Conference on Experimental AIDS Research in Genoa [1].

The basis for HIV gene therapy

Gene therapy for HIV has developed from previous work that has attempted to simply bolster the immune defences of HIV-infected patients by using their own T cells that are removed and then propagated *ex vivo* before reinfusion back into the same individuals. This approach initially failed because of the poor survival of the reinfused cells, which lacked the growth factors to resist apoptosis or avoid senescence.

Recently developed cell culture techniques are now enabling researchers to stimulate T cells to mimic the growth signals normally provided by dendritic cells *in vivo*, by using antibodies against the CD28 and CD3 surface T-cell receptors. These manipulations significantly enhance the survival of the reinfused cells in patients, as reported recently in a Phase I safety trial [2]. Gene therapy goes a step further, by introducing foreign genes into the T cells before reinfusion that encode products able to boost T-cell defences against HIV infection.

Phase I trials

In a recent Phase I study by June and colleagues [3], the T cells of HIV-infected patients were manipulated to express a hybrid protein consisting of the external portion of the cell surface receptor CD4, to which HIV normally binds before entry, and the internal portion of the T-cell antigen receptor. Upon HIV binding, the fusion protein triggers T-cell activation, so that regardless of the natural antigen specificity of the transfected T cells, they should become active against the HIV virus.

The results of the trial showed good long-term survival of the manipulated T cells in patients, comprising 1% of the circulating T-cell pool for at least one year post-treatment; however, there was no significant reduction of the amount of HIV. To address this, a Phase II follow-up trial is now under way, testing the efficacy of including T-cell-specific growth factor interleukin-2 in daily infusions, to see whether this enhances the elimination of HIV.

A new approach

As an alternative approach, June's collaborators at ViRxSys (http://www.virxsys.com) have developed a new vector consisting of a gutted-out version of HIV itself. Stripped of structural genes that normally complete the formation of mature virions, the RNA vector cannot replicate. The key gene-therapy element is a portion of antisense RNA that binds to and blocks the HIV gene that encodes the coat protein, glycoprotein 120.

In vitro tests of HIV-infected cell lines and freshly isolated blood cells show that the vector can be transfected into cells with up to 90% efficiency and inhibits replication of a variety of HIV isolates, according to June. In accordance with guidelines from the National Institutes of Health (NIH; http://www.nih.gov) [4], June's team must first complete extensive safety tests before proceeding with clinical trials, in particular to ensure that the vector does not recombine with wildtype HIV once inside patients. These tests include use of the severe combined immunodeficient (SCID-hu) mouse of the Balb/c strain, which contains an engrafted human immune system.

The initial Phase I trial of HIV as a gene therapy vector will involve the sequential treatment of five patients whose HIV infection is resistant to protease inhibitor drugs. After a month of monitoring to ensure that no recombination with wild-type HIV has occurred, the researchers could proceed to treating the next patient. They will then measure the patients' viral load by PCR analysis. Ultimately, June plans to introduce the vector into other cell types as well: 'We think in the long run we can make a transgenic human immune system,' he said.

This work was welcomed by George Lewis, an immunologist at the Institute of Human Virology at the University of Maryland Biotechnology Institute (http://www.umbi.umd.edu): 'I'm encouraged by what I saw: they're doing it right, they're doing it carefully, and getting interesting results.'

References

1 June, C.H. (2002) Use of lentivirus vectors to engineer T cells for immunotherapy of HIV infection. *7th European Conference on Experimental AIDS Research*, 8–12 June 2002, Genoa, (Abstract PS19)

2 Levine, B.L. *et al.* (2002) Adoptive transfer of costimulated CD4+ T cells induces expansion of peripheral T cells and decreased CCR5 expression in HIV infection. *Nat. Med.* 8, 47–53

3 Deeks, S.G. *et al.* (2002) A Phase II randomized study of HIV-specific T-cell therapy in subjects with undetectable plasma viremia on combination antiretroviral therapy. *Mol. Ther.* 5, 788–797

4 Posakoff, G.M. (2001) Lentiviral vectors approach the clinic but fall back: National Institutes of Health Recombinant DNA Advisory Committee review of a first clinical protocol for use of a lentiviral vector. *Mol. Ther.* 4, 282–283

Corrigendum

Please note a correction to the News article entitled *Glyxins to treat neurological disorders*, by Martina Habeck, published in *Drug Discovery Today* Volume 7, No. 13, pp. 690–691.

In the third column of the text on p. 690 and in the figure legend on p. 691, it incorrectly states that the tetrapeptide NT-13 is made up of the amino acids proline-threonine-threonine-proline. The correct amino acid sequence is threonine-proline-proline-threonine.

The author would like to apologize for this inaccuracy and for any confusion that this might have caused.

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