VACCINES

Keep right on to the end of the road…

Will an effective HIV vaccine ever be developed? This question has been posed many times in recent years. In *Nature*, Emini and co-workers now report promising results for a modified adenoviral vector vaccine candidate in stimulating cytotoxic T lymphocytes (CTLs). However, in the same issue, Barouch and co-workers sound a note of caution for the development of such vaccines.

Emini and co-workers used rhesus monkeys to assess three vector delivery systems expressing a simian immunodeficiency virus (SIV) *gag* gene — a plasmid DNA vector, the modified vaccinia Ankara virus and a replication-deficient adenovirus type-5 vector (Ad5) — both alone and in combination. The efficacy of each regimen was tested by challenge with a pathogenic HIV–SIV hybrid virus (SHIV89.6P). Because each immunized animal was positive for the major histocompatibility complex allele *Mamu-A*01*, Emini and co-workers could track $CD8^+$-T-cell responses using a tetramer of the SIV gag epitope p11CM presented by Mamu-A*01. After vaccination, the greatest p11CM-specific responses were detected in monkeys that had received a DNA priming injection followed by an Ad5 vector boost. After virus challenge, these monkeys and monkeys that had been injected with the Ad5 vector alone showed attenuated infections compared with control animals, including reduced levels of peak viraemia, low-level $CD4^+$-T-cell attrition in the acute phase and low levels of viraemia in the chronic phase.

Barouch and co-workers describe a potential limitation of this vaccine approach. In a previous study, rhesus monkeys immunized with an *env–gag* DNA vaccine boosted with an interleukin-2–immunoglobulin fusion protein (or the DNA equivalent) developed potent CTL responses and controlled viral replication after challenge with SHIV89.6P, with no evidence of disease progression up to 140 days. However, the current study reports that one monkey has since developed disease, apparently as a result of a single point mutation in the immunodominant p11C epitope. Compared with the wild-type p11C epitope, the mutant had a low binding affinity for Mamu-A*01 and also lower recognition by CTLs when presented by Mamu-A*01.

So, although the ability to stimulate specific CTL responses is within reach, we have some way to go before we can be confident of the breadth and durability of CTL responses elicited by vaccines.

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References and links

ORIGINAL RESEARCH PAPERS Shiver, J. W. *et al.* Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. *Nature* **415**, 331–335 (2002) | Barouch, D. H. *et al.* Eventual AIDS vaccine failure by viral escape from cytotoxic T lymphocytes. *Nature* **415**, 335–339 (2002).

FURTHER READING Mascola, J. R. & Nabel, G. J. Vaccines for the prevention of HIV-1 disease. *Curr. Opin. Immunol.* **13**, 489–495 (2001).

WEB SITE

HIV InSite: http://hivinsite.ucsf.edu/InSite/