Immunogenicity and Prophylactic Efficacy of Arenavirus-Based SIV Vaccine in Macaques

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Introduction

- Although combination antiretroviral therapy is highly successful in treating and preventing HIV progression, there remains a need for therapeutic options that result in long-term immune mediated viral control and HIV cure
- HIV-infected long-term nonprogressors or elite controllers who maintain HIV viral load (VL) <50 copies/mL without treatment are characterized by robust, polyfunctional, and effective HIV-specific CD8$^+$ T-cell responses, with proliferative capacity and reduced expression of exhaustion markers[1,2]
- Role of CD8$^+$ T cells in HIV/simian immunodeficiency virus (SIV) infection:
  - In a Phase 2b trial testing the prophylactic efficacy of an adenovirus type 5 (Ad5)–based HIV vaccine (Vx), treatment-induced T cells were associated with reduced viremia[3]
  - In SIV-infected rhesus macaques, SIV-specific CD8$^+$ T cells have been associated with viral control and depletion of CD8$^+$ T cells resulted in rapid rebound of virus[4]
- Different approaches have been developed to augment such CD8$^+$ T-cell responses, including conserved element immunogen design, use of homologous or heterologous Vx platforms, modulating the dosing interval, and route of Vx delivery
  - The choice of Vx platform is important for driving efficacy; to date, several Vx platforms have been tested in SIV models, including nucleic acid vectors and viral vectors[5]
  - Arenavirus-based Vx vectors encoding SIV immunogens have shown robust immunogenicity in nonhuman primates[6]
  - In an ongoing Phase 1/2 study (NCT04180215) in human papilloma virus 16$^+$ cancer, arenavirus vectors induced strong tumor antigen-specific CD8 T-cell responses with favorable tolerability
  - These arenavirus-based vectors have demonstrated low seroprevalence and have emerged as a promising viral vector-based immunotherapy platform in recent years due to their ability to incorporate multiple foreign antigens in their genomes, with the capacity to induce strong T-cell responses[7]

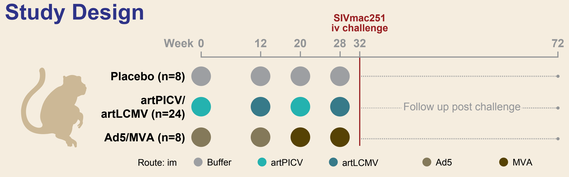
Objectives

- To assess the immunogenicity of multiple intramuscular (im) doses of artificial-Pichinde virus (artPICV)/artificial-lymphocytic choriomeningitis virus (artLCMV) vectors encoding SIVsmE543 viral antigens (group antigen [Gag], envelope [Env], and polymerase [Pol]) in healthy rhesus macaques
- To assess the efficacy of the artPICV/artLCMV Vx on intravenous (iv) SIV challenge of vaccinated animals by evaluating mean and set-point SIV VL

Methods

- Healthy rhesus macaques were immunized with replicating arenavirus-based vectors (artPICV and artLCMV) in alternating sequence, Ad5/modified vaccinia virus Ankara (MVA) vectors, or placebo; all viral vectors encoded SIVsmE543 Gag, Env, and Pol immunogens
- Vx dosing:
  - artPICV and artLCMV vectors expressing SIVsmE543 Gag and Env were administered in the left quadricep muscle, whereas vectors expressing SIVsmE543 Pol were administered in the right quadricep muscle; animals received 1x10^6 replication competent virus particles (RCV) of artPICV Gag, Env, and Pol1/Pol2 vectors, 4x10^6 RCV of artLCMV Gag and Env, and 2x10^6 RCV of artLCMV Pol1/Pol2
  - Ad5 and MVA vectors expressing Env were administered in the left quadricep muscle, whereas vectors expressing Gag and Pol were administered in the right quadricep muscle; animals received 5x10^{10} virus particles for Ad5 vectors expressing SIVsmE543 Gag, Env, and Pol, and 1x10^8 particle forming unit of MVA vectors expressing SIVsmE543 Gag, Env, and Pol
  - In the placebo group, animals were administered placebo buffer solution containing 0.1% macaque serum albumin in the left and right quadricep muscles

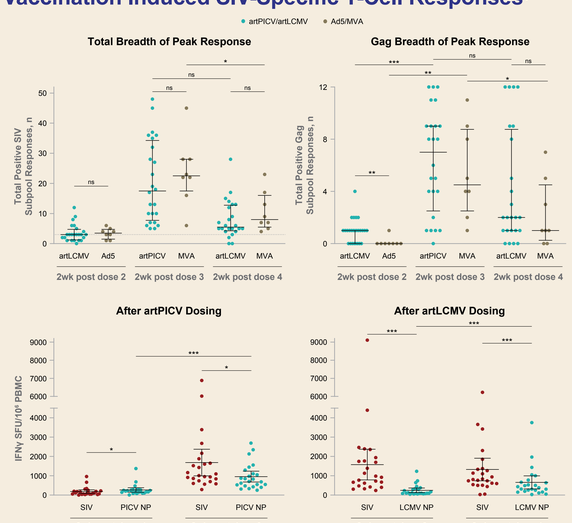
Study Design



- Vx immunogenicity was assessed by SIV-specific interferon (IFN)–γ enzyme-linked immunosorbent spot (ELISpot), using 51 SIV peptide subpools to determine cellular breadth
- SIV-specific T-cell polyfunctionality was determined by intracellular staining flow cytometry
- Env-binding and SIV-neutralizing antibodies (nAbs) were determined using enzyme-linked immunosorbent assay and cell-based luciferase reporter assays
- Anti-artLCMV vector-specific nAbs were evaluated in an image-based cellular green fluorescent protein reporter assay
- Vx efficacy was determined based on SIV VL reduction over 40 wk after iv challenge with high-dose 8.19TCID$_{50}$ SIVmac251

Results

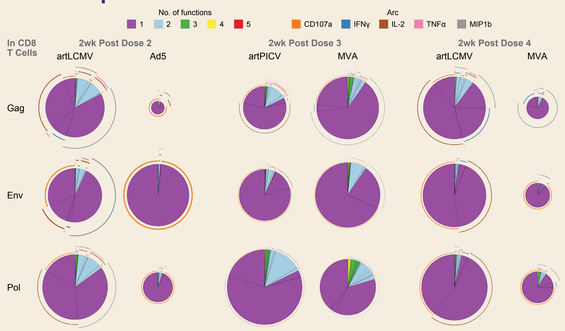
Vaccination Induced SIV-Specific T-Cell Responses†



*p<0.05, **p<0.01; ***p<0.001: Mann-Whitney test for artPICV/artLCMV vs Ad5/MVA and Wilcoxon-matched pairs signed-rank test for intragroup comparisons; †Responses evaluated at 2 wk after each dose; data are median ± interquartile range (IQR); n=24/group in artPICV/artLCMV and n=8/group in Ad5/MVA; threshold for breadth ELISpot response: ≥50 SFU/10^6 peripheral blood mononuclear cells (PBMCs) and 3-fold more than background. NP, nucleoprotein; ns, not significant; SFU, spot-forming units.

- High and comparable breadth of response was observed after artLCMV and MVA boost
- Significantly higher IFNγ responses were observed to SIV immunogens over either PICV or LCMV vector-specific NP

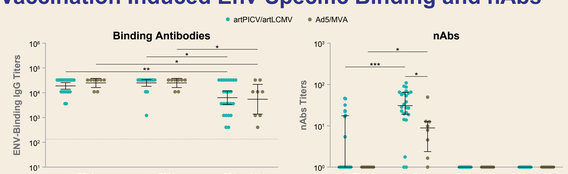
Vaccination Induced SIV-Specific Polyfunctional CD8 T-Cell Responses*



*Sizes of *pies* proportional to frequency of antigen-specific CD8 T cells. IL, interleukin; MIP, macrophage inflammatory protein; TNF, tumor necrosis factor.

- Higher SIV-specific polyfunctional CD8 responses were observed after artLCMV dose 1 vs after Ad5 dosing
- MVA dose 1 induced robust CD8 polyfunctional responses

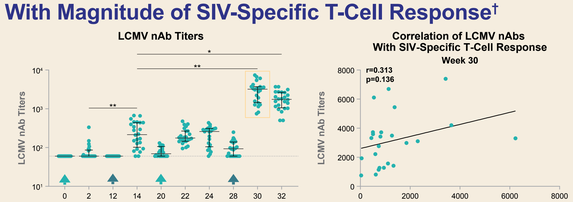
Vaccination Induced Env-Specific Binding and nAbs†



*p<0.05, **p<0.01, ***p<0.001: Wilcoxon signed-rank test for intragroup and Mann-Whitney test for intergroup comparisons; †Data plotted as geometric mean with 95% confidence interval; n=24/group in artPICV/artLCMV and n=8/group in Ad5/MVA; antibody titers at 2 wk after Vx dose 4; SIV tier 1: smE543 and smE660; tier 2: SIVmac251; and tier 3: SIVmac239. IgG, immunoglobulin G.

- Comparable binding antibody titers were observed for homologous and heterologous SIV Env following artPICV/artLCMV and Ad5/MVA vaccination
- Higher NAbs were detected against tier 1 virus (smE660) with artPICV/artLCMV vs Ad5/MVA vectors

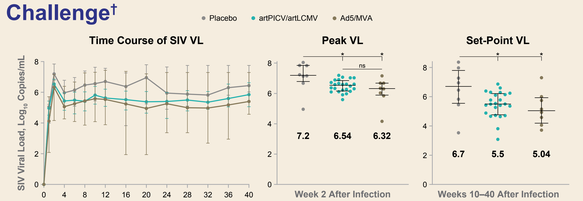
Generation of artLCMV Vector nAbs Did Not Interfere With Magnitude of SIV-Specific T-Cell Response†



*p<0.05, **p<0.01: statistical analysis by Kruskal-Wallis test for LCMV nAb titers and correlation analysis by nonparametric Spearman test; †Data are median ± IQR; n=24/group in artPICV/artLCMV; PICV nAb assay not available at time of sample analysis.

- Repeat dosing with artPICV/artLCMV increased LCMV vector nAb titers
- Peak LCMV nAb titers were observed 2 wk after the 2nd artLCMV boost (Vx dose 4)
- Vector nAbs did not correlate with SIV-specific T-cell response measured by IFNγ ELISpot

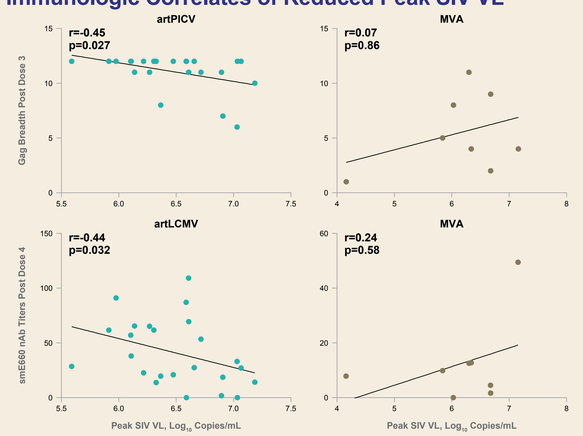
Vaccination Reduced Peak and Set-Point VL After SIV Challenge†



*p<0.05: Mann-Whitney test for comparison of vaccinated group vs placebo; †Data are median ± IQR; n=24/group in artPICV/artLCMV and n=8/group in Ad5/MVA; median VLs listed in graphs for peak and set-point VLs.

- Vaccination with artPICV/artLCMV and Ad5/MVA resulted in significant decreases in peak and set-point VLs vs placebo
- No significant difference in VL was observed between the 2 Vx vector platforms

Immunologic Correlates of Reduced Peak SIV VL*



*Nonparametric Spearman correlation analysis at 2 wk after doses 3 and 4.

- In artPICV/artLCMV-vaccinated animals, presence of Gag breadth after dose 3 and tier 1 smE660 nAbs after dose 4 inversely correlated with peak SIV VL
- This correlation was not observed in Ad5/MVA-vaccinated animals

Conclusions

- Alternating immunization with arenavirus vectors led to significant reductions in peak and set-point VLs after SIVmac251 challenge
- Alternating immunization with arenavirus vectors induced robust SIV-specific T- and B-cell responses that were not impacted by vector-specific nAbs
- The immunologic correlates generated after vaccination, Gag breadth after dose 3, and tier 1 Env nAbs after dose 4 inversely correlated with peak SIV VL, suggesting a role for vaccination-induced T- and B-cell responses in reducing SIV VL

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