Bone marrow transplant muffles HIV

An HIV-positive subject who received a bone marrow transplant for leukemia showed no evidence of the virus in his bloodstream after 20 months of follow-up, according to a report by Gero Hütter *et al.*[1]. In a rare and lucky match-up, his donor was not only compatible but also homozygous for mutations in the HIV receptor CCR5 that result in resistance to HIV infection. What do the findings mean for experimental stem cell therapies and efforts at targeting CCR5?

> "In the long run, the aim must be to achieve a sustained antiviral effect by direct *in vivo* gene transfer without prior cytoreductive therapy."—Dorothee von Laer

Carl June:

This study is simply a *tour de force* in the journey toward personalized medicine. The logistics of identifying a donor with these genetic characteristics were daunting.

What can we learn from this one-off experiment? Conventional wisdom would have predicted that residual host-derived CCR5-expressing cells would maintain infection; however, it is possible that this process is inefficient in a sea of CCR5-deficient $CD4^+$ cells. It is also possible that the HIV reservoir is confined to a population of radiosensitive cells, which would have been killed during the transplantation process.

Assuming the residual virus was fit, the question becomes what role does immunity have in the outcome? We have found that the homeostatic expansion of T cells that occurs in the context of an autologous stem cell transplant is a setting that generates potent immunity in otherwise immunosuppressed patients[2]. Perhaps Hutter *et al.*[1] have uncovered a unique approach for therapeutic vaccination?

Several more practical approaches to eliminate the HIV reservoir are being considered. For example, on the basis of preclinical research with zinc finger nucleases[3], we have initiated a pilot trial of adoptive transfers of CCR5-deficient $CD4^+$ T cells using an autologous source of T cells to generate the HIV-resistant cells (http://clinicaltrials.gov/ct2/show/NCT00842634/).

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John P Moore:

This study has received considerable media attention and has been hyped to an unwarranted extent by one or two AIDS support organizations (notably The American Foundation for AIDS Research). A more realistic view is that although the treatment has clearly benefited the individual patient, the approach has severe limitations when it comes to applying it more generally. Bone marrow ablation is a highly risky procedure that would only be used in extreme circumstances not applicable to the vast majority of cases of HIV-1 infection. The chances of a donor of replacement bone marrow having a genotype that is both suitable for transplantation and homozygous for the *CCR5* delta32 mutation are very slim. Some will argue that the study advances the case for gene therapies that target CCR5. But the theoretical arguments for such approaches have existed since 1996, and the substantive problems remain the ones common to these methods—such as safely knocking out *CCR5* in a sufficient number of target cells to make a difference to the viral load of a patient. Such real-world problems may not be unsolvable, but this study does not itself provide practical solutions.

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Dorothee von Laer:

Antiretroviral therapy must be lifelong, as it fails to purge the latent cellular reservoir of HIV-1 from which the virus rapidly rebounds if treatment is discontinued. The case described by Hutter *et al.*[1] provides evidence that it may be possible to eliminate this long-lived reservoir by myeloablation and T cell ablation followed by repopulation of the immune system with cells resistant to HIV-1. The results encourage the development of strategies involving transplantation of stem cells genetically modified to resist HIV-1 infection, especially for HIV-infected patients who need stem cell transplantation for the treatment of a malignant disease. The results are also in line with our thinking that, to be effective, a therapeutic antiviral gene must block the development of latently infected cells by targeting early steps of viral replication[4].

A pivotal question is whether the selective advantage of genetically modified cells will result in a therapeutic number of resistant cells in the subject. Clinical stem-cell gene therapy trials that can address this issue have been initiated in subjects with AIDS-related lymphoma (http://clinicaltrials.gov/ct2/show/NCT00569985; http://www.clinicaltrials.gov/ct2/show/NCT00858793). In the long run, however, the aim must be to achieve a sustained antiviral effect by direct *in vivo* gene transfer without prior cytoreductive therapy.

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1. Hütter, G. *et al.* Long-term control of HIV by *CCR5* delta32/delta32 stem-cell transplantation. *N. Engl. J. Med.* **360**, 692–698 (2009).
2. Rapoport, A. *et al.* Restoration of immunity in lymphopenic individuals with cancer by vaccination and adoptive T cell transfer. *Nat. Med.* **11**, 1230–1237 (2005).
3. Perez, E.E. *et al.* Establishment of HIV-1 resistance in $CD4^+$ T cells by genome editing using zinc-finger nucleases. *Nat. Biotechnol.* **26**, 808–816 (2008).
4. Von Laer, D., Hasselmann, S. & Hasselmann, K. Gene therapy for HIV infection: what does it need to make it work? *J. Gene Med.* **8**, 658–667 (2006).