The Role of Bromodomain Proteins in HIV Latency

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Latently infected memory T cells represent a major barrier to eradicating HIV from infected individuals, and efforts are underway to reverse HIV latency in an attempt to eradicate HIV from patients. Recently, small molecules targeting bromodomain and extra terminal domain (BET)-containing proteins have emerged as novel epigenetic therapeutics in hematological and virological disease. We showed that these inhibitors reactivate HIV from latency in cultured cells and a primary T-cell model of latency. Importantly, our data demonstrate that bromodomain inhibitors activate HIV latency by a Tat-independent mechanism and implicate previously unrecognized bromodomain family members, BRD2 and BRD8, in establishing and/or maintaining HIV latency. The goal of this proposal is to determine the role of the transcriptional regulators BRD2 and BRD8 in HIV latency.

The Ott laboratory has durable, highly complementary and productive research programs examining the biology of bromodomain-containing proteins and their interactions with acetylated proteins at the HIV promoter. This approach will allow us to make rapid and significant advances in our understanding of the molecular mechanisms regulating HIV latency and to generate new treatment strategies aimed at reversing HIV latency in primary T cells.

Our proposal combines hypothesis-driven functional studies aimed at providing new mechanistic insight into the role of bromodomain proteins in HIV latency. Aim 1 will define the Tat-independent mechanism of bromodomain inhibitor action. Aim 2 will investigate the molecular mechanisms of BRD2 and BRD8 function in HIV transcription and its interaction with the positive transcription elongation factor b (P-TEFb), a critical cofactor of HIV transcription. Aim 3 will optimize bromodomain inhibitor efficiency in primary T-cell models of latency. We show that bromodomain inhibitors reactivate latent HIV in Bcl- 2-transduced primary T cells (Siliciano model), but no effects were observed in non-polarized T-helper cells (Planelles model). We propose to compare both models and search for drug combinations to optimize reactivation of latent HIV in primary T cells.