

HIV Latency Reversal Agents: Effective for Cure?

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Editorial

Combinatorial antiretroviral therapy (ART) has successfully allowed rapid suppression of HIV replication in patients thereby reducing their viral burden [1]. However, ART is not curative and a minor fraction of the infected cells revert from their activated state to a quiescent state allowing persistence of the virus in the presence of ART [2]. These cells harboring the HIV-1 provirus contribute to the latent reservoir in patients [3]. Studies have shown the reservoir to be seeded very early after the primary infection of the host [4]. The absence of any detectable viral biomarkers on the cell surface prevent the cells harboring these provirus from detection by the immune system of the host, thereby evading the host immune responses and persisting for long periods, often the lifetime of the host. Researchers have recognized the herculean challenge of eradication of this persistent virus of prime importance and have tinkered with multitude of strategies to address the problem [5]. One approach that has received enormous attention is the “shock and kill” strategy that has used small molecules to induce provirus transcription followed by synthesis of HIV proteins and virion formation [6]. The premise of the strategy is that the cells harboring the virus would eventually die by virus mediated cytopathic effects or immune mediated clearance.

The past 5 years have seen a surge of small molecules that have aimed to sniff out the hidden provirus out of its hiding cell leading to initiation of more than 15 clinical trials as of 2017 [7]. Many of these agents have targeted specific signaling pathways in the cell that would cause the cell to migrate to an activated state and proliferate. Protein kinase activators like Bryostatins, Ingenols and Prostratin were among the initial members to demonstrate *in vitro* activation of engineered cell lines bearing HIV proviruses. Their unacceptable cytotoxicity limitations [8,9] prevented their trials *in vivo* or resulted in failure of HIV rebound in performed trial [10]. However modified bryostatin analogs with lowered toxicity have recently shown promising viral rebound in engineered humanized BLT mice [11]. These and similar refinement efforts could lead to valuable latency reversal candidates for clinical trials. Other signaling modifiers including disulfiram that inhibits PTEN enzyme in the cell, thereby targeting the Akt pathway and benzotriazole analogs that block the process of SUMOylation of STAT5, a transcription factor, have also shown to reactivate HIV [12,13], but were inadequate for robust *in vivo* reactivation or need co-stimulation with cytokines. The most extensively studied group of HIV reactivators belong to a class of epigenetic modifiers that inhibit an enzyme called Histone deacetylase (HDAC inhibitors) in the chromatin of the provirus-bearing cells [14-16]. A variety of these molecules have shown to reactivate provirus in engineered HIV cell lines *in vitro* and patient samples *ex vivo*. Clinical trials with these agents, albeit have shown modest to no viral rebound. Other epigenetic modifiers like bromodomain inhibitors [17,18] and SMYD inhibitors (methylation blockers) [19] have also been the target for HIV reactivation with limited success so far.

The wide variety of molecules that have been examined for HIV reactivation has indeed demonstrated that reactivation of the virus from its sleeping state is not achievable in a one-step mechanism. There is interdependency of the virus on probably numerous host factors to achieve even one single round of virus production. This realization did prompt many researchers to attempt combinatorial approaches to virus reactivation and even succeed with a better response than using

single agents, nevertheless the response seems modest for potential clinical use [20-22]. While the possibility of more potent candidates or combinations is perceivable, rationale suggests that most, if not all of these molecules induce clinical toxicity because of their dissemination into and thereby activation of bystander cells that do not harbor the virus. In fact, it has been experimentally demonstrated that many of the latency reversal agents fail at clinically relevant concentrations [23]. Many researchers have suggested focusing on “killing agents” such as apoptosis inducers as an alternative over “shocking” agents, as the latter would be dependent on downstream viral cytopathic effects [24]. However, this may not be a very valuable perception given the bystander effect mentioned above, unless the therapeutic index (ratio of potency over cytotoxicity) of these killing molecules are very high. Isolated attempts to address the therapeutic index were performed by using nanoparticles that were aimed to deliver HIV kill agents like melittin to infected cells with minimal cytotoxicity to bystander cells [25]. Whether such a potent molecule or a cocktail of potent molecules would effectively purge out all HIV by reactivating them from latently infected patient cells (leading to the reduction of viral burden in ART-suppressed patients), would require a great deal of insights into strategies that would effectively reduce their bystander effects and *in vivo* cytotoxicity while retaining potency.

References

1. Perelson AS, Essunger P, Cao Y, Vesanen M, Hurley A, et al. (1997) Decay characteristics of HIV-1-infected compartments during combination therapy. *Nature* 387: 188-191.
2. Martinez-Picado J, Deeks SG (2016) Persistent HIV-1 replication during antiretroviral therapy. *Curr Opin HIV AIDS* 11: 417-423.
3. Blankson JN, Persaud D, Siliciano RF (2002) The challenge of viral reservoirs in HIV-1 infection. *Annu Rev Med* 53: 557-593.
4. Whitney JB, Hill AL, Sanisetty S, Penaloza-MacMaster P, Liu J, et al. (2014) Rapid seeding of the viral reservoir prior to SIV viraemia in rhesus monkeys. *Nature* 512: 74-77.
5. Siliciano JD, Siliciano RF (2013) HIV-1 eradication strategies: design and assessment. *Curr Opin HIV AIDS* 8: 318-325.
6. Deeks SG (2012) HIV: Shock and kill. *Nature* 487: 439-440.
7. Rasmussen TA, Lewin SR (2016) Shocking HIV out of hiding: Where are we with clinical trials of latency reversing agents? *Curr Opin HIV AIDS* 11: 394-401.
8. Clutton G, Xu Y, Baldoni PL, Mollan KR, Kirchherr J, et al. (2016) The differential short- and long-term effects of HIV-1 latency-reversing agents on T cell function. *Sci Rep* 6: 30749.
9. Dental C, Proust A, Ouellet M, Barat C, Tremblay MJ (2017) HIV-1 latency-reversing agents prostratin and bryostatin-1 induce blood-brain barrier disruption/inflammation and modulate leukocyte adhesion/transmigration. *J Immunol* 198: 1229-1241.

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10. Gutierrez C, Serrano-Villar S, Madrid-Elena N, Perez-Elias MJ, Martin ME, et al. (2016) Bryostatin-1 for latent virus reactivation in HIV-infected patients on antiretroviral therapy. *AIDS* 30: 1385-1392.
11. Marsden MD, Loy BA, Wu X, Ramirez CM, Schrier AJ, et al. (2017) In vivo activation of latent HIV with a synthetic bryostatin analog effects both latent cell "kick" and "kill" in strategy for virus eradication. *PLoS Pathog* 13: e1006575.
12. Xing S, Bullen CK, Shroff NS, Shan L, Yang HC, et al. (2011) Disulfiram reactivates latent HIV-1 in a Bcl-2-transduced primary CD4+ T cell model without inducing global T cell activation. *J Virol* 85: 6060-6064.
13. Bosque A, Nilson KA, Macedo AB, Spivak AM, Archin NM, et al. (2017) Benzotriazoles reactivate latent HIV-1 through inactivation of STAT5 SUMOylation. *Cell Rep* 18: 1324-1334.
14. Archin NM, Kirchherr JL, Sung JA, Clutton G, Sholtis K, et al. (2017) Interval dosing with the HDAC inhibitor vorinostat effectively reverses HIV latency. *J Clin Invest* 127: 3126-3135.
15. Rasmussen TA, Tolstrup M, Brinkmann CR, Olesen R, Erikstrup C, et al. (2014) Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: A phase 1/2, single group, clinical trial. *Lancet HIV* 1: e13-e21.
16. Sogaard OS, Graversen ME, Leth S, Olesen R, Brinkmann CR, et al. (2015) The depsipeptide romidepsin reverses HIV-1 latency in vivo. *PLoS Pathog* 11: e1005142.
17. Boehm D, Calvanese V, Dar RD, Xing S, Schroeder S, et al. (2013) BET bromodomain-targeting compounds reactivate HIV from latency via a Tat-independent mechanism. *Cell Cycle* 12: 452-462.
18. Lu P, Qu X, Shen Y, Jiang Z, Wang P, et al. (2016) The BET inhibitor OTX015 reactivates latent HIV-1 through P-TEFb. *Sci Rep* 6: 24100.
19. Boehm D, Jeng M, Camus G, Gramatica A, Schwarzer R, et al. (2017) SMYD2-mediated histone methylation contributes to HIV-1 latency. *Cell Host Microbe* 21: 569-579.
20. Laird GM, Bullen CK, Rosenbloom DI, Martin AR, Hill AL, et al. (2015) Ex vivo analysis identifies effective HIV-1 latency-reversing drug combinations. *J Clin Invest* 125: 1901-1912.
21. Hashemi P, Barreto K, Bernhard W, Lomness A, Honson N, et al. (2017) Compounds producing an effective combinatorial regimen for disruption of HIV-1 latency. *EMBO Mol Med*.
22. Jiang G, Mendes EA, Kaiser P, Wong DP, Tang Y, et al. (2015) Synergistic reactivation of latent HIV expression by Ingenol-3-Angelate, PEP005, targeted NF- κ B signaling in combination with JQ1 Induced p-TEFb activation. *PLoS Pathog* 11: e1005066.
23. Bullen CK, Laird GM, Durand CM, Siliciano JD, Siliciano RF (2014) New ex vivo approaches distinguish effective and ineffective single agents for reversing HIV-1 latency in vivo. *Nat Med* 20: 425-429.
24. Kim Y, Anderson JL, Lewin SR (2018) Getting the "Kill" into "Shock and Kill": Strategies to eliminate latent HIV. *Cell Host Microbe* 23: 14-26.
25. Hood JL, Jallouk AP, Campbell N, Ratner L, Wickline SA (2013) Cytolytic nanoparticles attenuate HIV-1 infectivity. *Antivir Ther* 18: 95-103.