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.