Kicking latent HIV: New strategies to reactivate reservoirs of latent infection

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In cells with latent HIV infection, the virus is dormant, and such cells are therefore not attacked by the immune system or by standard antiretroviral therapy. To eradicate the virus from the human body and truly cure a patient, reservoirs of latently infected cells need to be activated and eliminated "the so-called "kick-and-kill" approach. Two studies published on July 30th in *PLOS Pathogens* report encouraging results on the use of a combination of several drugs to efficiently reactivate HIV in cells with latent infection.

Synergistic Reactivation of Latent HIV Expression by Ingenol-3-Angelate, PEP005, Targeted NF-kB Signaling in Combination with JQ1 Induced p-TEFb Activation

Stable latent viral reservoirs in HIV infected individuals are rapidly reactivated following the interruption of anti-retroviral therapy (ART). Despite an early initiation of ART, viral reservoirs are established and persist as demonstrated in the case of the Mississippi baby and from recent studies of the SIV model of AIDS. Therefore, new strategies are needed for the eradication of the latent HIV reservoirs. We found that ingenol-3-angelate (PEP005), a member of the new class of anti-cancer ingenol compounds, effectively reactivated HIV from latency in primary CD4+ T cells from HIV infected individuals receiving ART. Importantly, a combination of PEP005 and JQ1, a p-TEFb agonist, reactivated HIV from latency at level on average 7.5-fold higher compared to PEP005 alone. The potency of synergistic effects of PEP005 and JQ1 provide novel opportunities for advancing HIV eradication strategies in the future. In summary, ingenols represent a new group of lead compounds for combating HIV latency.

An In-Depth Comparison of Latency-Reversing Agent Combinations in Various In Vitro and Ex Vivo HIV-1 Latency Models Identified Bryostatin-1+JQ1 and Ingenol-B+JQ1 to Potently Reactivate Viral Gene Expression

Summary from Carine Van Lint, from the Free University of Brussels, Belgium, and colleagues:

Persistence of latently infected cells during cART is a major hurdle for HIV-1 eradication. A widely proposed strategy to purge these reservoirs involves the reactivation of latent proviruses. The low levels of active P-TEFb and the cytoplasmic sequestration of NF-?B in resting infected cells largely contribute to maintenance of HIV-1 latency. Therefore, utilization of chemical compounds that target both pathways may lead to more potent effects on HIV-1 reactivation than the effect mediated by the individual drug treatments. In this study, we showed that combined treatments of PKC agonists (prostratin, bryostatin-1 and ing-B) with compounds releasing P-TEFb (JQ1, I-BET, I-BET151 and HMBA) exhibited a synergistic increase in viral reactivation from latency. In-depth comparison of combined treatments in various in vitro cellular models of HIV-1 latency as well as in ex vivo primary cell cultures from cART-treated HIV+ aviremic patients identified bryostatin-1+JQ1 and ing-B+JQ1 to potently reactivate latent HIV-1. The potent effects of these two combinations were detected as early as 24 hours post-treatment. Importantly, bryostatin-1 was used at concentrations below the drug plasma levels achieved by doses used in children with refractory solid tumors. Our mechanistic data established a correlation between potentiated P-TEFb activation and potentiated or synergistic (depending on the HIV-1 latency cellular model used) induction of HIV-1 gene expression observed after the combined versus individual drug treatments. In conclusion, our results establish a proof-of-concept for PKC agonists combined with compounds releasing active P-TEFb as a strategy proposed for a cure or a durable remission of HIV infection.

More information: Jiang G, Mendes EA, Kaiser P, Wong DP, Tang Y, Cai I, et al. (2015)

Synergistic Reactivation of Latent HIV Expression by Ingenol-3-Angelate, PEP005, Targeted NF-kB Signaling in Combination with JQ1 Induced p-TEFb Activation. *PLoS Pathog* 11(7): e1005066. DOI: 10.1371/journal.ppat.1005066

Darcis G, Kula A, Bouchat S, Fujinaga K, Corazza F, Ait-Ammar A, et al. (2015) An In-Depth Comparison of Latency-Reversing Agent Combinations in Various In Vitro and Ex Vivo HIV-1 Latency Models Identified Bryostatin-1+JQ1 and Ingenol-B+JQ1 to Potently Reactivate Viral Gene Expression. *PLoS Pathog* 11(7): e1005063. DOI: 10.1371/journal.ppat.1005063

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