IMMUNE FEATURES ASSOCIATED WITH HIGHER T CELL RESPONSES TO AN HIV THERAPEUTIC VACCINE

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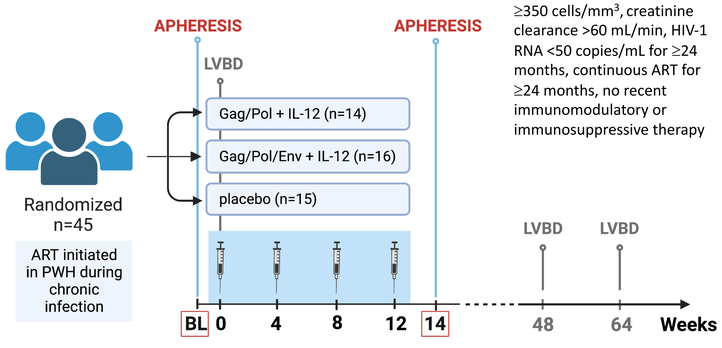
BACKGROUND

- Eliciting a robust T cell response is a central goal of many HIV therapeutic vaccines, but T cell responses are often heterogenous.
- We conducted a therapeutic vaccine study in 42 PWH who were randomized to receive a DNA vaccine containing consensus Gag/Pol (**GP**) or Gag/Pol/Env (**GPE**) sequences (PENNVAX) plus IL-12 plasmid adjuvant via electroporation, or placebo (NCT03606213).
- HIV-specific T cell response magnitude was measured by IFNγ ELISpot using vaccine-matched peptide pools (Fig. 1 and as reported CROI 2022 poster #284).
  - **HIV-specific T cell response to vaccination (average)** was defined as the fold change (FC) in the magnitude of HIV-specific T cell responses (averaged across HIV antigens in the given vaccine) from pre-vaccination to 2 weeks after last dose of vaccine (Week 14)
  - Median fold change 2.3x (GP), 1.7x (GPE)
- We performed systems immunology analyses to identify the immunologic signatures – at the cytokine, cellular and transcriptional level – that correlate with augmented HIV-specific T cell responses post-vaccination.

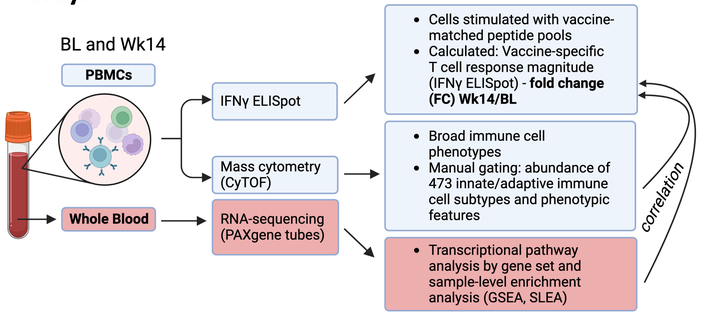
METHODS

Trial design:



Key Eligibility Criteria: Adults 18-65 years, CD4 T cell count ≥350 cells/mm^3, creatinine clearance >60 mL/min, HIV-1 RNA <50 copies/mL for ≥24 months, continuous ART for ≥24 months, no recent immunomodulatory or immunosuppressive therapy

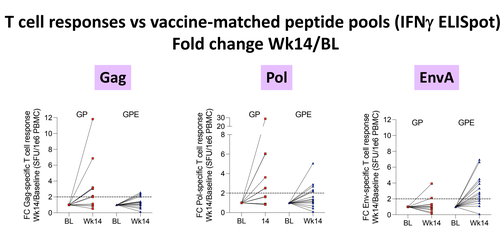
Assays:



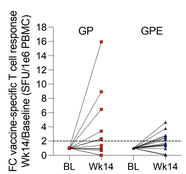
RESULTS

Fig 1: THERAPEUTIC VACCINATION INCREASES THE MAGNITUDE OF THE VACCINE-MATCHED HIV-SPECIFIC T CELL RESPONSE IN SOME PARTICPANTS

T cell responses vs vaccine-matched peptide pools (IFNγ ELISpot): Fold change Wk14/BL



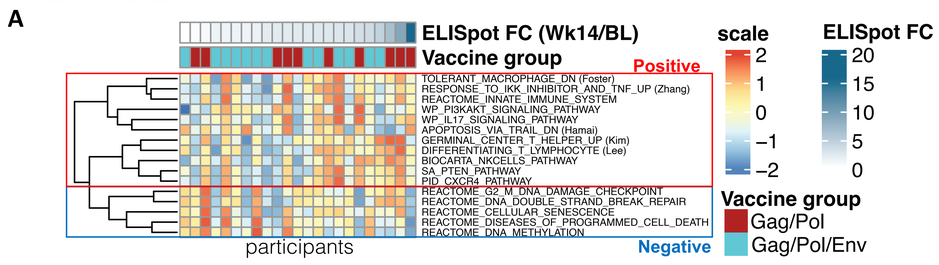
AVERAGE VACCINE-MATCHED HIV-SPECIFIC T CELL RESPONSE



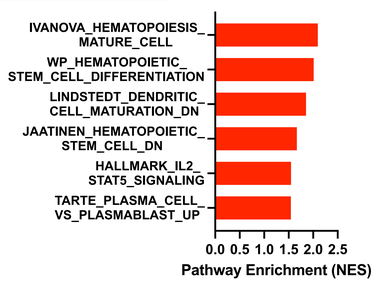
Average response = FC ELISpot response (Wk14/BL) averaged across HIV antigens in the administered vaccine (i.e., GP for GP group, GPE for GPE group)

Fig 2: DISTINCT BASELINE AND INDUCED TRANSCRIPTIONAL PATHWAYS CORRELATE WITH THE MAGNITUDE OF THE HIV-SPECIFIC T CELL RESPONSE TO VACCINATION (IFNγ ELISpot)

Baseline pathways/genes



Vaccine-induced pathways



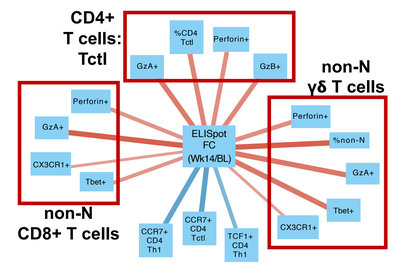
RNAseq was performed on whole blood (PAXgene tubes) at baseline (BL) and Week 14 (Wk14).

(A) Baseline sample: Sample-level (columns) depiction of transcriptional pathways (rows) that contain genes for which expression is significantly correlated (p.adj<0.05; positively-red or negatively-blue) with the fold change (FC) increase in the magnitude of average vaccine-specific T cell responses (Wk14/BL). Samples are ordered left-to-right by the magnitude of the FC in the IFNγ ELISpot response.

(B) Baseline sample: leading-edge genes from the positively correlated transcriptional pathways in (A). PRRs, pattern recognition receptors. TFs, transcription factors, MHC major histocompatibility complex.

(C) Transcriptional pathways for which fold change increase in gene expression (Wk14/BL) is significantly (p.adj<0.05) positively correlated with fold change in the magnitude of the vaccine-specific T cell response (Wk14/BL IFNγ ELISpot). NES, normalized enrichment score.

Fig 3: EXPANSION OF CYTOTOXIC CD4+, CD8+ AND $\gamma\delta$ T CELLS CORRELATES WITH IFNγ ELISpot T CELL RESPONSE TO VACCINATION



- CyTOF profiling of PBMCs to characterize broad immune phenotypes (monocytes, DCs, B/T/NK cells) was performed on baseline and Week 14 samples. Manual gating yielded n=473 innate/adaptive immune cell features. Non-N = non-naive
- Fold change in the abundance of cellular immune features (Wk14/BL) was correlated with fold change in the HIV-specific T cell response (IFNγ ELISpot) to vaccine-matched peptides (average, Wk14/BL).
- Significant correlations (p<0.05, Spearman correlation) are shown:
  Red line = positive correlation
  Blue line = negative correlation

CONCLUSIONS

- Individuals who develop a larger T cell response to a DNA HIV therapeutic vaccine have a baseline immune environment that promotes T cell survival and responsiveness to innate immune signaling, and they respond to vaccination with more robust IL-2/STAT5 signaling and hematopoiesis.
- Therapeutic vaccination with DNA/IL-12 promotes expansion of not only cytotoxic CD8+ T cells, but also cytotoxic CD4+ and $\gamma\delta$ T cells.
- Differences in host immune responses pre- and post-vaccination can impact vaccine immunogenicity and highlight that modulation of the pre-existing immune environment (e.g., with different adjuvants) may be critical to conditioning better vaccine responses.
- Future Directions: Planned analysis of baseline and induced plasma cytokines (Mesoscale), multiomics integration (MCIA), functional validation.

ADDITIONAL INFORMATION

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