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Development of a latency reversing activator vaccine (ACT-VEC) platform for HIV-1 cure therapy

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Background: HIV-1 persists within cellular reservoirs as a transcriptionally silent provirus, creating a significant roadblock to cure research. Numerous promising therapeutic and pharmacological interventions are currently being evaluated; however to date none have resulted in reservoir eradication. We have designed an activator vaccine (ACT-VEC), using autologous derived VLPs, which target the resting CD4 T cell reservoir, inducing latency reversal. We describe the safeguards incorporated into our VLPs as well as preliminary data from our in vitro latency reversal studies.

Methods: Plasmids used in these studies were derived from the laboratory strain NL4-3, envC3 1086 and patient derived HIV-1 inserted into the pRECΔgag-U3 VLP-vector. ACT-VEC were generated with deleted (Δ) 5’LTR, AAH>RRK integrase mutation and deletions within the RNA packaging element (ΔSL3). VLPs were then created by HEK293T transfection. Resulting VLPs were assessed by RT-PCR for RNA content and for the presence of viral proteins by western blot. VLPs were co-cultured with autologous patient derived DCs and then used to activate autologous CD4 T cells from PBMC. An IFN-γ ELISpot was used to quantify virus specific T cells, p24 ELISA to measure viral latency reversal, and 454 deep sequencing to characterize HIV resulting from latency reversal and compare to viral DNA isolated from PBMC.

Results: Here we show our ACT-VEC VLPs have reduced HIV-1 RNA packaging (up to 221-fold), while having no impact on viral protein production. This along with mutations in Integrase and ΔSL3 rendered our ACT-VEC incapable of reverse transcription, integration, or RNA packaging. Preliminary studies involving deep sequence analysis revealed ACT-VEC are genetically diverse and identical to virus generated by our latency reversal assays. Significantly, autologous ACT-VEC were able to stimulate 30-fold more HIV RNA from infected T cells than Flu/Tet/CMV recall antigens and more than NL4-3 controls. Our latency reversal studies showed ACT-VEC outperform clinically relevant compounds such as Romidepsin and Vorinostat.

Conclusions: Here we clearly demonstrate that our novel ACT-VEC formulations represent a safe vaccine platform for use as a therapeutic intervention and that ACT-VEC may signify a promising strategy to purge the latent viral reservoir and facilitate cure.

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