



## On the Road towards HIV Cure: Targeting Latent Reservoir to Inhibit Viral Re-activation

Huafeng Lin<sup>1,2\*</sup>

<sup>1</sup>Department of Biotechnology, College of Life Science and Technology, Jinan University, Guangzhou, Guangdong, P.R. China

<sup>2</sup>Institute Research of Food Safety and Nutrition, Jinan University, Guangzhou, P.R. China

\*Corresponding author: Huafeng Lin, Department of Biotechnology, College of Life Science and Technology, Jinan University, Guangzhou, Guangdong, P.R. China, E-mail: 88983088@qq.com

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### Short Communication

AIDS (Acquired Immune Deficiency Syndrome) is now no long a lethality infectious disease as previously reported, thanks to the suppression of HIV-1 (Human Immunodeficiency Virus Type 1) replication by antiretroviral drugs which leading to decrease in viral load. Using the combination antiretroviral therapy (cART) or highly active anti-retroviral therapy (HAART), researchers can eliminate most of viruses from patient's body. However, cART (or HAART) is not curative. The biggest hurdle for the treatment of HIV infection still focuses on the latent viral reservoir. Ho et al. pointed out that the size of the latent viral reservoir which identified by replication-competent noninduced pro-viruses may be at least 60-fold greater than previously estimated by induced pro-viruses [1]. Interestingly, due to the incorrectness for making spliced HIV-1 RNAs or the unsuccessful packaging genomes into virions, 98% of pro-viruses were probably replication defective [1,2]. Hence, enormous on-going endeavors on searching a way to target the latent virus in order to effectively inhibit the viral re-activation have been made. Up to now, what ways can we use to combat against HIV?

Recently, Borducchi et al. utilized a two-pronged method (the combined use of Vesatolimod (GS-9620) and Broadly Neutralizing Antibody PGT121) to target the latent HIV [3]. In this paper, Borducchi et al. used GS-9620 to simultaneously activate the CD4<sup>+</sup> T cell and NK cell, then in the present of PGT121, the roused NK cell mediate the programmed death of CD4<sup>+</sup> T cells that harbouring with latent viruses (hybridization of HIV and SIV (Simian Immunodeficiency Virus)). This study showed great promise in targeting latent viral reservoir and resisting the re-activation of viruses using a combination of drugs of GS-9620 and PGT121 in monkey models [3].

**Gene Therapy:** This novel genome editing technologies hold great promising in the treatment of HIV. Three kinds of genome editing tools: zinc-finger nucleases (ZFNs), transcription activator like effector nucleases (TALENs), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 system have been studied to target and disrupt HIV co-receptors (*CCR5* gene), intact pro-viral sequence and latent viral reservoirs [4-8]. More importantly, the combination of cART and CRISPR-based approaches has produced encouraging results for HIV re-activation [8, 9].

**Bone Marrow Transplantation:** The first case of cure is an HIV-infected patient in Berlin in 2009, who received an allogeneic bone marrow transplant from a donor who carrying homozygous *CCR5-*

$\Delta 32$  allele, which is naturally resistant to infection with HIV [10, 11]. In 2013, another two possible cure of HIV-infected individuals who received bone-marrow transplants with cells that having functional *CCR5* chemokine receptor. Very disappointedly, the viruses rebound had been reported in both of their body of the two 'Boston patients' after the drug interventions [12]. However, it is still not very clear that what mechanism works in helping 'Berlin patient' to achieve functional cure? Tracing it to its cause, apart from the deficiency of a functional *CCR5* (or *CXCR4*) co-receptor, it could be attributable to other influential factors such as the choice of transplant regimens for bone marrow, the chemotherapy of anti-T-cell, graft-versus-host effect and patients' constitution, etc. [13].

**New Strategies to Fight against HIV:** In addition to the three main anti-HIV choices mentioned above, researchers have developed a variety of alternative techniques to combat HIV. For example, JAK inhibitors such as FDA approved Tofacitinib and Ruxolitinib [14], the APOBEC protein family [15], and broadly neutralizing HIV-1 antibodies (bNAbs) [16], etc.

Researchers have dedicated themselves to develop drugs to eradicate HIV. From the points of Chinese medicine, to some extent, that is not quite enough. One thing is also important for the recovery of HIV patients-strengthening the body resistance to eliminate pathogenic factors [8]. Consequently, what we can do for the HIV-infected person? (1) Common concern and cooperation in combating to AIDS should be supported by the material, spiritual, international powers. (2) Early diagnosis and intervenient controlling of infection using ART or HAART could minimize the scale and complexity of the latent viral reservoir, and might lead to late disease mitigation and control. (3) Enhance the capacity of the host immunity to clear the virus, and develop new technology to target and eradicate the latent reservoir. Nowadays, success to destroy the HIV reservoir and attaining a functional cure has happened in an unexpected way seen from the 'Berlin patient' [17]. This really brings hope for HIV/AIDS therapy, and much more effort should be put forth on the way of HIV eradication.

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