Enhanced HIV Antibody Precursor Development with Early-Life Germline Targeting Immunization

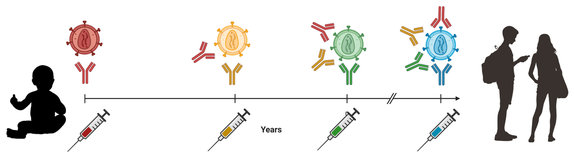
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INTRODUCTION

- An HIV vaccine that induces broadly neutralizing antibodies (bnAbs) prior to sexual debut is critical to reduce the ~400,000 new infections that occur annually among youth aged 15 to 24 years worldwide.
- Elicitation of bnAbs by vaccination is the most promising strategy as they can protect a diversity of HIV-1 isolates
- Children living with HIV develop bnAbs earlier and at a higher frequency than adults, suggesting that the infant immune landscape may be more amenable to the induction of bnAb B cell lineages by vaccination.
- BG505 SOSIP trimers are bioengineered mimics of the HIV env and have been found to induce durable, high-magnitude antibody responses.

Study Goal



Compare the ability of a bnAb B cell designed germ-line targeting SOSIP trimer immunization strategy to induce CD4bs precursor bnAb responses in infant and juvenile macaques.

METHODS

Infant (n=5) and juvenile (n=4) rhesus macaques (RMs) received 3 immunizations of the germline-targeting, clade A, BG505 GT1.1 SOSIP trimer (50μg) with the 3M-052-SE adjuvant 6 weeks apart, followed by boosting 12 weeks later with the WT BG505.664 SOSIP trimer 3 times in 6-month intervals. Subsequently, RMs received a nanoparticle vaccine (NP) containing Env trimers from AMC008, AMC009, AMC011, AMC016, and TRO.11 clade B viruses (Figure 1).

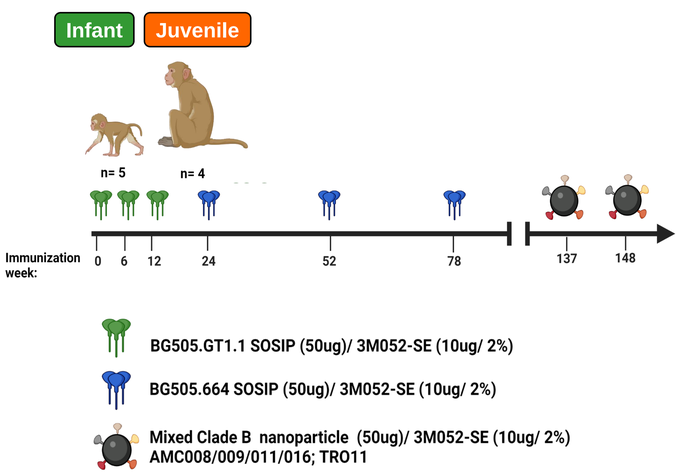


Figure 1. Timeline of the immunizations administered to infant and juvenile RMs

RESULTS

Higher plasma IgG binding responses in infant RMs

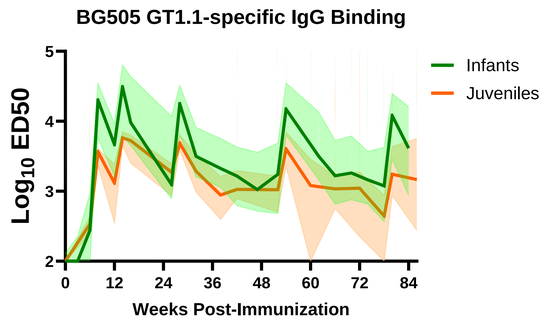


Figure 2. Plasma IgG binding responses were measured by ELISA to the BG505 GT1.1 SOSIP. Bold lines represent median, and shaded area represents the range.

BG505 GT1.1 immunization induces antibodies that can target diverse epitopes

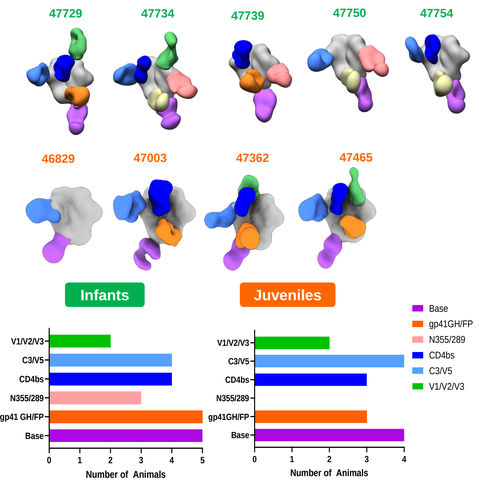


Figure 5. Negative staining Electron Microscopy Polyclonal Epitope Mapping (or nsEMPEM) was used to visualize the polyclonal nature of vaccine elicited antibodies. Structural images are representative of the antibody Fab portion binding to BG505 GT1.1 trimer epitopes.

Infant and juvenile RMs develop Tier 1& 2 autologous virus neutralizing antibodies

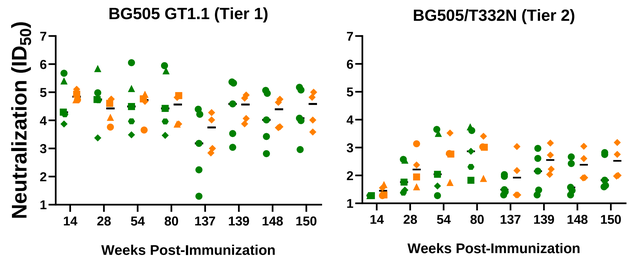


Figure 3. HIV-1 neutralization in sera was assayed in TZM-bl cells against BG505/T332N tier 2 virus. Both BG505 GT1.1 immunized infants and juveniles developed tier 2 virus neutralization.

Phenotyping of B and T follicular helper cell responses following immunization

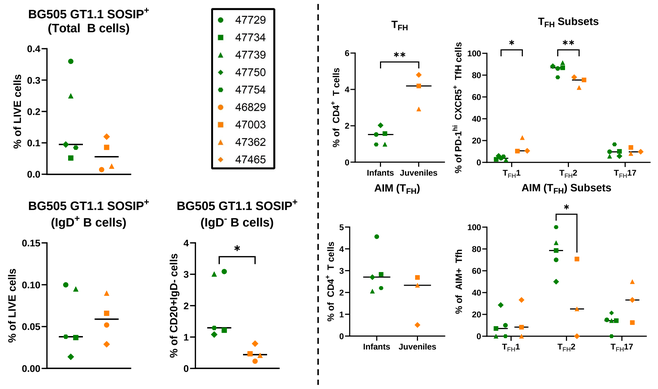


Figure 6. B cell phenotyping (left), PBMCs at week 14 were surface-stained and measured for different populations of B cells (unpaired t-test *p<0.028). For T_{FH} phenotyping (right), lymph node mononuclear cells were surface and intracellularly stained; subsets were determined based on surface and intercellular markers. For the Activation Induced Marker (AIM) assay, T_{FH} cells were stimulated with antigen and then stained with T_{FH} surface and intercellular markers (unpaired t test *p<0.0019; AVNOA, Multiple comparisons *p< 0.013, **p<0.004).

Development of CD4bs precursor bnAbs in four infants and one juvenile RM

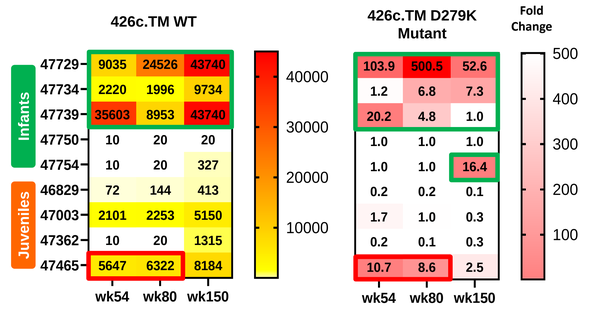


Figure 4. Sera was assayed against the 426c.TM/293S/GnT1- virus, which engages germline-reverted forms of VRC01-class bnAbs, and the CD4bs KO virus, 426c.TM.D279K/293S/GnT-. A VRC01-like precursor bnAb signature was assigned based on >3-fold reduction in neutralization, ID50, compared to parent virus (green and red boxes).

Infants show improved neutralization breadth against heterologous tier 2 viruses following clade B nanoparticle vaccination

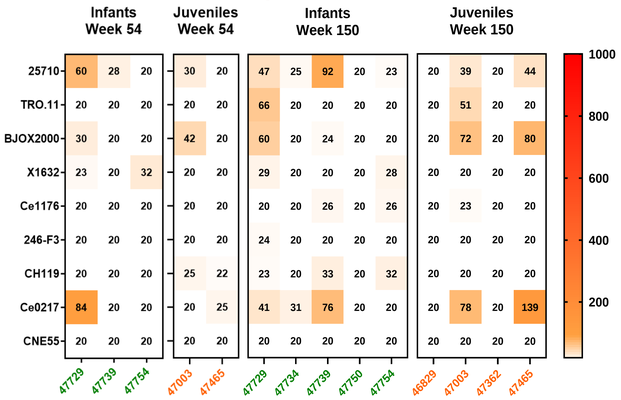


Figure 7 . Sera was screened at 2 weeks post- 5th immunizations for neutralization against a panel of tier 2 viruses representing global HIV-1 isolates . By week 54, 3 infants and 2 juveniles exhibited moderate neutralization breadth. Following nanoparticle immunization, all infants exhibited improved breadth in neutralization responses.

CONCLUSIONS

- BG505 GT1.1 SOSIP trimer immunization consistently induced higher magnitude antigen-specific IgG binding responses in infants compared to juvenile RMs, yet both groups generated similar levels of Tier 2 autologous virus-neutralizing antibodies
- Three out of the five GT1.1 SOSIP-immunized infants exhibited a plasma neutralization signature reflective of CD4 binding site-specific (CD4bs) bnAb precursor development. At the same time, only one out of four juvenile RMs had developed this response. Following two doses of the nanoparticle boost, four out of five infants developed the precursor response, while the one juvenile was not able to maintain that response
- nsEMPEM showed that the infants' antibodies target diverse epitopes and confirmed that the GT1.1 immunization elicited binding to the apex (V1/V2/V3) and CD4bs regions.
- Nanoparticle boost moderately improved the breadth of neutralizing antibodies in four infants compared to only two juveniles.
- Infants and juveniles mostly had comparable B and TfH responses. The infants had slightly higher antigen-specific cell responses, such as the proportion of antigen-specific B cells and AIM T_{FH} 2 cells.

Our data demonstrate that sequential immunization of infant RMs with germline-targeting BG505 SOSIP trimers can induce high serum neutralizing antibody titers and CD4bs bnAb precursors comparable to juveniles RMs receiving the same regimen, suggesting that the infant immune environment is well-suited for induction of plasma bnAb responses.

ACKNOWLEDGEMENTS

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