IN THE NEWS

Gene therapy for HIV

A new therapy that has been described as "probably the most exciting of the anti-HIV strategies around at the moment" (Alan Kingsman, Oxford Biomedica; *BBC News*) is producing encouraging results in Phase I safety trials, according to a report in *New Scientist* (15 May 2004).

VRX496 uses anti-sense technology to prevent HIV replication. T cells are isolated from patients and infected with a modified form of HIV containing an anti-sense gene. T cells containing the integrated viral genome are re-infused into patients so that when HIV tries to infect the modified T cells *in vivo*, the anti-sense mRNA is produced and binds to the sense viral mRNA, thereby preventing translation of viral proteins.

So far, three patients who had failed two regimens of anti-retroviral drug therapy have been treated with VRX496. Boro Dropulic, Founder and Chief Scientific Officer of VIRxSYS Corporation, which is developing VRX496, says that no adverse events have been observed in these patients and they are encouraged by the finding that "viral load results are not above pre-dose levels and CD4 counts have remained stable" (*VIRxSYS*). On the basis of these results, the Data Safety Monitoring Board, USA, recommended in April that a further two patients should be enrolled in the trial without delay.

Assuming that no safety concerns arise, the therapy could soon enter Phase II trials to determine efficacy. However, not everyone is convinced. This is the first time that a lentiviral vector has been used in a clinical trial in humans, and concerns about recombination and other safety issues have led many researchers to abandon research into gene therapy, according to Richard Sutton of Baylor College of Medicine (*New Scientist*).

Kirsty Minton

AUTOIMMUNITY

The more the merrier

In a surprising new study published in *Cell*, Nora Sarvetnick and colleagues have shown that autoimmunity can be caused by insufficient numbers of T cells. This indicates that having a crowded immune system can actually be good for you and provides a possible explanation for the beneficial effects of a 'less-than-hygienic' environment.

They showed that female autoimmune-prone non-obese diabetic (NOD) mice have fewer peripheral $CD4^+$ T cells than control strains that do not develop autoimmunity. This lymphopaenia was associated with disease development, as increasing the number of T cells in NOD mice by injection of complete Freund's adjuvant (CFA; which contains T-cell stimulatory mycobacterial cell-wall components) protected the mice from developing diabetes. Furthermore, the effect was due to T-cell number rather than phenotype as the transfer of T cells from NOD littermates also prevented diabetes.

The artificial induction of lymphopaenia — for example, by irradiation — results in proliferation of the remaining T cells to fill the 'space' that is left. To see if this homeostatic expansion occurs in NOD mice, the authors monitored labelled NOD T cells expressing a T-cell receptor (TCR) specific for pancreatic β-cells after transfer to various hosts. These TCR-transgenic T cells only proliferated in lymphopenic NOD mice and not in NOD mice treated with CFA. Analysis of cell-surface markers such as CD62L to distinguish between classically activated and homeostatically expanding T cells was also used to show that a far greater percentage of the natural T-cell populations of NOD mice is undergoing homeostatic expansion compared with non-lymphopenic, non-autoimmune-prone mice. Importantly, NOD mice with the most proliferating T cells had the most severe pancreatic insulitis, which indicates that there is a direct link between homeostatic expansion and disease.

Part of the explanation for the lymphopenia of NOD mice might lie in the observation that they have increased levels of interleukin-21 (IL-21) production, leading to upregulation of IL-21 receptor (IL-21R) expression by T cells, and clear

HIV

Pulling out the stops

In the absence of an effective vaccine, blocking infection and transmission of HIV at mucosal surfaces might be our best chance of stemming the spread of HIV infection. Reporting in *The Journal of Experimental Medicine*, Qinxue Hu *et al.* explore the potential of HIV-1-specific antibodies and compounds that target HIV-1-binding cell-surface receptors to inhibit HIV-1 infection of and dissemination from human cervical tissue.

To infect cells, HIV-1 must interact with two receptors, CD4 and a co-receptor — CC-chemokine receptor 5 (CCR5) for R5 viruses and CXC-chemokine receptor 4 (CXCR4) for X4 viruses. Using a CD4-specific antibody or small molecule inhibitors of CCR5 and CXCR4, the authors could inhibit localized infection of mucosal tissue by R5 and X4 viruses, respectively. Although *in vitro* studies have identified viruses that can use other co-receptors, here, they show that infection of human cervical tissue using co-receptors other than CXCR4 or CCR5 is unlikely.

In addition to direct infection of mucosal tissue, HIV-1 can become attached to migratory cells, facilitating viral transmission and infection in lymphoid organs. Dendritic cells (DCs) that express the mannose-binding C-type lectin DC-SIGN are thought to be involved in this process. So, the authors collected migratory cells (which included both $DC\text{-}SIGN^-$ and $DC\text{-}SIGN^+$ DCs) emigrating from cervical explants after HIV-1 inoculation in the presence or absence of inhibitors, and assayed for infection of indicator cells in co-cultures. In contrast to infection of cervical tissue, uptake of HIV-1 by migratory cells was not inhibited by a combination of CXCR4 and CCR5 inhibitors, but was inhibited when CD4-specific antibodies and mannan were present. Presence of DC-SIGN-specific antibody also inhibited the capture of infectious virus by migratory cells, albeit to a lesser extent, indicating an important but not exclusive role for this receptor in virus capture and transmission.