IN THE NEWS

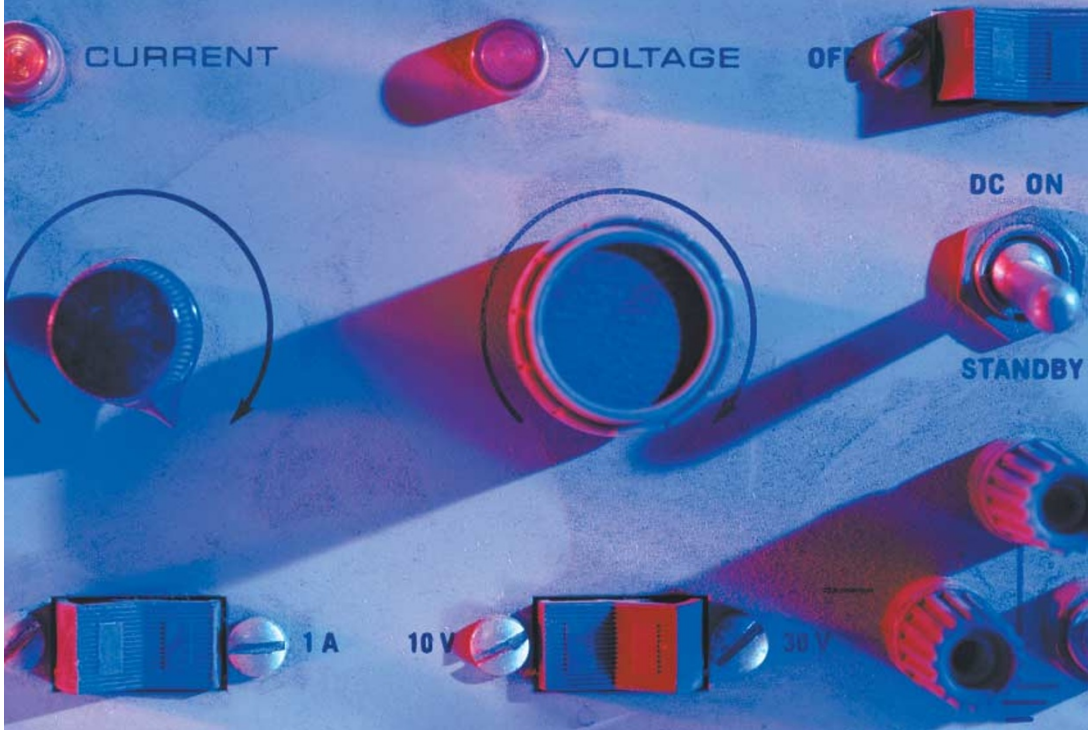
HIV vaccine trials begin

Trials of an HIV vaccine that is designed to protect uninfected people from infection have begun in South Africa, a country with one of the highest HIV infection rates in the world. Dr Seth Berkley, President and CEO of the International AIDS Vaccine Initiative, said, "This marks one of the great moments in the global effort to stop the spread of the HIV/AIDS epidemic by developing a preventative vaccine".

The vaccine (AVX101), which was designed by AlphaVax Inc., consists of a weakened strain of Venezuelan equine encephalitis virus, which acts as a vector to carry HIV genetic material into host cells. AVX101 is the first vaccine to be tested that has been designed specifically to target HIV-1 subtype C, which is most prevalent in South Africa, rather than subtype B, which is predominant in the developed world and for which other vaccine trials are underway. The trial aims to test the safety and dosage of the vaccine.

Glenda Gray, a researcher at the HIV Vaccine Trials Network, explained to *The New Scientist* that due to the escalating epidemic occurring in South Africa, "People are despondent about HIV — this represents a ray of light. It is obviously the beginning of a long haul, but we have begun the process". However, Tim Tucker, from the South African AIDS Vaccine Initiative, predicted it would be at least ten years before an effective vaccine would be ready for widespread distribution (reported by *Associated Press*).

Jenny Buckland



T-CELL DEVELOPMENT

CTL function — not just an on/off switch

The role of transcription factors in the development of CD4$^+$ T-cell lineages has been the subject of much research. T-bet has been identified as a master switch for controlling commitment to the T helper 1 (T_H1)-cell lineage, and GATA3 is important for T_H2-cell development. However, the factor(s) involved in determining the development of effector CD8$^+$ T-cell function have been less well understood. Now, Steve Reiner's group show that the T-box transcription factor Eomesodermin (Eomes) complements the actions of T-bet in determining the development of cytolytic function in CD8$^+$ T cells.

Mice that lack T-bet have a defect in the development of T_H1 cells, and CD4$^+$ T cells and natural killer (NK) cells from these mice show defective production of interferon-γ (IFN-γ). Despite the absence of T-bet, IFN-γ production and cytolytic effector function in CD8$^+$ T cells is unaffected, implying that these functions can develop independently of T-bet. However, to their surprise, the Reiner group found that introduction of a dominant-negative form of T-bet (DN T-bet) decreased the expression of IFN-γ by CD8$^+$ T cells from T-bet-deficient animals. This seemed to indicate that, as T-bet itself is absent, a T-bet-related factor is important for IFN-γ production by CD8$^+$ T cells.

To identify the T-bet-related factor in activated CD8$^+$ T cells, the authors used degenerate oligonucleotides to a conserved region of the T-box domain to amplify complementary DNAs. Eighteen clones were obtained; eight of these encoded T-bet itself and ten encoded Eomes — a T-box factor that is important for initiating the fate of mesodermal cells in vertebrates. Using specific molecular probes, marked Eomes expression was shown to be restricted to activated CD8$^+$ T cells. Similar to the effect of DN T-bet, DN Eomes inhibited IFN-γ production by wild-type and T-bet-deficient CD8$^+$ T cells.

Overexpression of Eomes or T-bet by T_H2 cells or by T-bet-deficient CD4$^+$ T cells was sufficient to induce IFN-γ production. The expression of Eomes coordinated with the expression of the lytic molecules perforin and granzyme B by activated NK cells and CD8$^+$ T cells. Overexpression of Eomes or T-bet by developing T_H2 cells was sufficient to induce the expression of perforin and granzyme B.

Next, the authors investigated whether a causal relationship exists between Eomes expression and cytolytic function. Introduction of DN Eomes or DN T-bet (which targets both T-bet and Eomes) into CD8$^+$ T cells from wild-type mice led to a greater defect in granzyme B induction than did gene deletion of T-bet alone. Comparison of *Eomes*$^{+/+}$ and *Eomes*$^{+/-}$ mice showed that haploinsufficiency of Eomes was accompanied by a marked reduction of perforin messenger RNA in activated cells.

Together, these results show that the development of cytolytic function of CD8$^+$ T cells is not quite as simple as flicking a single master switch. Eomes seems to complement T-bet in controlling the production of IFN-γ and cytolytic molecules by these cells. Further work will be required to determine the precise mechanisms that control CD8$^+$ effector T-cell development.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Pearce E. L. *et al.* Control of effector CD8$^+$ T cell function by the transcription factor Eomesodermin. *Science* **302**, 1041–1043 (2003)

WEB SITE

Steve Reiner's lab: http://www.uphs.upenn.edu/abramson/reiner.html