaches — using tissue-specific promoters to target anti-apoptotic proteins to professional APCs and pro-apoptotic proteins to non-professional APCs — could further improve vaccine efficacy.

Kirsty Minton

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