



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

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Delivering Therapeutics to Residual Active HIV Reservoirs

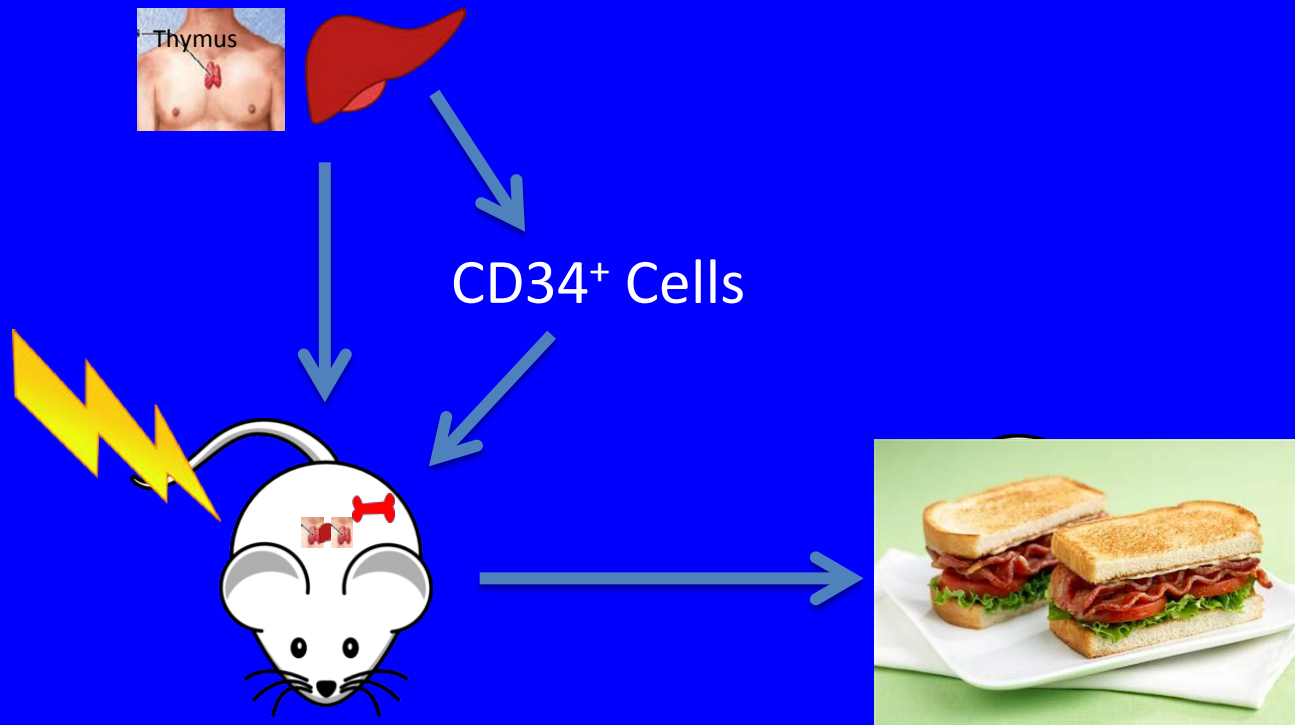
Experimental Goal: To eliminate cellular reservoirs of HIV that continue to actively produce virus in tissue compartments despite suppression of plasma viremia with antiretroviral therapy.

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.

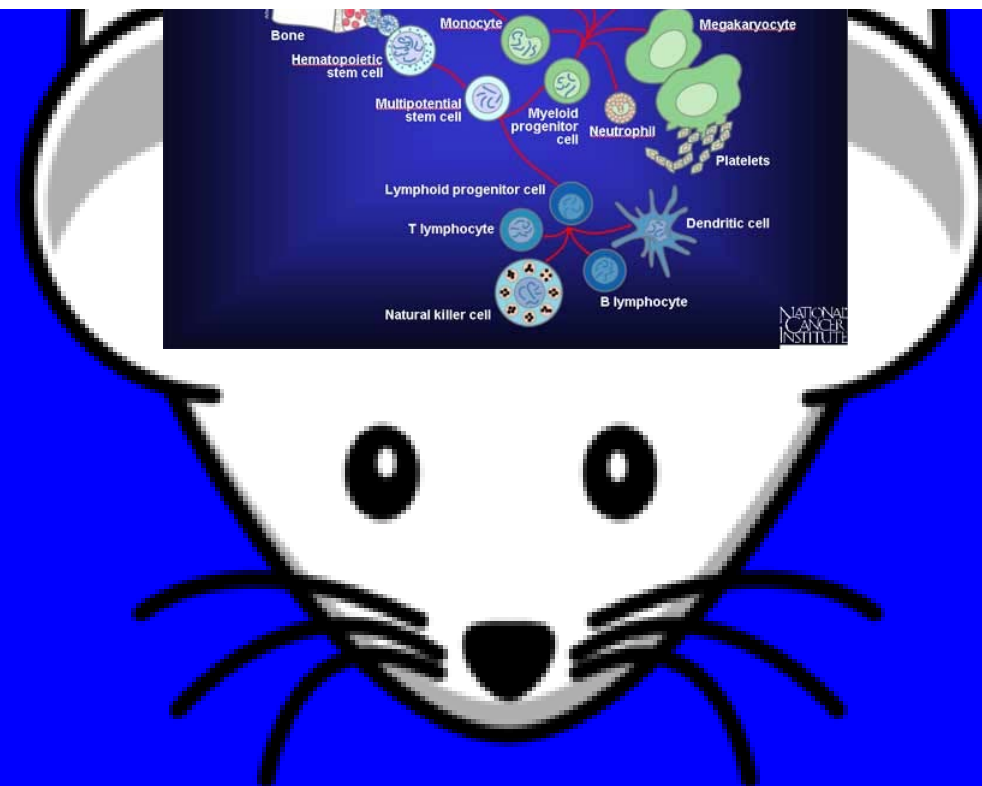
Experimental Approach to Generate Bone Marrow/Thymus/Liver (BLT) Mice



Generation of HIV Latency in Humanized BLT Mice

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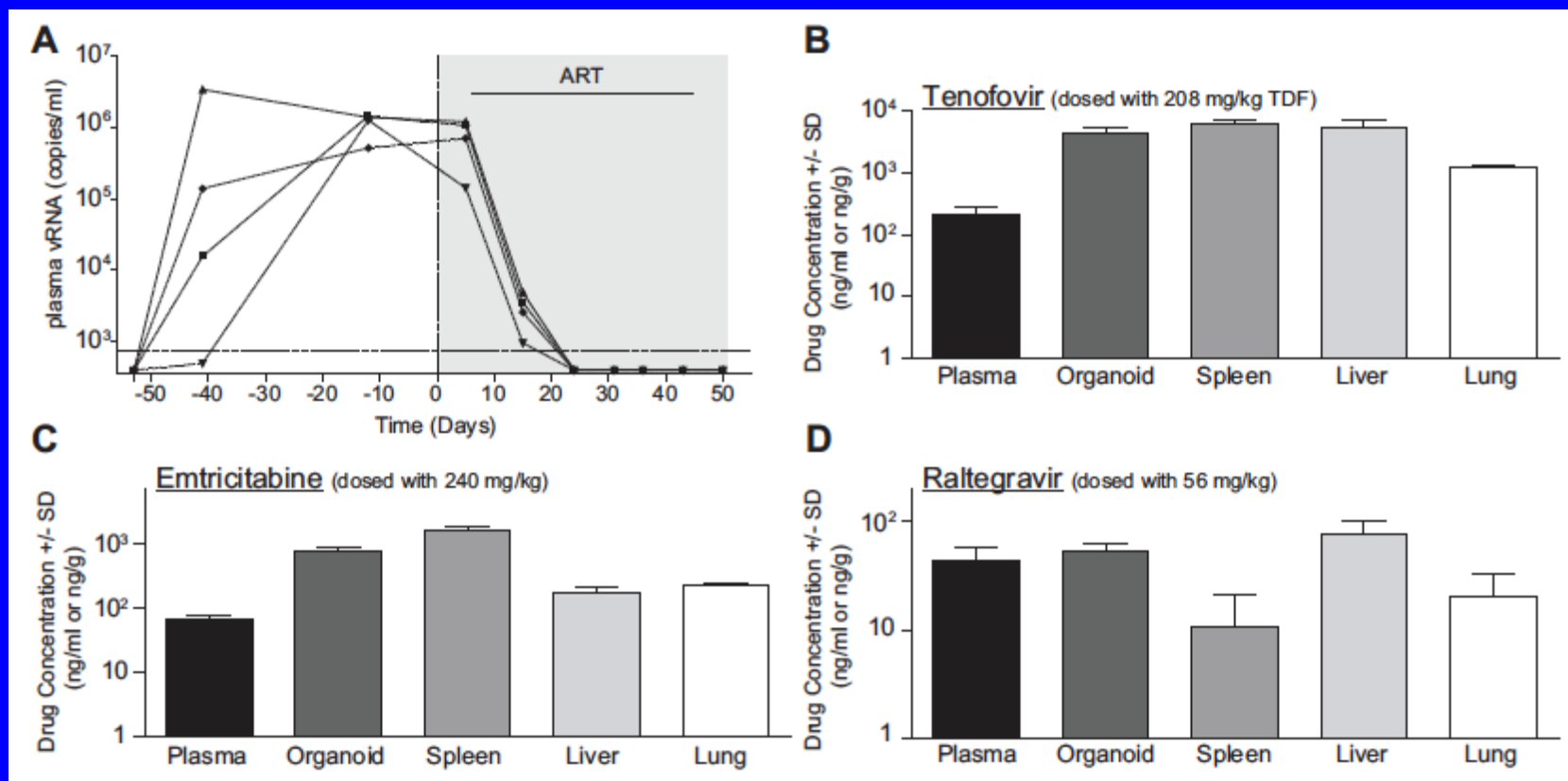
Division of Infectious Diseases, Department of Internal Medicine, Center for AIDS Research,^a and Departments of Microbiology and Immunology,^b and Department of Epidemiology,^c University of North Carolina, Chapel Hill, North Carolina, USA, and Department of Infectious Diseases, Aarhus University Hospital, Shejby, Denmark^d



Approach

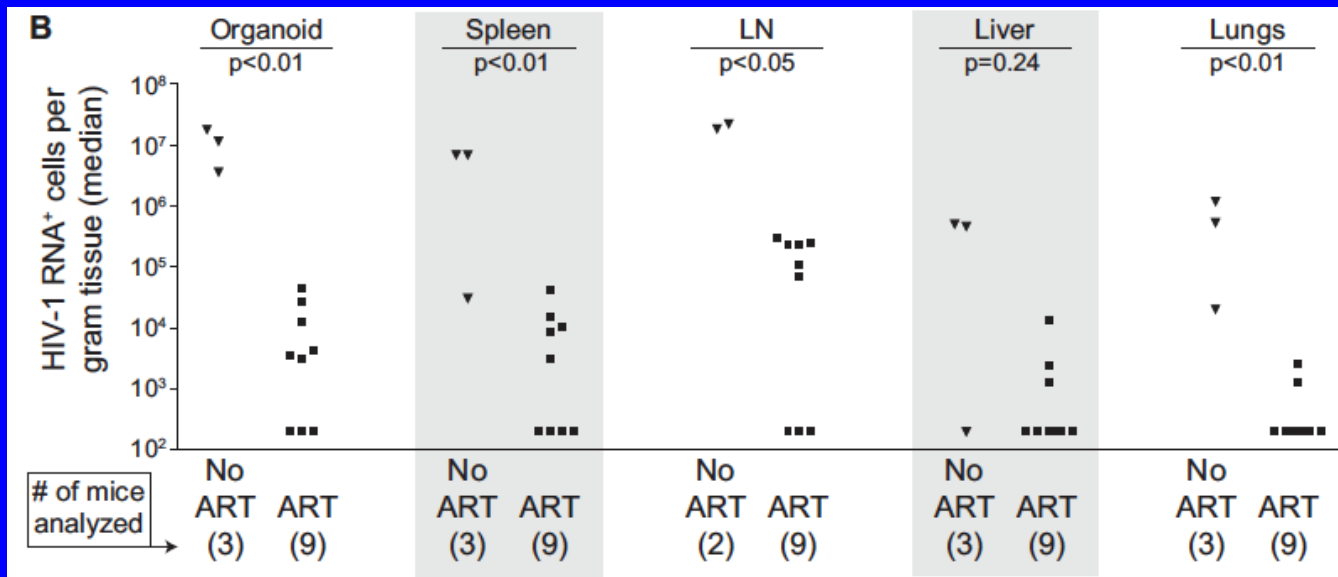
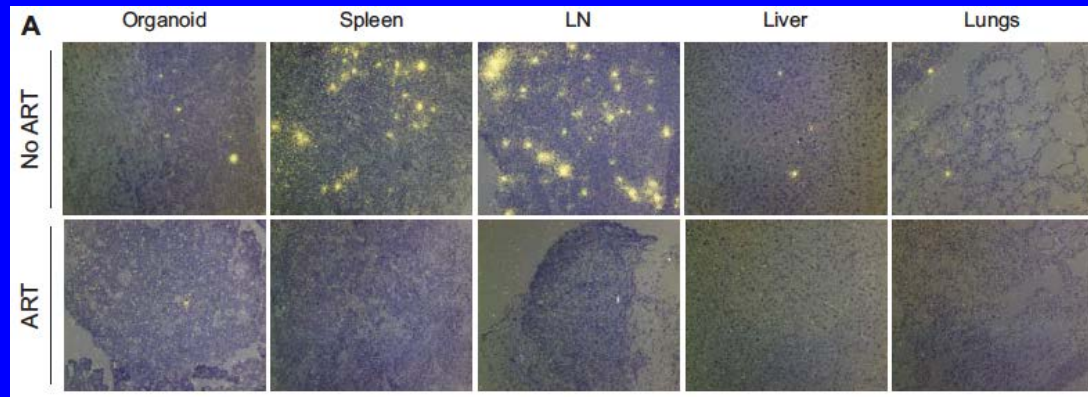
- Generate BLT mice
- Infect with HIV-1_{JR-CSF}
- Administer ART
- Monitor HIV RNA plasma levels
- Measure drug concentrations in tissues and plasma
- Quantitate absolute numbers of productively infected cells
- Quantitate levels of viral RNA in tissues

Establishment of a drug regimen capable of inhibiting virus production in blood and tissues



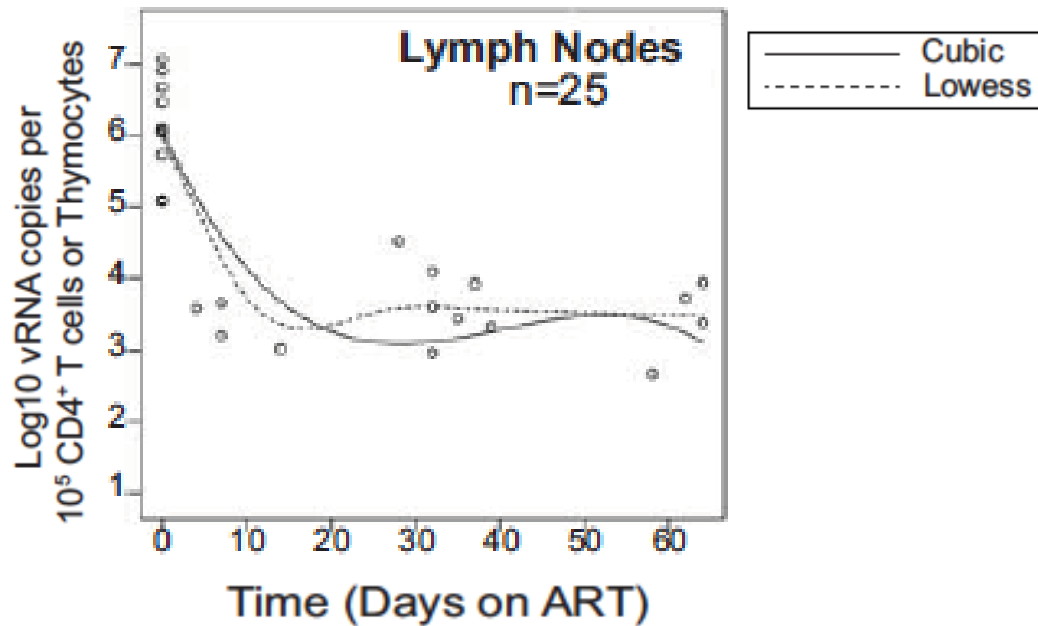
HIV-1_{JR-CSF7} CCR5/T-cell tropic virus, daily single i.p. drug administration

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

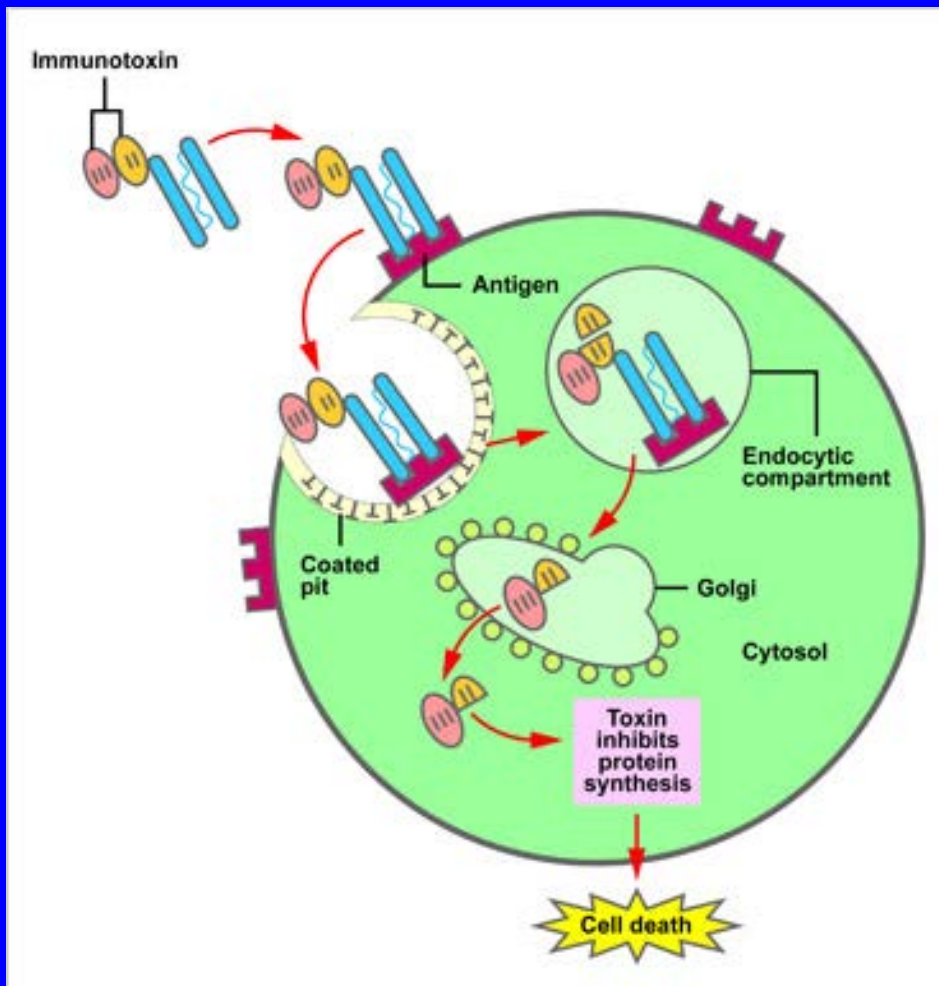
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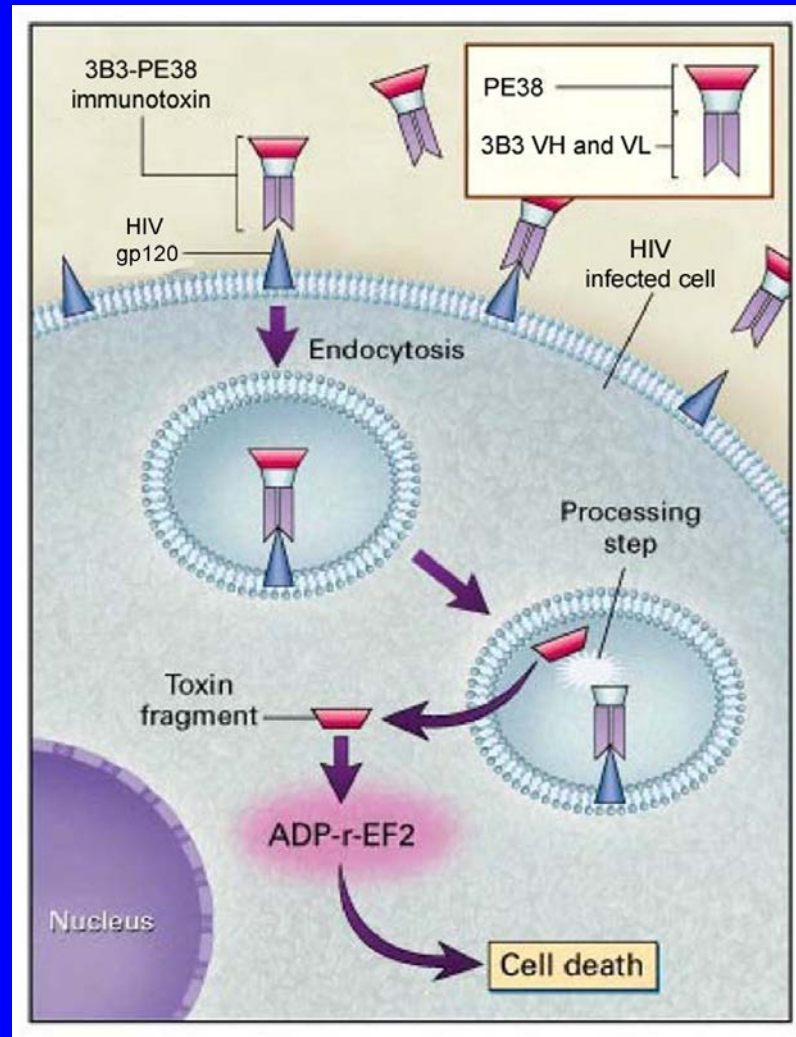
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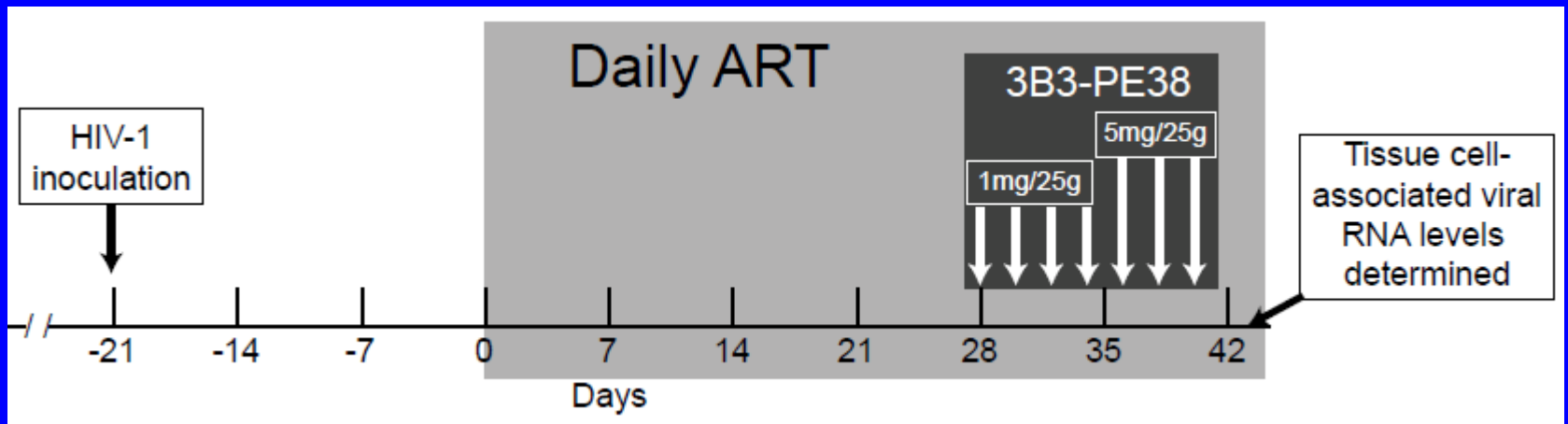
Step 3: Use animal models to demonstrate proof-of-concept for these strategies.



Targeting Residual Active Reservoir During ART



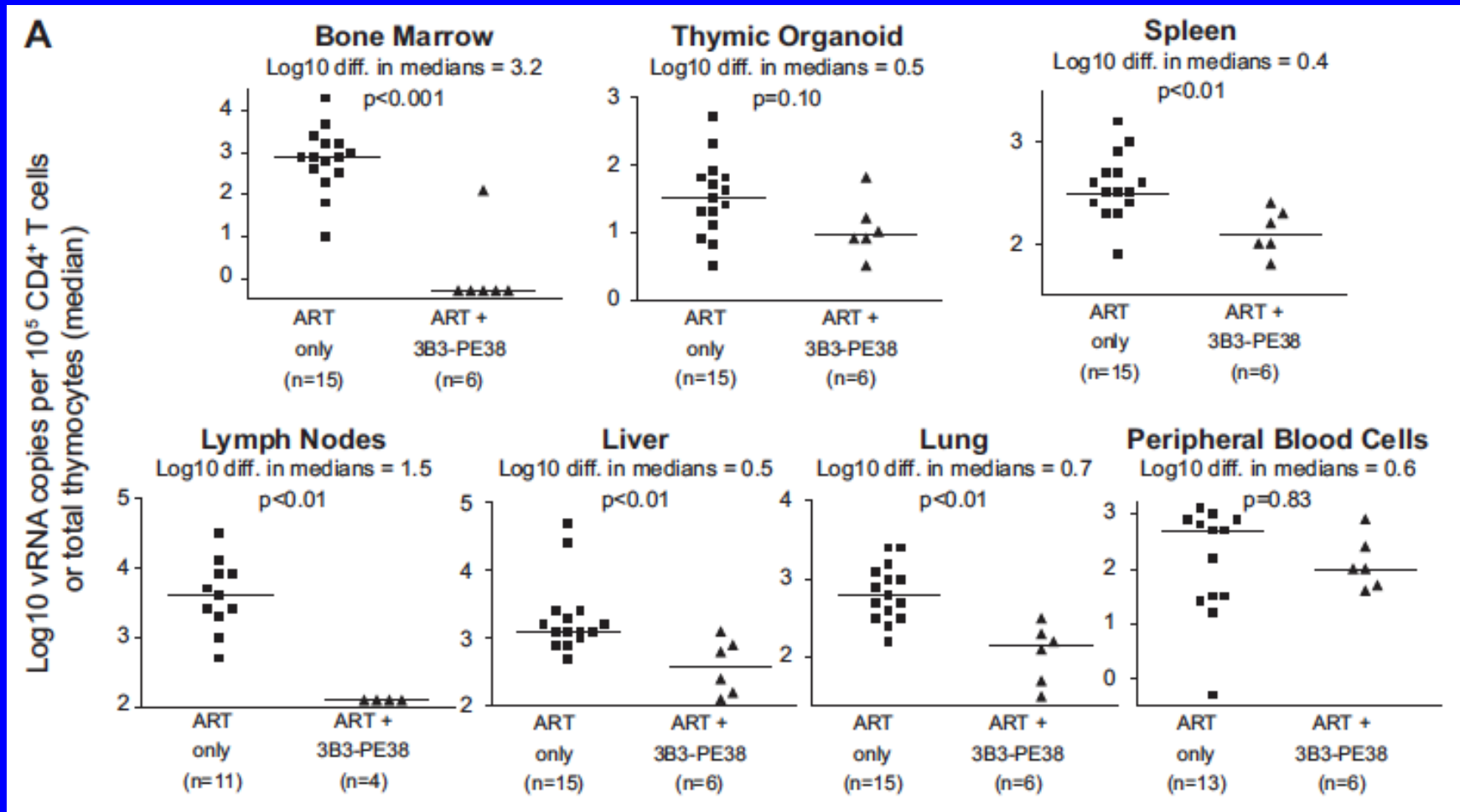
Experimental Approach for Targeted Immunotoxin Destruction of HIV Infected Cells



Prospective, open-label, single center,
dose escalation, efficacy and safety,
phase I/II trial of 3B3-PE38 in HIV
infected BLT mice undergoing ART

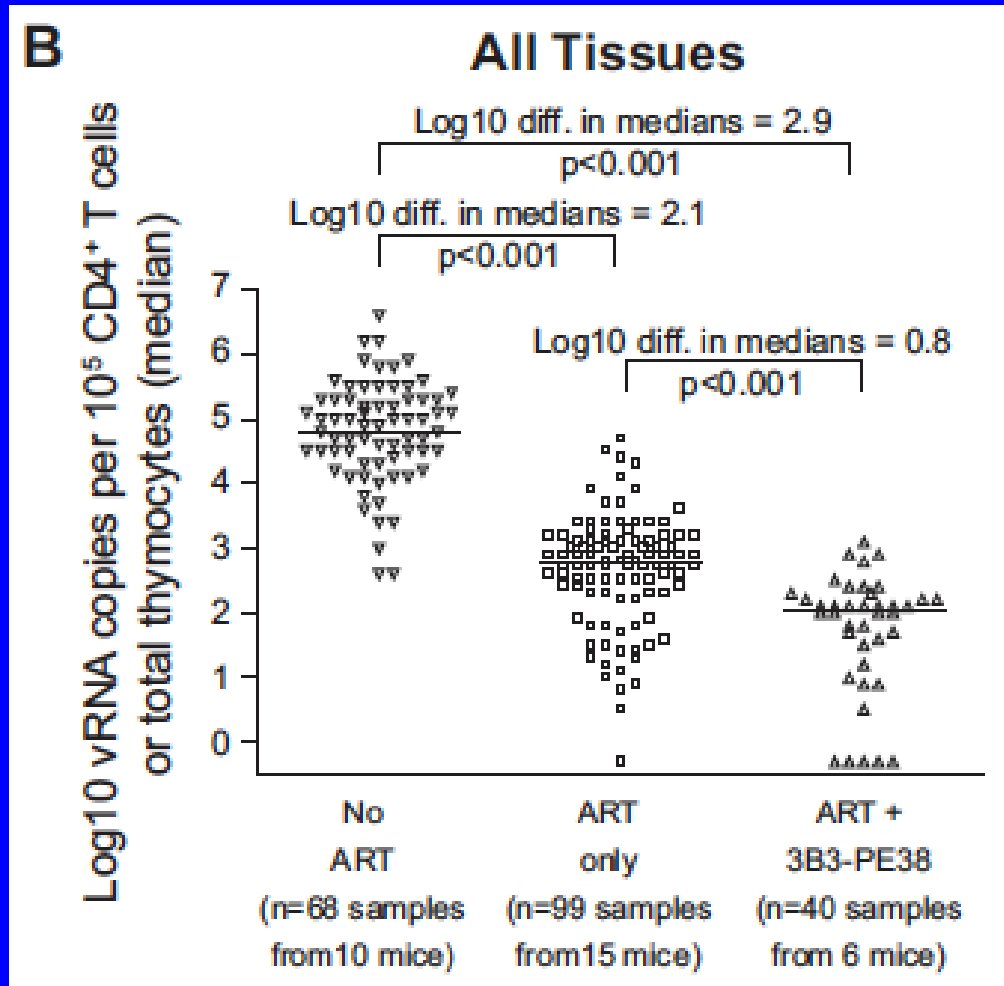
POLSCDEP3HIBUA

Effect of Env-specific Immunotoxin on the residual active reservoir



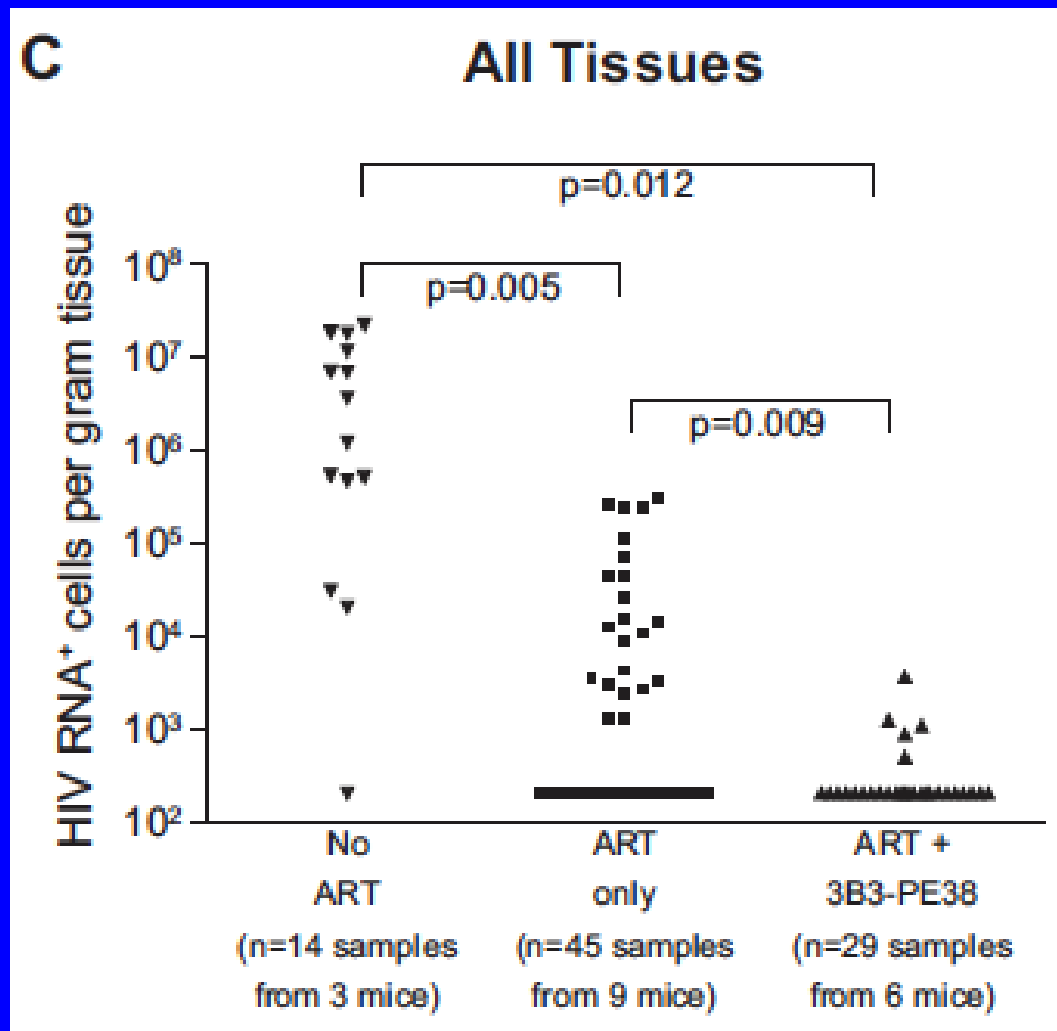
*Mann-Whitney

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



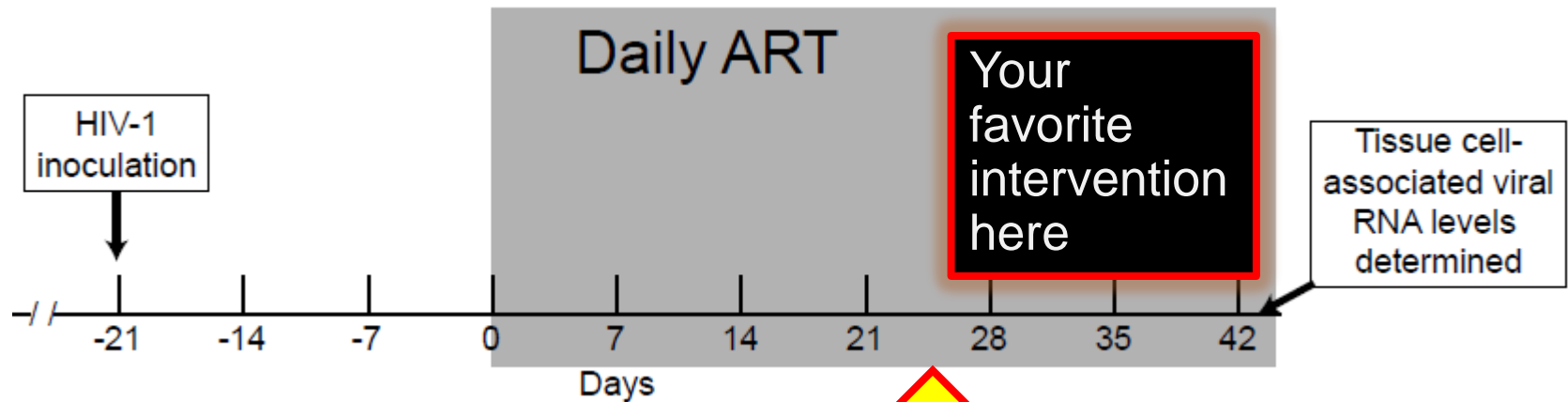
*Wilcoxon rank-sum

Destruction of HIV Infected Cells Mediated by the Env-specific Immunotoxin



*Exact log rank test

Experimental Platform for Targeted Destruction of HIV Infected Cells



Induction Therapy

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