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Grant Title: Reversal of HIV Latency by Galectin-9 in vivo

Abstract: The main barrier to a cure for HIV infection is the continued presence of a small number of HIV-infected cells in which the virus hides in a 'latent' state, i.e., the virus does not cause overt symptoms and does not alert the killer immune cells. We need a means to draw out the virus from its hidden reservoirs and allow the immune system to eliminate it. We recently discovered that the naturally-occurring human protein galectin-9 (Gal-9) potentially shocks latent HIV out of hiding *in-vitro* and *ex-vivo*. However, we also recently demonstrated that Gal-9 modulates HIV transcription through activating the TCR-downstream ERK signaling pathway. We also showed that this same signaling pathway that induces HIV transcription also induces undesirable responses due to T cell activation. Whether Gal-9 treatment would be beneficial or detrimental in the quest of curing HIV is unknown. We aimed to evaluate the safety and efficacy of galectin-9 in a humanized mouse model of HIV infection (the bone marrow-liver-thymus humanized (BLT) mouse model of HIV latency).

We prepared BLT humanized mice and infected them with HIV for three weeks. Mice were then placed on ART for four weeks and then treated with either saline control or recombinant Galectin-9 (at escalating doses) for two weeks. Mice were then sacrificed, and blood and tissues were collected. We first examined the levels of cell-associated HIV RNA and DNA in the tissues from these animals (using qPCR). We found that Gal-9 treatment significantly induced the levels of both cell-associated HIV RNA and DNA in the tissues of these mice. We also examined T cell activation (longitudinally) using blood samples collected from these mice (using flow cytometry). We noticed that Gal-9 induced human T cell activation *in vivo*. Finally, we examined the plasma levels of several cytokines on plasma samples collected at the end of the study (using multiplex cytokine arrays). Gal-9 reduced IL-33 but did not impact other pro-and anti-inflammatory cytokines measured.

In summary, our data suggest that while Gal-9 may induce HIV transcription, it also expands the levels of HIV-infected cells (possibly by inducing T cell activation). These data suggest that the adverse Gal-9-mediated adverse effects on T cells may outweigh the beneficial effects of Gal-9, and the overall consequence of Gal-9 treatment would be to expand HIV reservoirs. Interventions that target Gal-9 inhibition may be a better option to inhibit chronic immune activation during HIV infection. This inhibition may ultimately reduce the development of HIV-associated co-morbidities and levels of HIV persistence.