IN THE NEWS

AIDS vaccine fails

On 24 February, VaxGen announced the failure of the first Phase III AIDS-vaccine trial. But, as an article in *The New York Times* pointed out, many leading AIDS researchers did not expect this gp120-subunit vaccine to be effective, owing to its limited immunogenicity.

The vaccine was designed to target two strains of HIV subtype-B that predominate in North America and western Europe, and the trial, started in 1998, involved 5,100 homosexual or bisexual men and 300 female sex workers.

VaxGen are keen to emphasize the one glimmer of hope emerging from the trial — that rates of infection amongst the black and hispanic participants did seem to be lower than amongst controls. Neil Flynn, a researcher involved in the trial, told *Reuters*, "there is enough here to warrant a lot more study, particularly in people of African American descent". Some AIDS-vaccine campaigners took comfort in this news: Peter Piot, Director of UNAIDS said, "the trial provides clear evidence that a vaccine can work" (*BBC News*). The United States National Institute of Allergy and Infectious Diseases announced plans to investigate why the vaccine was more effective in black and hispanic individuals (reported in *The New York Times*).

But, others responded more cautiously: "This is at best premature and irresponsible data reporting", warned Martin Delaney of the AIDS information group Project Inform (*Reuters*), and *The New York Times* reported claims made by a prominent biostatistician that proper statistical adjustments had not been made and so the efficacy of the vaccine had possibly been overstated.

Jennifer Bell

IMMUNODEFICIENCY

Targeting WASP

The T-cell signalling defect that is associated with Wiskott-Aldrich syndrome (WAS) can be improved by gene therapy, according to a recent paper in *Blood*.

WAS, an X-linked primary deficiency caused by mutations in the *WASP* gene, is characterized by a range of immunological abnormalities, including thrombocytopaenia, a progressive decline in T-cell numbers, impaired antibody production and defective T-cell receptor (TCR) signalling. Previous studies have shown that retroviral infection of human *WASP*$^{-/-}$ cells with *WASP* can rescue some of these defects *in vitro*.

Here, Klein *et al.* tested whether this approach would work *in vivo*, by transplanting *Wasp*-transfected *Wasp*$^{-/-}$ haematopoietic stem cells (HSCs) into irradiated recipient mice. *Wasp*$^{-/-}$ mice develop several of the clinical features that are characteristic of WAS, including defective TCR-induced T-cell proliferation and aberrant regulation of the actin cytoskeleton. However, in addition, severe colitis occurs in these mice following radiation, so the authors used lymphopenic *Rag2*$^{-/-}$ mice as the recipients in this study.

Transplantation of *Wasp*-transfected HSCs resulted in the development of normal numbers of T and B cells in the recipient mice, and there was no evidence of abnormal expression of activation markers by these cells. T cells obtained from these mice proliferated after stimulation with antibodies specific for CD3, indicating that the TCR-signalling defect was corrected, at least partially, in these cells. This approach resulted in clinical benefits in these mice, as the susceptibility to colitis, which develops in *Rag2*$^{-/-}$ mice after transfer of *Wasp*$^{-/-}$ cells, was markedly reduced by transplantation of Wasp-expressing cells. Finally, the authors showed that Wasp-expressing cells have a selective survival advantage over *Wasp*$^{-/-}$ cells, a situation that is thought to improve the outcome of gene-therapy approaches.

Although antibiotic treatments and other supportive therapies can prolong the life of individuals with WAS, the only curative treatment that is available at present is allogeneic HSC transplantation, and only then if a donor is available. Despite recent concerns over the use of retroviral vectors for immunotherapy, these results are encouraging for the development of gene-therapy approaches for this disease.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Klein, C. *et al.* Gene therapy for Wiskott-Aldrich syndrome: rescue of T-cell signalling and amelioration of colitis upon transplantation of retrovirally transduced haematopoietic stem cells in mice. *Blood* **101**, 2159–2166 (2003)

FURTHER READING Thrasher, A. J. WASp in immune-system organization and function. *Nature Rev. Immunol.* **2**, 635–646 (2002)

CYTOKINES

Common-chain confusion

The heterodimeric cytokine interleukin-12 (IL-12) — which is composed of p35 and p40 subunits — is important for the differentiation of naive T cells to T helper 1 (T_H1) cells and for T-cell responses *in vivo*. But, many of the studies investigating the function of IL-12 have used IL-12 p40-deficient mice or antibodies specific for the p40 subunit, which is also a component of the recently characterized cytokine IL-23. Now, Daniel Cua and colleagues have generated mice deficient for IL-23 alone, and they show that IL-23, not IL-12, is the crucial cytokine controlling autoimmune inflammation in the brain.

IL-23-deficient mice were generated by targeting the p19 subunit of IL-23. The role of IL-23 was assessed using a MOG (myelin oligodendrocyte 35–55)-induced model of experimental autoimmune encephalomyelitis (EAE), in which inflammation of the central nervous system (CNS) is mediated by T_H1 cells and inflammatory macrophages. p35-deficient mice (lacking IL-12 only) were susceptible to EAE, whereas p40-deficient mice