

Poster presentation

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## **PI6-40. Inhibition of histone deacetylases modulates CD8+ T-lymphocyte mediated virus suppression by HIV-1 viral controllers**

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from AIDS Vaccine 2009  
Paris, France. 19–22 October 2009

Published: 22 October 2009

*Retrovirology* 2009, **6**(Suppl 3):P269 doi:10.1186/1742-4690-6-S3-P269

This abstract is available from: <http://www.retrovirology.com/content/6/S3/P269>

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### **Background**

CD8<sup>+</sup> T-lymphocytes suppress HIV-1 replication through unknown factors that inhibit HIV-1 transcription initiation. Understanding the regulation of these CD8<sup>+</sup> T cell derived factors can provide important insights into how to elicit these factors with a vaccine. For a small subset of human genes, histone deacetylases (HDACs) are epigenetic regulators that condense chromatin to repress transcription. We examined an HDAC inhibitor's ability to modulate the expression of suppressive factors from primary CD8<sup>+</sup> T cells from HIV-1<sup>+</sup> subjects controlling virus infection.

### **Methods**

CD4<sup>+</sup>-enriched PBMC from seronegative donors were infected with HIV-1<sub>NL4-3</sub> pseudotyped reporter virus. Infected cells were cultured in direct contact or in a transwell system with CD8<sup>+</sup> T-lymphocytes from HIV-1<sup>+</sup> viral controllers. HIV-1 suppression was determined in the absence and presence of an HDAC inhibitor that targets HDACs 1–5 and 7–9 using an LTR-driven luciferase reporter.

### **Results**

HIV-1 suppression by primary CD8<sup>+</sup> T-lymphocytes from HIV-1<sup>+</sup> viral controllers was reversed up to 40% by the addition of an HDAC inhibitor. Virus suppression by HVS-transformed CD8<sup>+</sup> T-lymphocytes was inhibited by 45% in the presence of an HDAC inhibitor. The portion of the overall suppressive activity mediated by soluble factors was completely reversed by the HDAC inhibitor. Pre-

incubation of HVS-transformed or primary CD8<sup>+</sup> T-lymphocytes by the HDAC inhibitor decreased their subsequent suppressive ability by 3.5 and 2.4-fold respectively.

### **Conclusion**

Blocking HDACs impairs the ability of CD8<sup>+</sup> T-lymphocytes to repress HIV-1 transcription; suggesting the expression of the suppressive factors is regulated by epigenetics. With 2–5% of genes being regulated by HDAC, our data provides a way to focus the search for the suppressive factors. The ability to modulate expression of the suppressive factors can facilitate their identification and aid in determining how to elicit these factors with a HIV-1 vaccine.