2019

Arenavirus-Based Vectors Generate Robust SIV Immunity in Nonhuman Primates

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Introduction

- HIV integrates into cellular DNA following infection, eventually establishing a latent reservoir that is refractory to antiretroviral therapy
- Antiretroviral therapy is the standard of care for HIV and keeps the virus in check, leading to undetectable viral loads, but it does not eliminate viral reservoirs and HIV rebounds if treatment is interrupted
- HIV-specific CD8 T-cell immunity has been documented to play an important role in controlling the virus naturally in nonprogressors[1,2]
- Vaccines that effectively engage T and B immune cells could induce sustained immune-mediated HIV control
- Immunogenic viral vectors have been shown to generate HIV/simian immunodeficiency virus (SIV) antigen-specific immune responses in both human and nonhuman primate models[3,4]; however, preexisting and induced antivector immunity can limit viral vector effectiveness
- Lymphocytic choriomeningitis virus (LCMV) and Pichinde virus infections (PICV) are rare in humans (≤5% of reported cases with LCMV),[5,6] presenting a promising opportunity as a viral vector platform with limited to no preexisting immunity against the arenavirus-based delivery
- Nonreplicating arenavirus vectors elicited both cellular and humoral immune responses after administration of multiple vaccine doses in cytomegalovirus phase 1 clinical trials[7]; replicating arenavirus vectors are also being tested in clinical trials as cancer therapeutics

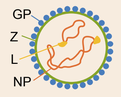
Objectives

- To investigate if arenavirus-based vectors can induce SIV-specific T- and B-cell immune responses
- To determine the optimal prime/boost immunization regimen, vector platform(s), and route of administration for eliciting robust vaccine immunogenicity against SIV antigens

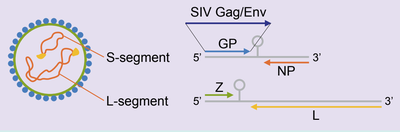
Methods

Vector Constructs

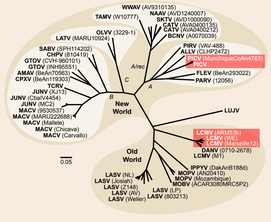
Arenavirus Vectors LCMV and PICV



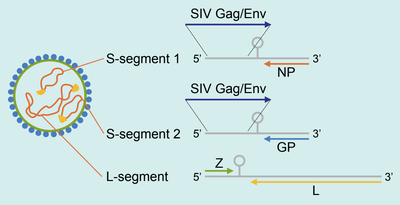
Nonreplicating Arenavirus Vector Platform (bisegmented) rLCMV and rPICV



Arenavirus Phylogenetic Tree*

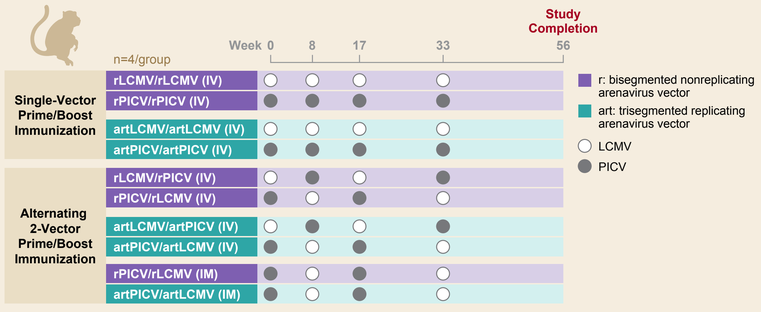


Replicating Arenavirus Vector Platform (trisegmented) artLCMV and artPICV



*Adapted from Briese T, et al.[8] art, artificial genome organization; Env, envelope; Gag, group antigen; GP, glycoprotein; L, polymerase; L-segment, large genome segment; NP, nucleoprotein; r, recombinant; S-segment, small genome segment; Z, matrix protein.

Study Design*

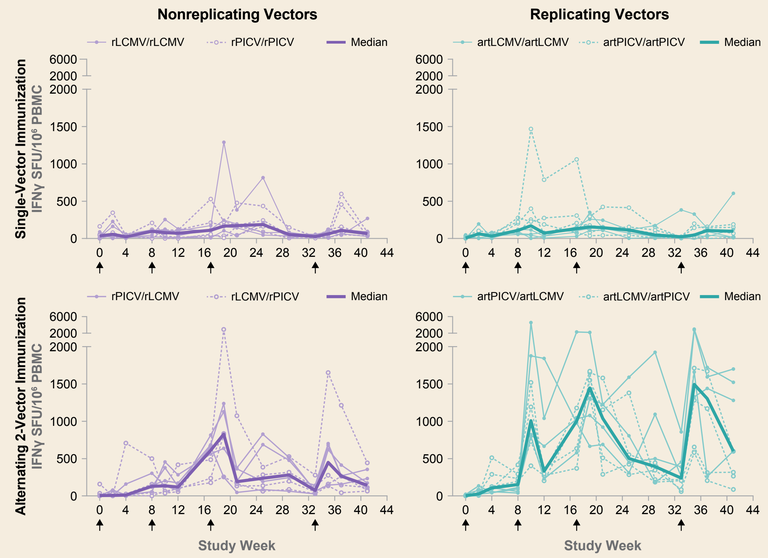


*rLCMV/rPICV dose: 10^7 focus-forming units (FFU); artLCMV/artPICV dose: 10^6 replication competent virus particles (~10^7 FFU); vaccine immunogen: SIVsmE543 Gag and Env.

- Vaccine immunogenicity was evaluated via SIV-specific (Gag and Env) interferon-γ (IFNγ) enzyme-linked immune absorbent spot (ELISpot) assay for T-cell responses and Env-binding (SIV smE543 and SIVmac251 gp120) enzyme-linked immunosorbent assay for B-cell responses; binding antibody responses were reported as endpoint titers; breadths of SIV Gag and Env responses were assessed using IFNγ ELISpot assay for 28 peptide subpools: 12 Gag and 16 Env

Results

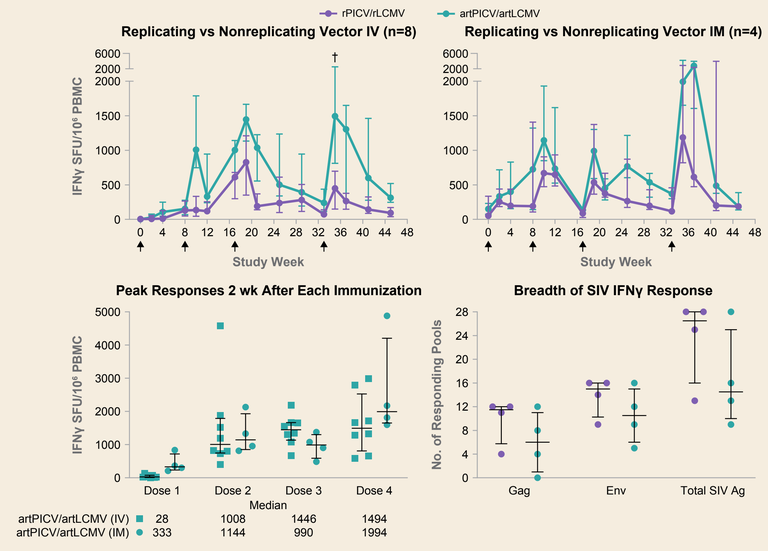
Alternating 2-Vector (PICV/LCMV) Immunization Induced Robust T-Cell Response Against SIV Antigens*



Arrows indicate vaccine dose time points; animals were bled for peripheral blood mononuclear cell (PBMC) isolation, which were restimulated ex vivo with peptide pools derived from Gag and Env, and analyzed by IFNγ ELISpot.

- Alternating 2-vector immunization with arenavirus vectors elicited higher SIV immunogenicity than a single vector

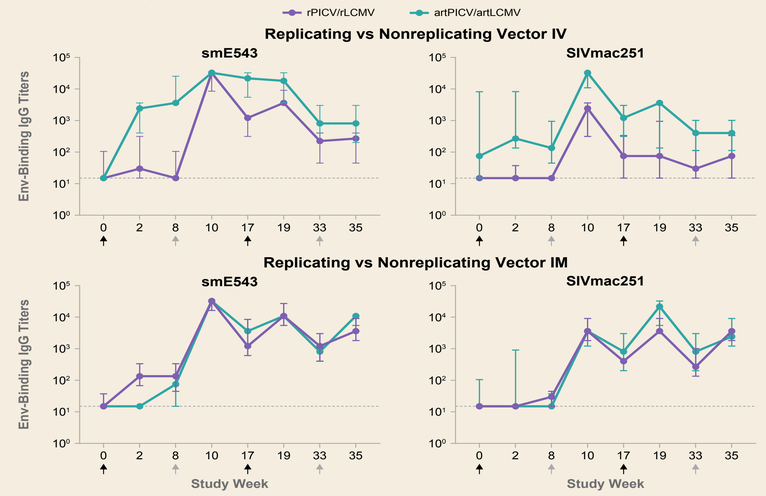
Alternating Immunization With Replicating PICV/LCMV Induced a Broad SIV T-Cell Response Independent of Route of Administration (IV or IM)*



*Alternating LCMV and PICV vectors for prime vs boost yielded comparable magnitude ELISpot responses by IV route (data not shown); thus both nonreplicating (rLCMV/rPICV and rPICV/rLCMV) and both replicating (artLCMV/artPICV and artPICV/artLCMV) group responses were combined into a single group (each n=8); *arrows* indicate vaccine dose time points; animals were bled for PBMC isolation, which were restimulated ex vivo with peptide pools derived from Gag and Env, and analyzed by IFNγ ELISpot; ELISpot response breadth was evaluated using 12 Gag and 16 Env peptide subpools at 2 wk after 4th dose of rPICV/rLCMV and artPICV/artLCMV IM; response was defined as >3x background signal; *lines* and *error bars* are median ± interquartile range (IQR); †p<0.05.

- T-cell ELISpot response:
  - rPICV/rLCMV and artPICV/artLCMV both induced T-cell responses after IV administration; there was a trend of greater immunogenicity with artPICV/artLCMV vs rPICV/rLCMV (IV)
  - Peak response was maintained or improved with each boost
  - Route of administration had a modest impact on response magnitude; a slight advantage of IM vs IV was observed after the 4th dose
  - Alternating 2-vector immunization with both arenavirus vaccine platforms induced broad ELISpot responses with 9–28 of 28 possible antigen subpool responses (measured 2 wk after the 4th dose)

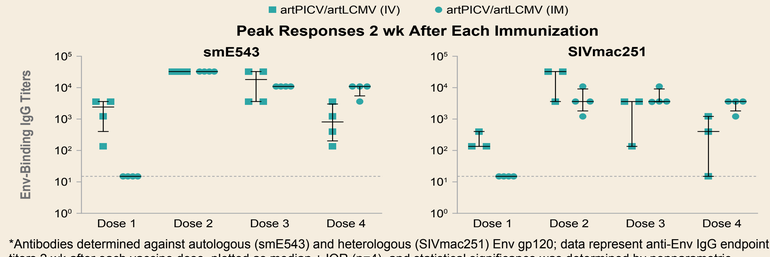
Intramuscular Immunization With Alternating Arenavirus Vectors Induced High Env-Binding IgG Levels Against Autologous and Heterologous SIV*



*Antibodies determined against autologous (smE543) and heterologous (SIVmac251) Env gp120; *black arrows* indicate PICV administration and *grey arrows* indicate LCMV administration; data represent anti-Env immunoglobulin-G (IgG) endpoint titers over course of study, plotted as median ± IQR (n=4), and statistical significance was determined by nonparametric Kruskal Wallis-test.

- Alternating 2-vector immunization with replicating and nonreplicating vector platforms generated strong autologous and heterologous Env-binding IgG titers
- Nonreplicating vectors generated lower heterologous Env-binding IgG titers than replicating vectors when administered IV; however, they were comparable with IM administration

Comparison Between IV and IM Administration for Generating Env-Binding IgGs*



*Antibodies determined against autologous (smE543) and heterologous (SIVmac251) Env gp120; data represent anti-Env IgG endpoint titers 2 wk after each vaccine dose, plotted as median ± IQR (n=4), and statistical significance was determined by nonparametric Kruskal Wallis-test.

- Intramuscular SIV vaccination with alternating 2-vector immunization led to stable anti-Env-binding IgG response

Conclusions

- Alternating 2-vector immunization elicited a more robust SIV IFNγ response than single-vector immunization
- Alternating 2-vector immunization regimen with replicating vectors led to higher T-cell immunogenicity vs nonreplicating vectors ($p<0.05$ after 4th dose)
- Intramuscular administration showed a modest (nonsignificant) benefit over intravenous in the magnitude of T-cell response
- Intravenous administration of replicating arenavirus vectors induced Env-binding antibodies more rapidly and to higher titers than nonreplicating vectors
- Intramuscular immunization resulted in more stable antibody responses than intravenous for both vector platforms, with no difference between the 2 intramuscular regimens
- Overall, both replicating and nonreplicating arenavirus vectors generated robust T- and B-cell–mediated immunity to SIV antigens in naïve nonhuman primates; these results support further evaluation of intramuscular immunization of these vectors in a clinical setting for HIV therapy

References: **1.** Collins DR, et al. Nat Rev Immunol 2020;20:471-82; **2.** Janes H, et al. J Infect Dis 2013;208:1231-9; **3.** Barouch DH, et al. Nature 2012;482:89-93; **4.** Colby DJ, et al. Nat Med 2020;26:498-501; **5.** Childs JE, et al. Am J Trop Med Hyg 1991;44:117-21; **6.** Park JY, et al. Am J Trop Med Hyg 1997;57:37-41; **7.** Schwendinger M, et al. J Infect Dis 2022;225:1399-410; **8.** Briese T, et al. PLoS Pathog 2009;5:e1000455. **Acknowledgments:** This study was funded by Gilead Sciences, Inc. Vector generation and platform support were provided by Hookipa Pharma Inc, New York, NY. Nonhuman primate studies were conducted at Bioqual, Inc., Rockville, MD. ELISpot assays were performed at ABL Inc., Rockville. Editing and production assistance were provided by BioScience Communications, New York, NY, funded by Gilead.

Presented at Keystone Symposium: Progress in Vaccine Development for Infectious Diseases, June 1–4, 2022, Beaver Run Resort, CO