BIOBUSINESS BRIEFS

TRIAL WATCH

Novel HIV gene therapy enters Phase I trial

Most HIV strains use the chemokine receptor CCR5 to mediate entry into T cells. Indeed, a small-molecule drug that blocks CCR5, maraviroc (Selzentry/Celsentri; Pfizer), is approved for the treatment of HIV infection in combination with other classes of antiretroviral drugs (*Nature Rev. Drug Discov.* **7**, 15–16; 2008).

A recent initiation of a Phase I clinical trial highlights a novel genetic approach that aims to make T cells of patients infected with HIV resistant to CCR5-mediated viral entry. The trial involves modifying patients' own $CD4^+$ T cells using CCR5-specific zinc finger nucleases (ZFNs) (BOX 1) to disrupt the *CCR5* gene, before returning the T cells to the patient.

As Ramesh Akkina, Professor in the Department of Microbiology, Immunology and Pathology at Colorado State University, USA, explains: "If you can protect the patient's own T cells from HIV infection by approaches such as with ZFNs, this will help restore immunological function, without the need for cell transplantation and problem of graft rejection. If successful, this might ultimately help the body resist the virus by itself without the use of drugs."

The study, initiated by Sangamo Biosciences, will assess safety, the expansion and persistence of ZFN-modified cells, $CD4^+$ cell counts and viral load in patients who have failed to respond to more than two highly active antiretroviral therapy regimens, and in patients who are responsive to their current therapy.

Because this is the first time such an approach to HIV therapy has been studied in humans, there are numerous questions that remain to be answered.

"As with other somatic gene therapy approaches, the most important concerns are the efficiency of transduction, and the long-term persistence of the transduced $CD4^+$ cells. If these cells disappear quickly from the host, then the approach may have low potential for success," says Charles Flexner, Professor of Medicine, Pharmacology and International Health at Johns Hopkins University, USA. "An interesting question is what will happen if only a few cells are permanently transduced, but the patient is still susceptible to HIV-1 infection. Will the transduced T cells be sufficiently robust to make the patient immunologically normal?"

There are also uncertainties relating to genotoxicity due to off-target effects on other genes, long-term immunological consequences and the cost-effectiveness of the approach for use in large numbers of at-risk individuals. Moreover, as Akkina points out, "...disruption of CCR5 alone would not be adequate in the long run because there are other strains of HIV that do not depend on CCR5 for infection." However, if this strategy is successful, other genes that are essential for viral replication might be targeted simultaneously with this technology in the future, he notes.

A recent case report (*N. Engl. J. Med.* **360**, 692–698; 2009) adds support to the potential benefits of *CCR5* gene disruption in HIV. In this study, stem cells from a donor who was homozygous for *CCR5 Δ32* — an allele mutation that confers absolute resistance to the CCR5 receptor-using virus — were transplanted into a patient with acute myeloid leukaemia and HIV-1 infection. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy. However, this approach is unlikely to be a practical option for most patients with HIV.

Box 1 | **Zinc finger nucleases**

Zinc finger nucleases are recombinant proteins that contain multimers of zinc fingers — DNA-binding domains that coordinate a Zn^{2+} ion through cysteine and histidine residues (*Nature Rev. Drug Discov.* **2**, 361–368; 2003) — fused to a restriction enzyme. The zinc finger proteins enable a high specificity of nucleotide sequence recognition, and the restriction enzyme introduces double-stranded breaks into the genome. DNA repair mechanisms then lead to nucleotide deletions and insertions, resulting in disrupted gene function. The resultant defective protein is then degraded and not expressed on the cell surface.