Credit: Bloomberg/Rob Waters via Getty Images

MILESTONE 18

Editing a cure

Timothy Ray Brown—also known as the 'Berlin patient'—is the only person ever to be cured of HIV. His story and the research that followed are intimately linked to the discovery, back in 1996, that homozygosity for a CCR5 allele with a 32-base-pair deletion (delta32/delta32) renders some individuals resistant to infection despite exposure through sexual intercourse with HIV-positive partners (MILESTONE 15).

Brown was diagnosed with HIV in 1995 and a decade later underwent allogeneic hematopoietic stem cell transplantation (HSCT) for relapsed acute myeloid leukemia. But the transplant, performed by Gero Hütter of Charité–Universitätsmedizin Berlin, had a twist. Hütter used peripheral blood stem cells from a human leukocyte antigen (HLA)-identical donor that harbored the *CCR5* delta32 allele.

The procedure led to complete remission of the cancer and, remarkably, despite the long-lived viral reservoir (MILESTONE 11, 16) being expected to lead to HIV rebound and disease progression during the process of immune reconstitution, no active virus and no viral RNA or proviral DNA could be detected in the blood, bone marrow or rectal mucosa, even almost two years after transplantation and interruption of antiretroviral therapy (ART).

Although at the time of transplant Brown also carried HIV variants tropic for the CXCR4 chemokine receptor, Hütter reasoned that their numbers might have been too low to allow reseeding of the new immune system. A follow-up study showed that Brown's long-lived $CD4^+$ HIV target cells had been successfully replaced with donor-derived cells. Thus, the *CCR5* deletion in donor stem cells and their ability to engraft—killing Brown's infected cells—may have together contributed to the functional cure of HIV.

Yet, a similar approach subsequently performed in the so-called 'Boston patients' proved the latent reservoir of HIV to be far more resilient than previously thought. Timothy Henrich and Daniel Kuritzkes at Brigham and Women's Hospital in Boston gave HSCT to two HIV-infected men diagnosed with lymphoma, but used donor cells with wild-type *CCR5*. In this approach, despite a significant reduction in the size of the reservoir following transplant, both patients eventually experienced rebound viremia after cessation of ART.

Still, these landmark studies demonstrated the critical role that CCR5 has in maintaining HIV-1 infection and prompted further research into gene-based therapies to target HIV.

> "genome editing had been proven efficient in rendering T cells refractory to HIV infection"

Although genome editing had been proven efficient in rendering T cells refractory to HIV infection, it was not until years later, in 2014, that a team led by Pablo Tebas and Carl June at the University of Pennsylvania in Philadelphia showed this could be done in infected individuals. The clinical trial enrolled 12 patients who were infused with autologous $CD4^+$ T cells modified at the *CCR5* locus by zinc-finger nucleases (ZFNs). The patients who stopped ART after cell transfusion exhibited slow viral rebound and proliferation of the modified T cells, indicating enhanced control of the virus. Moreover, one study participant with no viral rebound during ART interruption was found to harbor a single mutated copy of *CCR5* and after transfusion a large proportion of this patient's T cells were resistant to HIV.

Together, these findings demonstrated that gene-targeting approaches could provide a safer and more practical approach than the risky and restrictive HSCT and opened the door for ZFNs and other gene-editing methods, such as TALENs and CRISPR, to be exploited in the targeting of latently infected cells.

Although many challenges remain, these groundbreaking discoveries, together with those on early ART initiation (MILESTONE 20, 21), broadly neutralizing antibodies (MILESTONE 19) and new-generation latency-reversing agents, are paving the way toward the development of a broad-scale and safe strategy for the complete eradication of HIV or its control in the absence of lifelong therapy.

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