IL-7 AND IL-15 IMPROVE HUMORAL RESPONSES OF A SHIV DNA VACCINE IN ANIMAL MODELS

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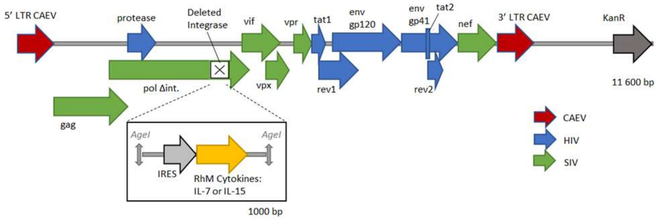
BACKGROUND

CAL-SHIV-IN$^-$ lentiDNA vaccine based on $SHIV_{KU2}$ backbone
- deleted for *Integrase* gene
- **constitutive**, Tat-independent CAEV LTRs
- elicits **Gag-** and **Nef-specific CD4$^+$** and **CD8$^+$** T precursors (PHPC), Tcm and Tem cells **up to 80 weeks** post-immunization (p-i) in cynomolgus macaques.

IL-7 and IL-15: homeostatic compounds known for increasing **number**, **function** and **differentiation** of T-cells.
- insertion IL-7 or IL-15 genes in parental CAL-SHIV-IN$^-$

→ Evaluation of IL-7 and IL-15 adjuvants to improve the pool of vaccine-specific memory T cells in comparison with the non-adjuvanted parental lentiDNA, in mouse and rhesus macaque.

METHODS



Immunization with lentiDNA vector CAL-SHIV-IN$^-$ (group 1) or CAL-SHIV-IN$^-$ IRES IL-7 + CAL-SHIV-IN$^-$ IRES IL-15 (group 2)
- **BALB/c mice** (n=20/group) : 100 µg
  (50 µg ID and 50 µg IM + electroporation (EP))
  Homologous boost 6 weeks p-i
  → Study of vaccine-specific T cells in spleen at 2, 4, 8 and 10 weeks p-i (multiparametric flow cytometry)
- **Rhesus macaques** (n=3/group) : 5 mg
  (1 mg ID and 4 mg IM + EP)
  Homologous boost 16 weeks p-i
  → Study of vaccine-specific T cells in PBMCs up to 36 weeks p-i (ELISpot IFN-γ)
  → Study of HIV-1 Env specific Ab in serum and in rectal secretion up to 40 weeks p-i (ELISA)

IL-7 / IL-15 adjuvants augment **proportion** and **longevity** of:
- vaccine-specific CD4$^+$ and CD8$^+$ T cells in mouse splenocytes and macaque PBMCs,
- **plasma IgG** and **mucosal IgA** in macaque rectal secretions.

RESULTS

Mice (Fig. 1): Group 1: low CD4$^+$/CD8$^+$ T cell responses to Gag.
Group 2: **higher proportions** of IFN-γ / IL-2 producing Gag-specific CD4$^+$/CD8$^+$ T cells (week 8-10 p-i).

Macaques (Fig. 2):
- Env-specific Ab titers maintained in both groups until week 22 (6 weeks post-boost).

Group 2: high Ab titers **maintained by week 40** (> 5 months post-boost), but **decreased in group 1** (Fig. 2a). ADCC activity but no neutralizing responses detected against HIV-1_{JR-FL} tier 2 virus.

- **Mucosal IgA** only detectable in group 2 rectal secretions. Prolonged anamnestic response after boost (week 16). IgA still detectable (up to 1:250) after contraction phase, **up to 40 weeks** p-i (Figure 2b).

Figure 1

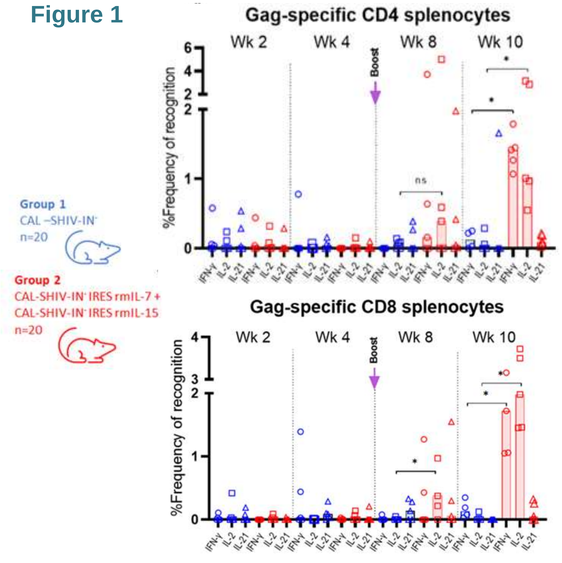
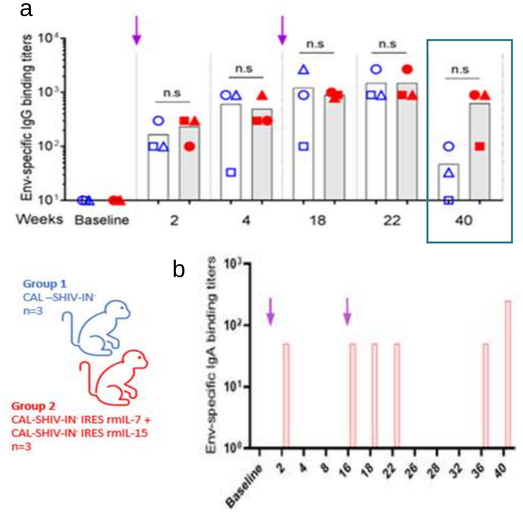


Figure 2



CONCLUSIONS

Co-expression of both IL-7 and IL-15 in our lentiDNA vaccine enhanced **multifunctional** Ag-specific CD4$^+$ and CD8$^+$ T cells and their **maintenance** in mice.
In macaque model, data suggest a role for IL-7 and IL-15 in the **homeostasis/maintenance** of **plasma** and **mucosal** cells secreting HIV-1 Env-specific Abs.

Future studies will determine whether such responses can contain challenges with pathogenic SHIVs to provide proof of the protective capacity of the immunity conferred by these vaccines and this original strategy.

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