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Heterologous ChAd/samRNA SIV Vaccine Induces Robust T-Cell Responses in Macaques

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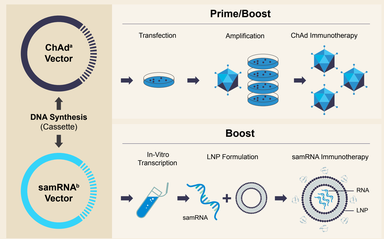
Introduction

- B- and T-cell responses to HIV are detected in most people living with HIV, but are largely insufficient to control the infection without antiretroviral therapy
- Highly functional T-cell responses, especially of cluster of differentiation (CD)-8$^+$ T cells, have been implicated in maintaining viral control in a small subset of people with HIV[1]
- In addition, human leukocyte antigen (HLA) class I alleles have been associated with HIV control in genome-wide association studies[2,3]; thus, therapeutic vaccines that can activate T-cell responses required for immune control of HIV-1 infection may represent a key component of a future HIV-1 remission/cure regimen
- To induce high-titer, antigen-specific, cytotoxic CD8$^+$ T cells, Gritstone bio has developed a heterologous prime/boost vaccine regimen comprised of a chimpanzee adenoviral (ChAd) vector prime, followed by boost vaccinations with self-amplifying messenger RNA (samRNA) formulated in lipid nanoparticles (LNPs)
  - This regimen has demonstrated strong T-cell immune responses in nonhuman primates and ongoing oncologic clinical trials[4]

ChAd/samRNA Vaccine Platform



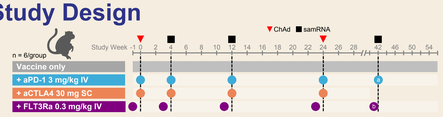
[a]ChAd 68; [b]Based on Venezuelan equine encephalitis virus.

Objectives

- To evaluate the safety and immunogenicity of a novel heterologous simian immunodeficiency virus (SIV) vaccine in combination with immune modulators in macaques

Methods

Study Design

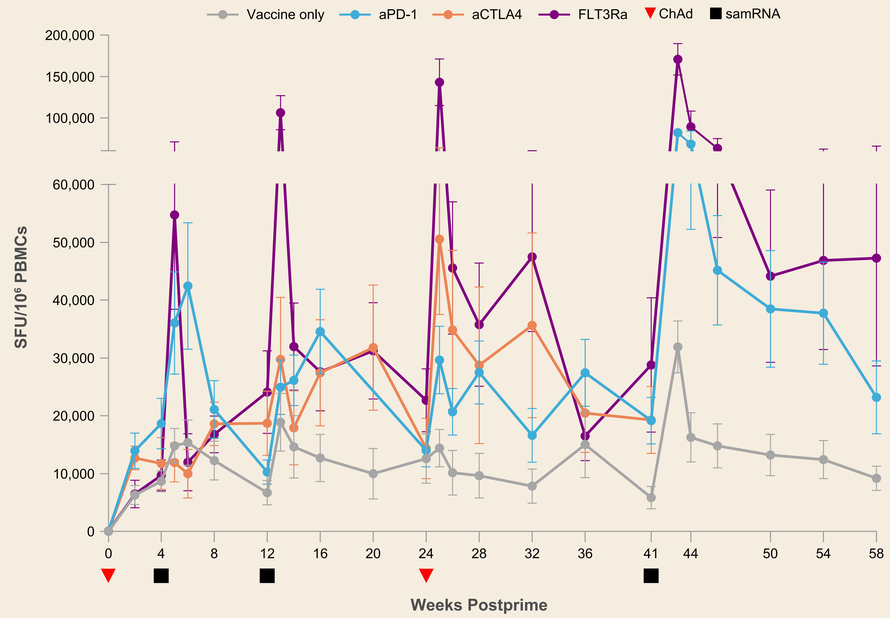


[a]Anti-programmed cell death protein 1 antibody (aPD-1) 60 mg SC; [b]fms-like tyrosine kinase-3 receptor agonist (FLT3Ra) 1 mg/kg IV. aCTLA4 = anticytotoxic T-lymphocyte-associated protein-4 antibody.

- Naive rhesus macaques (n = 6/group) were immunized with a ChAd and samRNA-based vaccine alone or in combination with aPD-1, aCTLA4, or FLT3Ra
- ChAd and samRNA vectors encoding full-length SIV group-specific antigen (Gag), polymerase (Pol), and envelope (Env) antigens were administered intramuscularly
- aPD-1 and aCTLA4 were dosed subcutaneously or intravenously concomitant with immunization
- FLT3Ra was dosed intravenously 1 week prior to each immunization
- Immunogenicity was characterized by ex vivo overnight interferon (IFN)-γ enzyme-linked immunosorbent spot (ELISpot) and multiparameter flow cytometry

Results

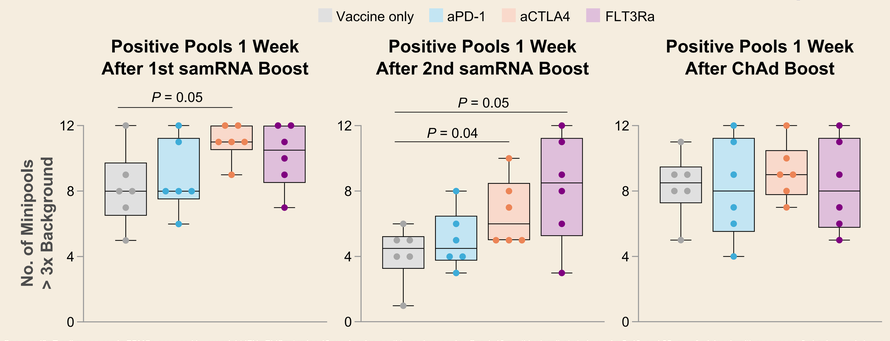
Heterologous ChAd/samRNA Vaccine Regimen Drove Potent and Durable SIV-Specific T-Cell Responses, Which Were Enhanced by Combination With aPD-1, aCTLA4, or FLT3Ra



SIV-specific T-cell responses in peripheral blood mononuclear cells (PBMCs) assessed by overnight IFNγ ELISpot at specified time point postimmunization; sum of 13 overlapping peptide pools spanning Gag, Pol, and Env were background subtracted; data presented as mean ± standard error of mean (SEM); n = 6/group.

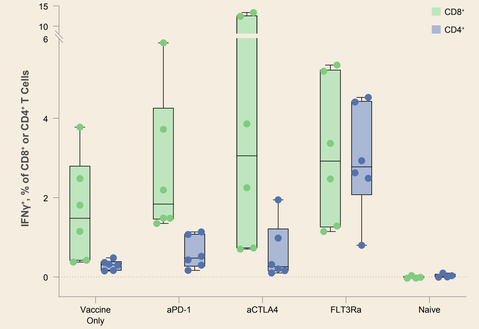
- All regimens were well tolerated, with transient small increases in inflammatory markers and body temperature
- The vaccine elicited strong IFNγ T-cell responses 4 weeks post-ChAd prime (mean ± SEM 8724 ± 1845 SFU/10^6 PBMCs), which were further augmented by boosts with samRNA (mean 1.8-, 3.7-, and 11.5-fold increases after each boost) and ChAd (1.7-fold increase)
- The responses peaked at a mean ± SEM 32,234 ± 4433 SFU/10^6 PBMCs and were durable through ≥ 16 weeks after last immunization (range 3398-15,360 SFU/10^6 PBMCs)
- Combination with aPD-1, aCTLA4, or FLT3Ra further augmented mean peak T-cell response magnitudes by 2.8-, 2.4-, and 5.7-fold, respectively

Combination With aCTLA4 or FLT3Ra Increased Breadth of T-Cell Response



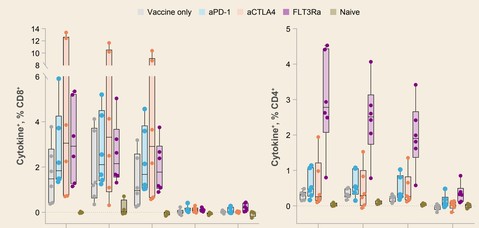
Gag-specific T-cell responses in PBMCs assessed by overnight IFNγ ELISpot using 12 overlapping peptide pools spanning Gag (~10 peptides/pool) at study weeks 5, 13, and 25; no. of minipools with response > 3x background shown for each animal; data presented as median (interquartile range [IQR]); Mann-Whitney test: only *P* values ≤ 0.05 are shown.

Vaccine Drove Predominantly CD8$^+$ T-Cell Response; Combination With FLT3Ra Also Expanded CD4$^+$ T-Cell Population



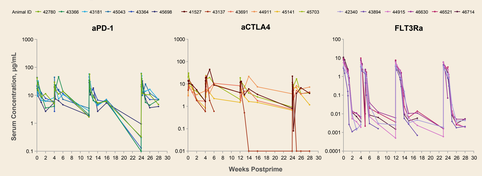
Intracellular cytokine staining of PBMCs at week 14 following overnight stimulation with 4 overlapping peptide pools spanning Gag, Pol, and Env background subtracted; sum of pools presented as median (IQR).

Vaccine Induced Predominantly IFNγ$^+$ TNFα$^+$ Polyfunctional T Cells, Which Were Increased by Combination With aPD-1, aCTLA-4, or FLT3Ra



Intracellular cytokine staining of PBMCs at week 14 following overnight stimulation with 4 overlapping peptide pools spanning Gag, Pol, and Env background subtracted; sum of pools presented as median (IQR). IL-2 = interleukin 2; TNFα = tumor necrosis factor-α.

Serum Exposures of aPD-1, aCTLA4, and FLT3Ra Were Consistent Across Animals and Repeat Doses

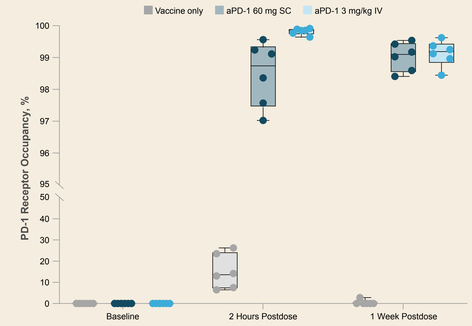


Treatment	Dose, mg/kg	Dose 1 C_{max}, µg/mL	Dose 1 $AUC_{0\text{-}28d}$, d·µg/mL	Dose 4 C_{max}, µg/mL	Dose 4 $AUC_{0\text{-}28d}$, d·µg/mL	AR
aPD-1	3.0	31.8 ± 9.43	246 ± 58.2	33.5 ± 14.4	301 ± 81.2	1.2
aCTLA4	9.1	13.9 ± 8.93	128 ± 36.6	11.9 ± 6.57	124 ± 64.9	1
FLT3Ra	0.3	6.53 ± 3.19	26.3 ± 13.6	5.23 ± 1.10	22.2 ± 6.53	0.8

AR = accumulation ratio; $AUC_{0\text{-}28d}$ = area under serum concentration vs time curve from predose to 28 d postdose; C_{max} = observed peak serum concentration.

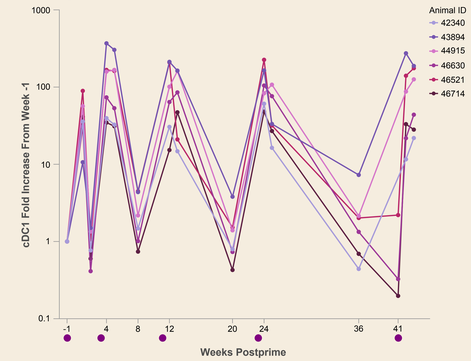
- Consistent aPD-1, aCTLA4, and Flt3Ra exposures were observed across animals and repeat doses with no accumulation (1 animal [#43137] receiving aCTLA4 developed apparent immunogenicity)

Complete Blockade of PD-1 Receptor Following aPD-1 Treatment Via Subcutaneous or Intravenous Route



Programmed cell death protein-1 (PD-1) receptor occupancy assessed by flow cytometry of PBMCs at specified time point following aPD-1 treatment; normalized to baseline values; data presented as median (IQR).

FLT3Ra in Combination With Vaccine Led to Expansion of cDC1 Cells in PBMCs



Conventional type 1 dendritic cell (cDC1) population (defined as CD14$^-$CD123$^-$/CD11c$^+$HLA-DR$^+$/Clec9a$^+$CD1c$^-$ of viable singlets) assessed in PBMCs for each animal by flow cytometry at specified time points; normalized to baseline value for each animal; *purple circles* indicate FLT3Ra dosing.

Conclusions

- The ChAd/samRNA heterologous SIV vaccine was well tolerated, and induced robust and broad antigen-specific T-cell responses in uninfected rhesus macaques
- T-cell responses were predominantly CD8$^+$ and polyfunctional
- Magnitude and/or breadth of SIV-specific T-cell responses were augmented by aPD-1, aCTLA4, or FLT3Ra, warranting their further exploration as part of a combination therapeutic approach for HIV cure, depending on clinical safety profiles

References: **1.** Deeks SG, Walker BD. Immunity 2007;27:406-16; **2.** Fellay J, et al. Science 2007;317:944-7; **3.** International HIV Controllers Study. Science 2010;330:1551-7; **4.** Palmer CD, et al. Nat Med 2022;28:1619-29.

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Disclosures: **A Rappaport, G Boucher, C Corzo, S-J Hong, H Larson, C Scallan, B Wang, K Jooss:** employees and shareholders of Gritstone; **E Bekerman, J Sung, B Carr, R Geleziunas, D SenGupta:** employees and shareholders of Gilead.

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