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Development of CAR-T cells for long-term eradication and surveillance of HIV-1 reservoir

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Human immunodeficiency virus type 1 (HIV-1) reservoir is a pool of latently infected cells harboring replication-competent proviral DNA that limits antiretroviral therapy. Suppression of HIV-1 by combination antiretroviral therapy (cART) delays progression of the disease but does not eliminate the viral reservoir, necessitating lifetime daily administration of antiretroviral drugs. To achieve durable suppression of viremia without daily therapy, various strategies have been developed, including long-acting antiretroviral drugs (LA-ARVs), broadly neutralizing antibodies (bNAbs), and chimeric antigen receptor T (CAR-T) cells. Here, we summarize and discuss recent breakthroughs in CAR-T cell therapies toward the eradication of HIV-1 reservoir. Although substantial challenges exist, CAR-T cell technology may serve as a promising strategy toward HIV-1 functional cure.

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Introduction

The latent reservoir of human immunodeficiency virus type 1 (HIV-1) is a long-lived pool of latently infected cells harboring replication-competent viral DNA, which poses a major hindrance to cure HIV-1 infection [1,2]. Combination antiretroviral therapy (cART) significantly suppresses HIV-1 to an undetectable level in the blood, improves immune function, delays progression of the disease, and decreases mortality of HIV-1 patients. However, cART cannot eliminate the viral reservoir, and patients continue to take antiretroviral drugs for life [3]. In addition, toxicity and high costs often lead to discontinuation of cART in patients [4]. Therefore, the development of novel treatment strategies without such limitations are highly desirable.

HIV-1 latent reservoir is quite stable, with a half-life of 44 months, requiring nearly 73.4 years for complete clearance [5]. In addition to resting $CD4^+$ T cells, other cellular HIV-1 reservoirs include monocytes, macrophages, dendritic cells, hematopoietic progenitor cells, and microglial cells [6–11]. Since a 'sterilizing' cure for HIV-1 is difficult to achieve, a 'functional' cure for HIV-1 has become a global research priority [12]. For this purpose, several strategies have been proposed and attempted, including full/partial replacement of the immune system, 'shock and kill', and 'permanent silencing' [13]. However, to date, most of these strategies are still in the experimental stages, and none have been shown to eliminate the reservoir completely, many challenges still remain.

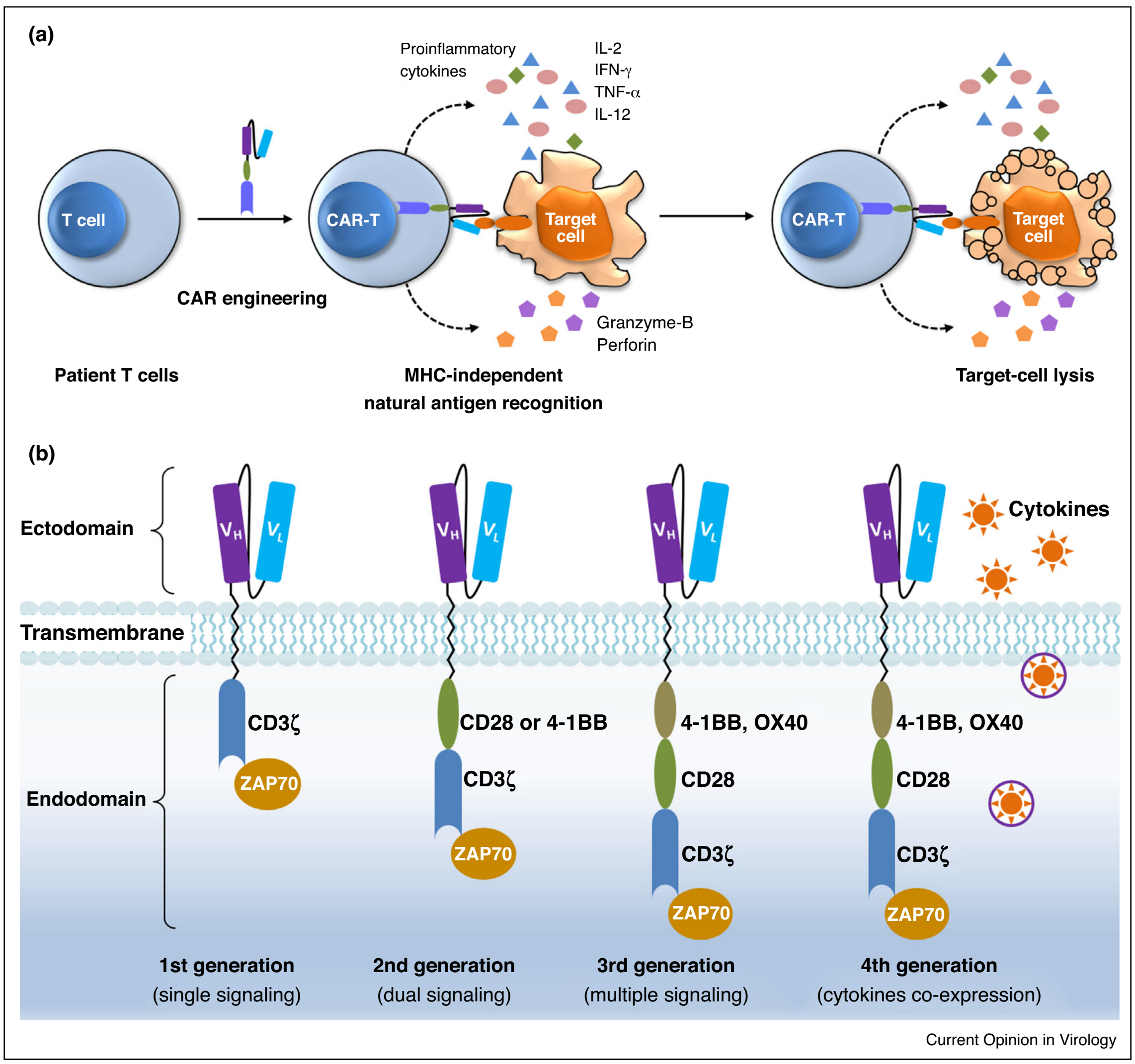
'Shock and kill' strategy requires re-establishment of potent antiviral immune surveillance

The 'shock and kill' strategy has been extensively tested and debated. By reactivating latent viruses from the reservoir, the immune surveillance system is expected to recognize and eradicate the HIV-1-expressing cells by cytotoxic T lymphocyte (CTL) response or antibody-dependent cellular cytotoxicity (ADCC). Several latency-reversing agents (LRAs) have been developed, including protein kinase C/nuclear factor-κB pathway activators, histone deacetylase inhibitors, H3K9 histone methyltransferase inhibitors, DNA methylation inhibitors, BET bromodomain inhibitors, and others [14–19]. However, recent data have shown that $CD8^+$ T cells in HIV-1-infected individuals on cART could not eliminate latently infected cells even after successful reactivation [20,21]. Therefore, recovery of the potent antiviral function of the immune system is required for the 'kill' strategy to work. For this purpose, rebuilding immune surveillance in patients by autologous adoptive transfer of *ex vivo* expanded HIV-1-specific $CD8^+$ T cells might be a feasible strategy [22–24]. Furthermore, with the discovery of broad-spectrum viral-specific CTL response, autologous adoptive transfer of HIV-1-specific $CD8^+$ T cells by broad-spectrum CTL epitopes could be developed as a therapeutic maneuver to promote the clearance of HIV-1 infected cells [25]. However, the dysfunction or exhaustion of HIV-1-specific CTLs, as well as the physical segregation between CTLs and infected cells, have prevented the endogenous immune responses from clearing HIV-1 infection [26–28].

CAR-T therapies flourish in the fight against cancers

Modification of $CD8^+$ T cells with chimeric antigen receptors (CARs), originated in the 1990s, has become a valuable modality for cancer treatment [29]. CAR-T cells are generated by combining an extracellular antigen-binding domain with an intracellular T cell activation domain to re-program T cells to overcome the barriers that confront natural T cells [30]. Compared with the tumor-infiltrating T cells/T cell receptor (TCR)-T cells, these CAR moieties allow T cells to target the native antigens with high affinity and in a major histocompatibility complex (MHC) independent manner [30] (Figure 1a). The intracellular portion of CAR-T design includes activation domains from different membrane-bound molecules. Three generations of CAR-T cells have been developed and tested in clinical trials. Recently, the so-called fourth generation of CAR-T cells have been created, which express various co-stimulatory ligands or pro-inflammatory cytokines including IL-2, IL-5, and IL-12 (Figure 1b) [31]. By the end of 2018, approximately 300 clinical trials involving CAR-T cells have been reported globally. Nearly 65% of these trials targeted hematological malignancies, and 80% involved CD19 CAR-T cells targeting B-cell leukemias or lymphomas

Figure 1



Depiction of mechanism and evolution of the CAR moiety.
(a) T cells isolated from the blood of patient are genetically engineered to express the CAR construct and endowed with antigen specificity. The binding of a CAR to the natural antigen delivers a potent activating signal that triggers T cell cytotoxicity, resulting in elimination of the target cell.
(b) Schematic representation of four generations of CARs. CARs are designed by the fusion of an antigen-binding domain derived from a mAb scFv with a hinge region, a transmembrane domain, and intracellular signaling domains. Each CAR has the CD3ζ chain as its main signaling domain. Additionally, CARs from the first generation have no co-stimulatory domain, whereas CARs from the second and the third generations have one and two co-stimulatory domains, respectively. Pro-inflammatory cytokines co-expressed by the CAR-T cells are depicted for the fourth generation.

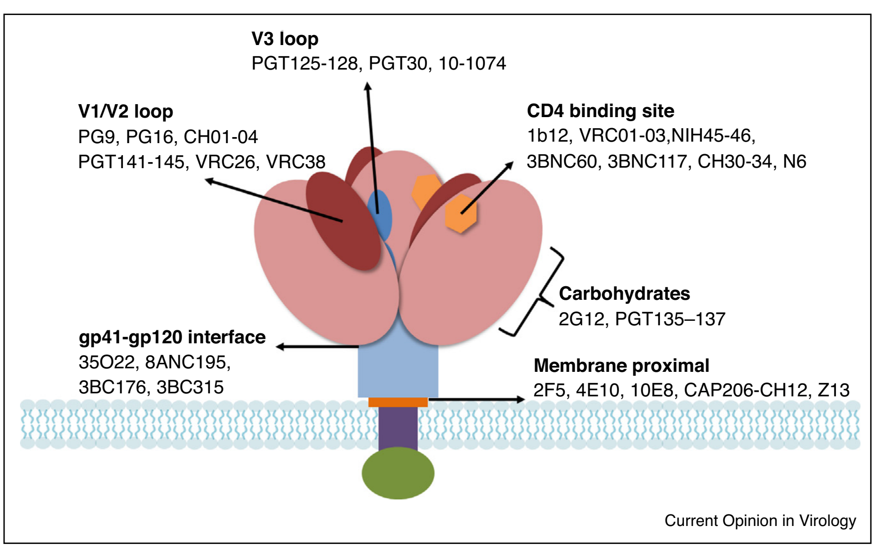
[32–35]. The clinical usage of CARs for cancer adoptive therapy is safe and highly effective, resulting in remission in approximately 83% of acute lymphocytic leukemia patients [33,36]. In 2017, CD19-targeted tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) have become the first two CAR-T therapies approved by FDA to treat relapsed/refractory B-cell precursor acute lymphoblastic leukemia and diffuse large B-cell lymphoma, respectively [37,38]. In addition to CD19, novel targets such as CD20, CD22, CD30, CD33, BCMA, and others, have been tested in the context of CAR-T for treating hematological malignancies [39–44]. Moreover, CAR-T studies began to explore the viability of other antigens of solid tumors and pathogens including HIV-1, hepatitis B virus, hepatitis C virus, and influenzas virus [45–48]. Despite significant progress of CAR-T therapy, several issues need to be addressed, (1) cytokine release syndrome (CRS), (2) neurological toxicity, (3) anaphylaxis, (4) on-target/off-tumor recognition, (5) insertional mutagenesis, and (6) durability of transferred cells [49].

Development of CD4-based, bNAb-derived scFv-based, and bispecific scFv-based CAR-T cells for clearing HIV-1-infected cells

Compared to CAR-T cells targeting tumor-antigens such as CD19 and CD20, which are also expressed in normal tissues, the HIV-1-specific CAR-T cells target HIV-1 envelope (Env) protein which is only expressed on the surface of virus-producing cells. An example of this technology is to fuse the extracellular domain of CD4 with the intracellular domain of the CD3ζ chain (CD4ζ-CAR) [50–52]. CD4 molecule on CAR-T or CAR-natural killer (NK) cells interacts with HIV-1 gp120 and redirects the specificity of T-effectors to virus-infected cells *in vitro* [50–52]. Compared to natural HIV-1-specific CTLs, viral mutants are unlikely to escape from CD4-based CARs because of a substantial replicative fitness cost [53]. This novel strategy was brought to the clinic in 1994 and was shown to be safe and feasible. However, the antiviral efficacy was modest and durable control of virus was not observed [54–58]. After these initial clinical trials, a new generation of CD4-CARs with advanced design are developed by including different parts of the co-stimulatory signaling moieties in the intracellular structure, such as those in CD28, CD127, OX40, and/or 4-1BB molecules, to optimize specificity in cytotoxicity, survival and memory/exhaustion phenotype of the modified CAR-T cells [59–62]. To prevent recognition of the CD4-CARs by HIV-1 as the target cells, the novel CD4-CARs are designed to co-express HIV-1 fusion inhibitors, such as membrane-anchored C peptide (an extended form of enfuvirtide) or peptides from the gp41 heptad repeat-2 domain [63,64]. Alternatively, constructs have been created to co-express small hairpin RNA targeting HIV-1 co-receptor CC-chemokine receptor 5 (CCR5) and the HIV long terminal repeat sequence, to prevent HIV-1 entry and mediate viral RNA degradation [65]. However, the clinical efficacy of the optimized CD4-based CAR-T therapies remains to be fully evaluated.

It has been reported that various HIV-1-specific bNAbs, which target different sites at gp120 and gp41, can block cell-cell transmission of HIV-1 and suppress viral replication (Figure 2) [66–71]. Subsequently, antigen-binding moieties of CARs containing single-chain variable fragments (scFvs) derived from bNAbs were developed, which target conserved sites within the Env protein, including the CD4-binding site, V1/V2 loop, V3 loop,

Figure 2



Binding-sites of bNAbs scFv-based CAR on the pre-fusion, closed HIV-1 Env trimer.

the gp41 membrane-proximal external region, and the variable glycan regions [53]. These bNAb-derived scFvs were connected to a second or third-generation intracellular CAR moiety [72–74]. These CAR-T cells effectively kill the reactivated viral reservoir isolated from HIV-1-infected individuals receiving cART, making it a particularly suitable therapeutic approach for eradication of HIV-1 reservoir [72]. Since the HIV-1 bNAb-derived scFvs have a stronger binding affinity to gp120 subunit than the CD4 moiety, the scFv-based CAR-T cells are more effective than CD4-CAR-T cells in cytolysis experiments [72,73]. Furthermore, the interaction between the bNAb-derived scFv and gp120 did not lead to fusion of viral membrane with cell membrane, thus reducing the ability of the virus to enter the modified $CD8^+$ T lymphocytes [72]. Moreover, to become a broadly applicable therapy, scFv-based CAR-T cells must overcome HIV-1 escape mutations in various viral strains and should not be immunogenic, so that they could persist for a long duration *in vivo*. Therefore, to prevent the pre-existing escape mutations that abrogate the recognition by bNAbs, CAR design enables simultaneous recognition of Env at two distinct sites (bi-specific CARs), which may increase the specificity and binding affinity to augment the potency of CAR-T cells against HIV-1 infection. For example, the extracellular CD4 segment is connected to either an HIV-1 bNAb-based scFv or the carbohydrate recognition domain of a human C-type lectin [75,76]. Currently, a modified bNAb-based CAR-T cell therapy developed by our group is undergoing clinical trial for latent reservoir eradication (NCT03240328). Another CD4-based CAR-T cell therapy with *CCR5* disruption, which developed by a group from the University of Pennsylvania, is also in clinical trial to eradicate HIV-1 reservoir (NCT03617198). The clinical safety and effectiveness of these therapies will be evaluated.

Enhancing the potency and safety of CAR-T cell therapy

Since only minimal amounts of antigen are present during the initial infusion of CAR-T cells into HIV-1-infected individuals on cART, the threat of a cytokine storm is unlikely. Even if the transferred CAR-T cells fail to control the viral rebound after treatment interruption, the possible cytokine storm driven by expanded antigens could be reduced by IL-6 blockade and the rebound virus could be suppressed soon after cART is reintroduced [77]. Several strategies have been proposed to minimize safety risk of these approaches. Directing a CD19-specific CAR to the T-cell receptor α locus results in CAR integration into specific genomic loci using the adeno-associated virus [78]. This method could also be applied in the HIV-1 immunotherapy to produce uniform HIV-1-specific CAR-T cells lacking CCR5 expression [74]. Furthermore, to improve the safety of HIV-1-specific CAR-T cells which persistently survive *in vivo* for a long time, the engineered CAR-T cells could carry suicide genes, such as herpes simplex virus thymidine kinase and inducible caspase 9, as a safety switch to eliminate potential adverse effects [79–81].

According to previous studies, infected $CD4^+$ $CXCR5^+$ T follicular helper cells (T_{FH} cells) in follicles of lymphoid tissue constitute a major reservoir for HIV-1 during cART [82,83]. The expression of CXC chemokine receptor 5 (CXCR5) on the cell surface is responsible for the cytotoxic potency and trafficking of cells into the B cell zone through interaction with the CXC-chemokine ligand 13 [84,85]. Unfortunately, recent studies have shown that the majority of virus-specific CTLs have markedly reduced expression of CXCR5 and are absent from the follicles [86,87]. Alternatively, several studies show that effector T cells lose their efficacy over time and may become exhausted (T_{EX}) in chronic viral infection during cART, with marked upregulation of check-point blockers such as CTLA4, PD-1, Lag-3, Tim-3, Tigit, or CD160 [88–91]. Accordingly, ectopic expression of CXCR5 on HIV-specific CAR-T cells might promote their homing to lymph nodes to target latently infected T_{FH} cells [92,93]. Meanwhile, blockade of check-points may decrease the exhaustion state and maintain the cytolytic function [94–96]. Such modifications allow CAR-T cells to clear these latent viral reservoirs efficiently and completely.

Long-term efficient eradication and surveillance of HIV-1 latent reservoir

Several novel methods have been explored for both as add-on therapy to existing cART and as agents to be used during treatment interruption. The current approaches include long-acting antiretroviral drugs (LA-ARVs), monoclonal antibodies or modified immune cells, which have been developed to varying stages and showed limitations in the early clinical trials. Through engineering release pharmacokinetics or bioactive properties, theLA-ARVs are developed with extended half-lives and durable antiviral activity, addressing poor adherence or treatment fatigue due to daily use of antiretroviral agents [97]. For instance, rilpivirine and cabotegravir, two novel long-acting injectable antiviral agents, have exhibited a promising profile of safety, tolerability, and prolonged activity in early clinical trials [98,99]. Polymer implant 4′-ethynyl-2-fluoro-2′-deoxyadenosine (MK8591, $T_{1/2} > 72$ hours) is another long-acting orally administered antiviral agent, acting as a nucleoside reverse transcriptase translocation inhibitor [100,101]. Despite treatment advances of LA-ARVs, there are issues including high cost, drug–drug interactions, intractable side effects, latent viral infection within reservoir sites, and development of resistance. There is also a risk of prolonged fetal exposure if pregnancy occurs before systemic clearance of the LA-ARVs [97]. These issues highlight the need for novel antiretroviral therapies.

Re-activation of potent HIV-1-specific immune surveillance is a feasible approach for long-term suppression of the reactivated latent viral reservoir without continuation of cART. Through ADCC and antibody-mediated phagocytosis, bNAbs could effectively recognize the virus-producing cells and mediate the eradication of HIV-1-producing cells. Therefore, use of bNAbs to eradicate HIV-1 reservoirs has been proposed and tested. Studies have shown that potent monoclonal antibodies effectively control viral replication in humanized mice and rhesus macaques [102–106]. In several early clinical trials, 3BNC117 or VRC01, two bNAbs that target the CD4 binding site on the HIV-1 envelope spike, led to significant reduction in viremia in cART-untreated patients [107,108]. Notably, four to six infusions of these bNAbs enhanced the clearance of HIV-1 from infected cells and led to a delay of viral rebound between 4–10 weeks after cART interruption [109,110]. Given that HIV-1 quickly mutates to escape from a single antibody, combination of bNAbs (3BNC117 and 10-1074) significantly inhibited viremia rebound for as long as 21 weeks in some HIV-1-infected individuals after cART interruption, and none of the enrolled individuals developed resistant viruses to either of these two antibodies [111]. Although the bNAb therapy represents a promising strategy for reactivating a durable antiviral immune surveillance, their delivery into patients is a passive immunization mode and the half-span of these bNAbs are approximately 7–21 days in the HIV-1-infected individuals, which hinders the utility of this therapy for long-term viral suppression (Figure 3).

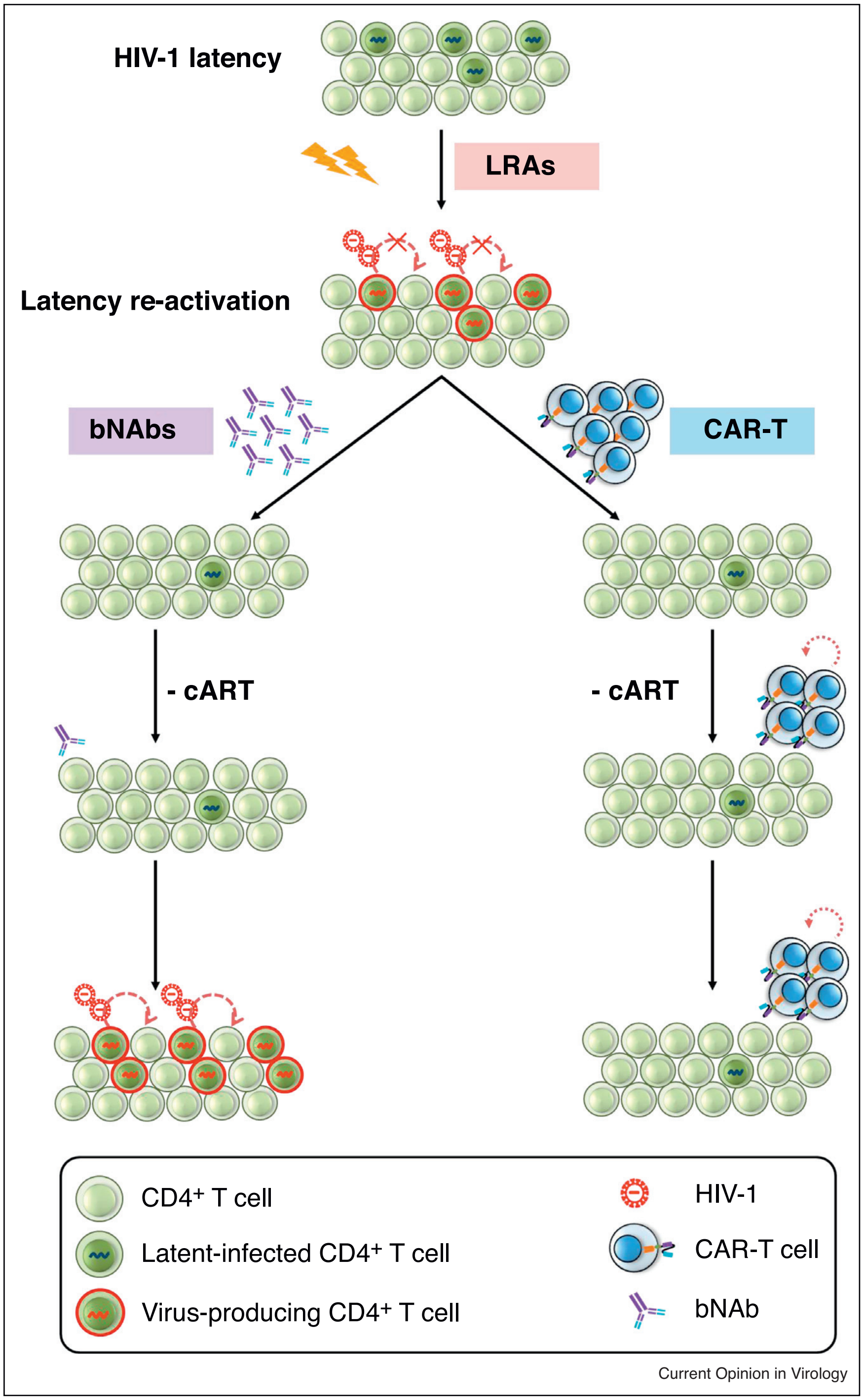
In contrast to small molecule drugs or antibodies, the transferred CAR-T cells act as a 'living drug' with the potential long-term survival *in vivo* [112,113]. The half-life of CD4ζ CAR-T cells *in vivo* could be as long as 10 years [57]. Although the immune response and the quantity of infused CAR-T cells may decrease due to clearance, the remaining effectors could turn into the memory state and traffic to immune cell niche [62]. If viremia rebound occurs, antigen-specific CAR-T clones could expand rapidly. Thus, CAR-T cells may provide long-term immune surveillance on the viral reservoir without the continuation of cART (Figure 3). It is known that *in vivo* persistence of CAR-T cells correlates with clinical responses for their anti-tumor effect. Previous reports also show that *in vivo* persistence of CAR-T cells correlate with the specific cell subsets, such as central memory T (T_{CM}) cells or stem cells memory T (T_{SCM}) cells, which exhibit greater antitumor potency by increased resistance to cell death, while preserving the ability to migrate to secondary lymphoid organs [114,115]. Besides, the infused CAR-T cells homing to the spleen, bone marrow, and other lymphoid organs were observed in long-term engraftment in the xenograft mouse model [116]. Interestingly, a recent study showed a significant *in vivo* expansion of CAR-T cells that originated from a single clone in which the lentiviral vector-mediated insertion of the transgene disrupted the *TET2* gene [117]. The expanded CAR-T cells display a significant T_{CM} phenotype and long-term survival *in vivo* [117]. As a result, these CAR-T cells induce complete remission of lymphoma. Alternatively, a recent report showed that a transcription factor NR4A played an important role in the cell-intrinsic program of T cell exhaustion [118]. The *Nr4a*-knockout CAR-T cells promote tumor regression and prolong the survival of tumor-bearing mice [118]. These interesting observations show that knockout of genes such as TET2 or NR4A may be promising strategies for improving the long-term stability of CAR-T cells *in vivo*. In addition, to overcome the limited persistence of peripheral T cell-based therapy, hematopoietic stem and/or progenitor cell (HSPC)-based gene therapy were developed by incorporating HIV-1-specific TCR or CAR moieties, which could reduce the magnitude of rebound viremia in the animal model [65,119]. The CAR-engineered HSPCs maintain the potential to differentiate into multiple hematopoietic lineages and infiltrate into different tissues, which may contribute to the long-term anti-viral immune surveillance and to eradicate the hidden reservoir [119].

Since mutations create HIV-1 resistance to the LA-ARVs and single bNAb therapy, a combination of CAR-T cells recognizing multiple distinct regions on the HIV-1 Env should potentiate their long-term surveillance on the viral reservoir. Besides, the combination of CAR-T cell therapy with highly efficient LRAs merits evaluation for functional cure of HIV-1 in future clinical trials.

Perspectives

Compared to tumor-associated antigens which express in both normal and tumor tissues, anti-HIV-1 CAR-T cells engage the HIV-1 Env protein, which is expressed only on the surface of virus-producing cells [53]. Furthermore, compared to solid tumor antigenicity, the antigenicity of HIV-1 Env is relatively strong. The mutation rate is within control when effective cART is administered. The latently HIV-1-infected cells are relatively more accessible. The antigen presentation is predictable to a great extent. Finally, the microenvironment around HIV-1-infected cells is not immune-suppressive as seen in solid tumors. Therefore, the chance of immune cell-therapy to successfully suppress HIV-1 viremia with long-term efficiency is much higher than suppressing the growth of various solid tumors. However, despite advantages with each type of antigen-targeting moiety, it is anticipated that more potent scFv-based CAR-T cells will be generated by improving CARs design. Moreover, the good manufacturing practice compliant manufacturing protocols, clinical safety, efficacy, and durability require further optimization [120]. We are optimistic that the CAR-T cell strategy, in combination with adaptively transferred broad-spectrum CTLs or bNAbs, should eradicate the persistent HIV-1-producing cells by enhancing the immune surveillance and maintain a long-term viral suppression without the continuation of cART.

Figure 3



The CAR-T cells possess the possibility of long-term immune surveillance on HIV-1 reservoir.
The 'shock and kill' strategy could be useful in reducing the size of HIV-1 reservoir. Although bNAb could eradicate the residual HIV-1-producing cells and persistently suppress viral replication, it suffers from a short half-life *in vivo*. Thus, this approach requires frequent injections, otherwise the viremia would rebound soon. In contrast, CAR-T cells could act as a 'living drug' with the potential of self-renewal and long-term survival *in vivo*. This approach therefore may provide long-term immune surveillance on viral reservoir without the continuation of cART.

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