Destruction of the Residual Active HIV-1 Reservoir by Env-specific Immunotoxin

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Delivering Therapeutics to Residual Active HIV Reservoirs

Experimental Goal: To eliminate cellular reservoirs of HIV that continue to actively produce virus in tissue compartments despite suppression of plasma viremia with antiretroviral therapy.

**Step 1:** Study drug concentrations in vivo to identify antiretrovirals with good tissue penetration that are particularly well suited for inhibiting systemic virus production.

**Step 2:** Identification and in vitro testing of new strategies for killing or limiting the survival of cells that constitute the active reservoir.

**Step 3:** Use animal models to demonstrate proof-of-concept for these strategies.
Experimental Approach to Generate Bone Marrow/Thymus/Liver (BLT) Mice

CD34^+ Cells
Generation of HIV Latency in Humanized BLT Mice

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Approach

- Generate BLT mice
- Infect with HIV-1\textsubscript{JR-CSF}
- Administer ART
- Monitor HIV RNA plasma levels
- Measure drug concentrations in tissues and plasma
- Quantitate absolute numbers of productively infected cells
- Quantitate levels of viral RNA in tissues
Establishment of a drug regimen capable of inhibiting virus production in blood and tissues

HIV-1 JR-CSR, CCR5/T-cell tropic virus, daily single i.p. drug administration
Durable reduction of the number of vRNA+ cells occurs during ART

*Exact log rank test*
Viral RNA production during ART rapidly declines and then remains stable in all tissues.

*Lowess and cubic regression models were fit using R v2.14.1*
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Targeting Residual Active Reservoir During ART

Edward Berger and Ira Pastan

(adapted from Kreitman, et al. NEJM-2001)
Experimental Approach for Targeted Immunotoxin Destruction of HIV Infected Cells
Prospective, open-label, single center, dose escalation, efficacy and safety, phase I/II trial of 3B3-PE38 in HIV infected BLT mice undergoing ART

POLSCDEP3HIBUA
Effect of Env-specific Immunotoxin on the residual active reservoir

*Mann-Whitney*
Reduction of HIV RNA Levels Mediated by the Env-specific Immunotoxin

*B*Wilcoxon rank-sum
Destruction of HIV Infected Cells Mediated by the Env-specific Immunotoxin

*Exact log rank test
Summary

• ART efficiently reduces viral load in peripheral blood.

• After an initial rapid decline in peripheral and systemic RNA production HIV RNA levels are maintained at a significantly reduced level.

• 3B3-PE38 immunotoxin administration further reduced tissue RNA levels as much as 1,000-fold in individual tissues and systemically by 0.8 logs over ART alone.

• The mechanism of the reduced viral RNA levels is a loss of productively infected cells.
Experimental Platform for Targeted Destruction of HIV Infected Cells

Induction Therapy
Acknowledgments

Paul W. Denton¹  
Julie M. Long¹  
Rae Ann Spagnuolo¹  
Nancie M. Archin¹  
Shailesh K. Choudhary¹  
Olivia D. Snyder¹  
David M. Margolis¹  
Steven W. Wietgrefe²  
Katherine Perkey²  
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