Curing HIV/AIDS Beyond HSCT?

Gene M. Shearer PhD\textsuperscript{1}, Mario Clerici MD\textsuperscript{2}, David R. Graham PhD\textsuperscript{3}, Adriano Boasso PhD\textsuperscript{4}

\textsuperscript{1} Experimental Immunology Branch, Center for Cancer Research, National Institutes of Health, Bethesda, MD, USA
\textsuperscript{2} Department of Physiopathology and Transplants, University of Milano and Don C. Gnocchi Foundation ONLUS, IRCCS, Milano, Italy
\textsuperscript{3} Department of Molecular and Comparative Pathobiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
\textsuperscript{4} Centre for Immunology and Vaccinology, Chelsea and Westminster Hospital, Imperial College London, London, UK.

Corresponding authors:

\textbf{Adriano Boasso PhD}
Imperial College London
Centre for Immunology and Vaccinology
Chelsea and Westminster Hospital
369 Fulham Road
London SW10 9NH
United Kingdom
e-mail: a.boasso@imperial.ac.uk

\textbf{Gene M Shearer PhD}
Experimental Immunology Branch
Center for Cancer Research
National Institutes of Health
Bldg 10, RM 4B-36
Bethesda, MD 20892
USA
e-mail: shearerg@dc10a.nci.nih.gov

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The case of Timothy Ray Brown, who received hematopoietic stem cell transplant (HSCT) from a CCR5 Δ32 donor to treat AIDS-related lymphoma (ARL), remains the only example of a patient cured from HIV infection[1]. HSCT from CCR5 wild-type donors failed to cure HIV in two other ARL patients, but delayed viral rebound after combined anti-retroviral therapy (cART) interruption[2, 3]. At least one of two conditions must be fulfilled to achieve HIV cure: elimination of all latent HIV reservoirs, or protection of CD4 T cells from de novo infection.

Purging viral reservoirs requires that all cells bearing functional HIV provirus are accessible for activation and susceptible to viral cytopathicity, and/or immune-mediated clearance. For the latter, it is essential that HIV-specific cytotoxic T lymphocyte (CTL) responses be restored[4].

Preventing infection of new targets may be more challenging. Transplants of rare heterologous human leukocyte antigen (HLA)-matched CCR5-Δ32 or autologous genetically-modified CCR5-KO HSC[5] may require immunoablation to ensure total resistance to infection.

There is general consensus on the hypothesis that some degree of graft-vs-host (GVH) reactivity may have reduced the viral reservoir in the HSCT patients who showed delayed viraemia rebound[5]. Thus, similar to the extensively-studied graft-vs-leukemia phenomenon[6], a graft-versus-viral reservoir effect (GVVR) could target host cells that survived immunoablation, thus shrinking the HIV reservoir. Could GVVR be exploited independently of immunoablation? Would it be advantageous, and how could it be delivered and tested?

Several independent reports spanning 40 years suggest a strategy for addressing these issues. Exposing non-ablated, cART-treated HIV patients to HLA-allogeneic leukocytes could simultaneously: 1) induce GVVR; 2) re-activate latent HIV reservoirs; 3) enhance or restore host HIV-specific immunity; and 4) activate restriction factors that prevent CD4 T cell infection (Figure 1).

Approximately 1:1000 T lymphocytes recognize allogeneic major histocompatibility complex molecules (MHC), 1000-fold more frequent than peptide-specific T lymphocytes[7]. MHC-allospecific T helper cell responses are retained in most asymptomatic HIV-infected patients[8], but these responses would be eliminated by immunoablation. Immunization with allogeneic leukocytes in immunocompetent women experiencing recurrent spontaneous abortion caused no major side effects[9], and resulted in enhanced resistance of CD4 T cells to in vitro HIV infection[10].

The combined reactions of donor T cells against patient MHC (graft-vs-host, GVH), and of patient leukocytes against donor’s MHC (host-vs-graft, HVG) could lead to HIV reactivation and enhanced presentation of retroviral peptides in deep anatomical sites (Figure 1). Thus, activation of host latent murine leukemia retrovirus was reported in a murine GVH model, including latent provirus in bystander T cells which do not recognize allogeneic MHC[11]. Similar experiments in rats showed increased MHC expression in host epidermal cells, gut epithelium[12], and MHC-negative nervous tissue[13].

Treatment with allogeneic donor cells could also promote host HIV-specific CTL-mediated immunity (host-versus-viral reservoir, HVVR) (Figure 1). Thus, stimulation with allogeneic leukocytes restored T cell-
mediated help to autologous influenza virus-specific[14] and HIV-specific CTLs (MC and GMS, unpublished observations).

Finally, stimulation with allogeneic MHC can activate a broad range of restriction factors (APOBEC3G, RANTES, MIP-1α/β and CD8-derived suppressor factor)[[10, 15], that could synergize with cART to protect CD4+ cells from HIV during reservoir reactivation.

Infusion of allogeneic cells into non-ablated HIV+ patients is less likely to cause GVH disease (GVHD) than HSCT[1-3]. The number and type of T cells infused and the number of infusions over time could be optimized to achieve GVVR, while abating the risk of GVHD.

The strategy we propose can be tested in simian immunodeficiency infected (SIV)-infected macaques to determine whether the injection of T cells from uninfected HLA-mismatched macaques into ART-treated, SIV-infected animals results in: 1) increased MHC expression, recruitment of donor T cells, and activation of latent SIV in multiple tissues; 2) enhancement of SIV-specific CTL responses; 3) activation of innate antiretroviral factors; and ultimately 4) spontaneous control of viraemia after ART interruption. This animal model could also determine the half-life of injected allogeneic T cells to provide critical information on the cell number and frequency of infusions required, as well as monitor signs of GVHD or autoimmunity.

HSCT with CCR5-defective cells proved successful in one case, but is unsuitable for large scale application due to the risks posed by immunoablation, elevated costs of the procedure, and need for prophylaxis against opportunistic infections. Other strategies aimed at reactivating latent HIV reservoirs using modulators of gene expression and chromatin structure are being investigated, and might require supplementation with immunotherapy to revive HIV-specific T cell responses[16]. By contrast, the combination of GVVR and HVVR could simultaneously achieve both goals by exposing latently HIV-infected “sleeper cells” to a cross-fire from both host HIV-specific and donor allogeneic T cells.
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REFERENCES

FIGURE LEGEND

Figure 1. Schematic representation of the key mechanisms activated by allogeneic MHC recognition during GVH and HVG reactions in HIV+ subjects receiving cART. Infusion of leukocytes from allogeneic healthy uninfected donors in HIV+ subjects (hosts) receiving effective cART will target the latent viral reservoir by: A) GVH-mediated reactivation and clearance of latently-infected cells (GVVR effect); B) GVH- and HVG-mediated reactivation of latently infected cells and purging by cytopathic effect under cART or HIV-specific CTL activity; and C) HVG-mediated stimulation of CD4 T helper cells which activate HIV-specific CTL activity. D) Protection of host and donor CD4 T cells from de novo infection by underlying cART and a combination of GVH/HVG-activated restriction factors.
**GvH**
Cytotoxic T lymphocytes (CTL) from the donor eliminate latently HIV-infected CD4 T cells in an allo-antigen specific graft-vs-viral-reservoir (GVVR) effect.

**HIV and GvH**
Exposure to allogeneic leukocytes promotes the reactivation of latent reservoirs and enhances the presentation of HIV peptides on host MHC (either by direct activation of HIV-infected CD4 T cells which recognize allogeneic MHC or via bystander mechanisms following the GvH reaction). Viral reservoirs are purged by viral cytopathic effect under cART or by residual host HIV-specific CTL function.

**HIV**
Host CD4 T cells activated by allogeneic leukocytes provide efficient CD4 T cell-mediated help to autologous HIV-specific CTL.

**GvH and HIV**
Stimulation with allogeneic MHC activates a broad range of innate HIV restriction factors [APOBEC3G, RANTES, MIP-1α, MIP-1β], which synergize with antiretroviral therapy to prevent de novo infection of target CD4 T cells.

**Clearance of latently infected cells under cART coverage**

**Protection of uninfected CD4 T cells from de novo infection**