The Yellow Brick Road towards HIV Eradication

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Abstract

A London patient living with HIV has become the second person to achieve HIV remission for more than a year after having received a bone marrow stem cell transplant from a donor with cells resistant to CCR5-tropic HIV. This case provides important clues in the uncertain path towards HIV cure.

Tremendous progress has been achieved with regard to treatment and prevention of HIV in the last decades. Combinatory antiretroviral treatment (cART) has transformed a deadly disease into a manageable chronic infection. cART drastically reduces viremia to undetectable levels in blood through inhibition of new rounds of cellular infections but is not capable to eliminate already infected cells. HIV persists in so-called viral reservoirs from where it rebounds as soon as cART is stopped. A therapeutic strategy targeting eradication of HIV is heartily sook but encounters multiple hurdles. HIV most likely possesses several non-exclusive mechanisms to persist once the infection is established. These mechanisms include escape from immune surveillance, clonal proliferation of infected cells and residual viral replication in immunoprivileged sites of the body, such as B cell follicles. Although HIV persists predominantly in intestinal mucosae and lymph nodes, it can be detected in nearly every tissue of the body during cART [1].

Despite these multiple mechanisms of viral persistence, one patient has been reportedly cured from HIV [2]. Timothy Brown, a.k.a. the “Berlin patient”, was diagnosed with HIV in 1995. After controlling viremia for several years thanks to cART, he was diagnosed with acute myeloid leukemia and, in 2007 and 2008, received two allogeneic haematopoietic stem-cell transplantations (Allo-HSCT) from a HLA-matched donor carrying a homozygous 32 nucleotide deletion (Δ32) in the *CCR5* gene. This mutation, which is relatively frequent in Northern Europe, renders cells resistant to CCR5-tropic HIV. The Berlin patient has remained off cART since the first day of his SCT, ie for 12 years. However, because of the complexity of the intervention, it is unclear which parameters were ultimately responsible for the elimination of the virus and the optimal resolution of the infection.

Recently, an HIV-1-infected adult underwent allo-HSCT in London for Hodgkin’s lymphoma using cells from a *CCR5Δ32/Δ32* donor [3]. CCR5-tropic, but not CXCR4-tropic viruses were identified in HIV-1 DNA from $CD4^+$T cells prior to transplant. Host genotype was *CCR5wt/wt* and full chimerism with *CCR5Δ32/Δ32* cells was achieved after transplant. cART was interrupted 16 months after SCT and no viral rebound has been observed 19 months after treatment interruption. Another patient in Düsseldorf who received allo-HSCT from a *CCR5Δ32/Δ32* donor has not shown viral rebound so far, 3 months since cART interruption (Jensen B. *et al*, CROI 2019 #394 P-E10). The comparison between the Berlin and London patients can help to better understand the mechanisms that led to successful suppression of the virus. The Berlin patient was himself CCR5Δ32 heterozygous, subject to total body irradiation and strong conditioning with each HSCT, and discontinued cART immediately during the first HSCT. The case of the London patient would indicate that a similar outcome can be achieved in *CCR5WT* individuals after a single *CCR5Δ32/Δ32* allo-HSCT and mild

conditioning, without total body irradiation or cART discontinuation during HSCT. In contrast, some degree of graft-versus-host reaction and early and sustained full donor chimerism in T cells was observed in both patients and are likely important events associated with HIV clearing.

The ICISTEM consortium (www.icistem.org) has assembled a large international cohort of HIV-positive individuals who have undergone allo-HSCT to treat diverse hematologic disorders. So far, thirty-nine participants, having received HSCT from matched CCR5Δ32 or wild-type donors, have been included in the cohort. This study has shown that allo-HSCT is unambiguously associated with a drastic reduction in the HIV reservoir, independently of engraftment with CCR5Δ32 or wild-type cells (Figure 1). In most cases allo-HSCT in presence of cART was followed by drop of all virological markers below detectable limits, possibly related to graft-versus-HIV-reservoir like effects [4].

However, allo-HSCT is not a scalable therapy for HIV infection and also does not systematically leads to HIV remission, even when full donor chimerism is achieved. Recently, three individuals who had undergone allo-HSCT with cells from *CCR5* wild-type donors, were reported to maintain undetectable viremia for 3 to 9 months following cART discontinuation before the virus reappeared [5,6]. Another HIV-1 infected adult (the “Essen patient”) developing anaplastic large-cell lymphoma underwent SCT with a *CCR5Δ32/Δ32* donor [7]. The virus rebounded 3 weeks after transplantation and genotypic analyses of HIV-1 variants in this patient showed a shift from a dominantly CCR5-tropic HIV before SCT toward a CXCR4-tropic HIV after transplantation. All these reports indicate that despite the dramatic reduction on the HIV reservoir associated with allo-HSCT, the effect is not absolute, and very few remaining infected cells would result in, possibly delayed, but vigorous rebound in viremia if no additional barrier exists to contain infection. The Berlin and London cases convincingly endorse the idea that full engraftment with *CCR5Δ32/Δ32* cells constitutes an effective block favoring HIV remission upon allo-HSCT. Thus, a kill and block approach seems required (Figure 1). More than 22,000 *CCR5Δ32* homozygous donors have been identified so far in the context of the ICISTEM initiative and may help the selection of suitable donors for HIV-infected individuals in need of allo-HSCT. Gene therapy approaches aiming at knocking out *CCR5* are under study (Figure 1). However, this raises the question of how to prevent the risk of emergence of subdominant CXCR4 viruses as was the case in the Essen patient? The role of immune responses may be critical to durably control infection. However, it is still unclear how immune responses against HIV evolve following allo-HSCT. HIV-1 Gag-specific CD4 and CD8 T cell responses and HIV-1-specific antibodies seem to drop following transplantation [3,4]. If some level of exposure to antigen occurred after transplantation, this

appeared insufficient to confer protection in allo-HCST recipients, and complementary immunotherapies may be needed in these individuals to achieve remission.

The cases of the Berlin and London patients also highlight our limits to define HIV cure. No signs of the virus have been found in numerous assays with multiple samples from diverse tissues that Timothy Brown has generously contributed to advance research over the last 12 years. In the case of the London patient, HIV-1 RNA has been undetectable at less than 1 copy per milliliter of plasma along with undetectable HIV-1 DNA in blood $CD4^+$T cells. Quantitative viral outgrowth assays using a total 24 million resting $CD4^+$T cells were negative. However, the presence of the virus in tissues from this patient remains unexplored. One HIV-infected child who deceased of graft-versus-host disease after transplant with cells from a *CCR5Δ32/Δ32* donor showed undetectable virus post-transplantation in the blood while virus was readily detected in multiple tissues [8]. In most occasions, tests similar to those used to characterize the Berlin and London patients failed to detect the virus during cART treatment and even for several months after cART discontinuation in the allo-HSCT patients with viral relapse [5]. Ultimately, only treatment interruption allowed revealing remission. Since only 19 months have passed after cART interruption in the London patient, it is premature to conclude that this patient has been cured. Moreover, will the duration of the off-treatment period be sufficient to cross the gap between remission and cure? Some individuals, natural controllers and post-treatment controllers, are able to maintain undetectable viremia for decades [9]. Although in most of these controllers the viral DNA is still readily detectable in the blood, in some cases the control is very stringent (with undetectable viremia at the single copy level), displaying weakly reactive or negative western blots and some experiencing a progressive decline in cell-associated HIV DNA and virus-producing cells till reaching undetectable levels in standard assays [10](Saez-Cirion *et al* unpublished). The definition of which individuals are cured or in remission remains therefore a difficult task and the road which will finally lead to a scalable HIV cure uncertain.

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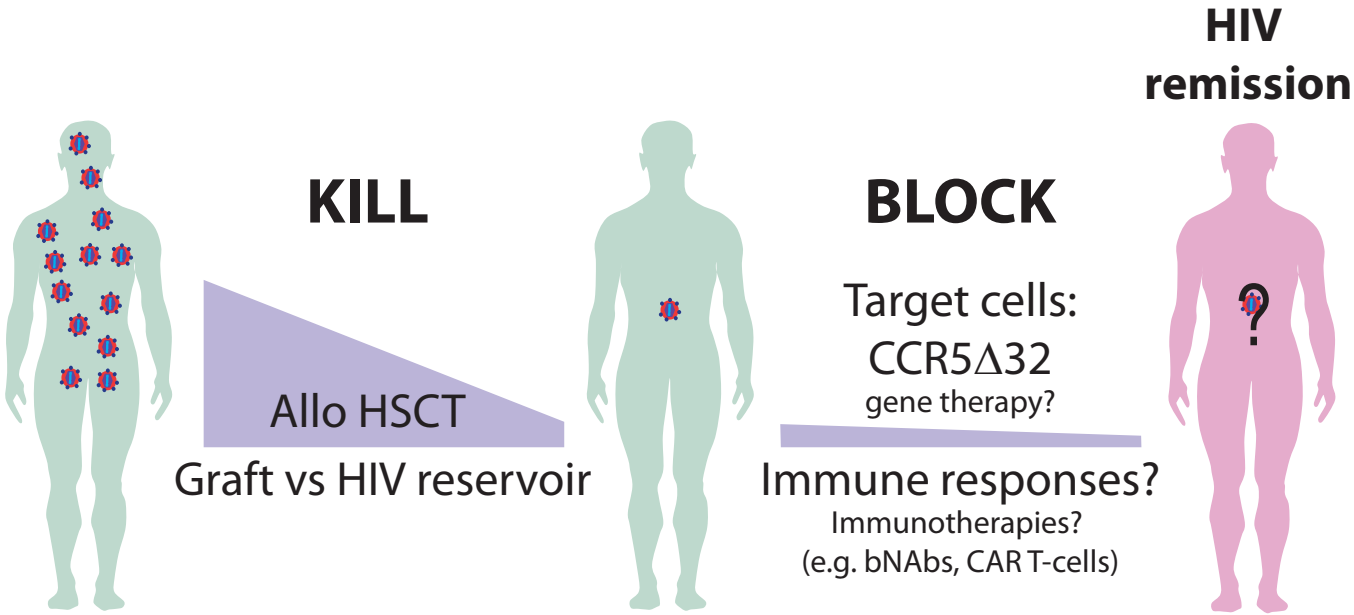
Figure 1. "Kill & block" strategy toward full remission of HIV infection. Allogenic haematopoietic stem-cell transplantation (Allo-HSCT) aiming at replacing the host cells by donor cells, is associated in HIV-infected individuals with a dramatic decrease of HIV reservoirs, probably favoured through graft-versus-HIV reservoir like mechanisms (the "kill" axis") [4]. However, some infected cells may remain, and to achieve durable remission of HIV infection, additional barriers to block the virus are possibly needed. One way to counteract infection is the engraftment with HIV-resistant (*CRR5Δ32/Δ32*) donor cells as demonstrated by the Berlin and London patients [2,3]. If no suitable donors are identified, alternative additional interventions might include the modification of target cells through gene therapy or boosting immune responses to control the remaining infected cells. bNab: broadly neutralizing Antibodies. CAR: Chimeric antigen receptor.


HIV
remission
KILL
BLOCK
Allo HSCT
Graft vs HIV reservoir
Target cells:
CCR5Δ32
gene therapy?
Immune responses?
Immunotherapies?
(e.g. bNAbs, CAR T-cells)
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