Dual approach to HIV-1 cure: Activation of latency and restoration of exhausted virus-specific T cell function

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Background:
The persistence of HIV-1 infection in patients suppressed by combination antiretroviral therapy (cART) is due to the presence of latent reservoir(s), including that within resting CD4+ T cells. An additional factor in persistence is the dysfunction of HIV-1-specific T-cells in infected individuals. Thus, elimination of the latent HIV-1 reservoir may require a therapeutic strategy that incorporates a combination of activation of latent HIV-1 virus as well as restoration of HIV-specific T-cell responses.

Methods:
We have developed multiple assays for identification of compounds that reactivate latent HIV-1. These assays involve an integrated and quiescent HIV-1 LTR-reporter present in both primary T cells and immortalized T cell lines. A parallel screening approach was employed. The ability of immunomodulatory therapies to affect human chronic viral infections also is being investigated with in vitro assays, in animal models and in clinical trials. As proof of concept, nivolumab (anti-PD-1; BMS-936558) has been tested in the context of chronic HCV in human subjects.

Results:
Triage of the hits from these screens has revealed compounds capable of activating latent HIV-1 reporters and virus in multiple contexts. Although this trial did not meet its primary endpoints, a minority of subjects experienced a significant virologic response.

Conclusion:
We hypothesize that a combination of approaches will be necessary for reduction of the HIV-1 reservoir leading to eradication of latent virus or functional cure. To this end, we have developed a dual approach to discover agents with complementary mechanisms of action and whose combination may eradicate latent HIV-1 infection. Future studies will be directed at a combination of these approaches.