An Env-only Vaccine Does Not Provide Sterilizing Protection of Rhesus Macaques Against High-dose SIVsmE600 Challenge

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Abstract

We reported previously on a vaccine approach conferring apparent sterilizing immunity to high-dose mucosal challenge with the SIVsmE660 quasispecies [Schell et al., (2011) J. Virol. 85: 5764-5772]. Four of six macaques were protected by vaccination with a prime-boost regimen using vectors based on recombinant vesicular stomatitis virus (VSV) and propagating Semliki Forest virus/VSVG replicons (SFVG) expressing SIV Gag and Env proteins. At the time of challenge, both protected and unprotected animals had high levels of neutralizing antibodies (nAb) to the vaccine envelope and to tier 1 envelopes. They did not have nAb to tier 2 envelopes or the viral challenge swarm. The cellular immune responses to both Gag and Env generated by the vaccine were weak and did not correlate with protection. All protected animals maintained apparent sterilizing immunity against a second high-dose mucosal challenge with SIVsmE660. The observed protection occurred in the absence of significant cellular immune responses to Env or Gag. Because these experiments suggested the possibility that humoral responses to Env were sufficient for protection, the following study used vectors expressing only the SIVsmE660 Env protein. Eight macaques were given the Env-only vaccine regimen and all developed SIVsmE660 nAb levels comparable to the previous Env+Gag vaccine study. The animals were then given the same high-dose mucosal challenge used in the previous studies. All vaccinated animals became infected with the challenge virus. While average peak viral loads in animals were slightly lower than seen in previous controls, the viral set-points were not significantly different. These data indicate that Gag, or the combination of Gag and Env antigens in the vaccine are critical for generation of apparent sterilizing immunity to challenge.

Background

Figure 1. Previous Vaccine Protection from SIVsmE660 Challenge.

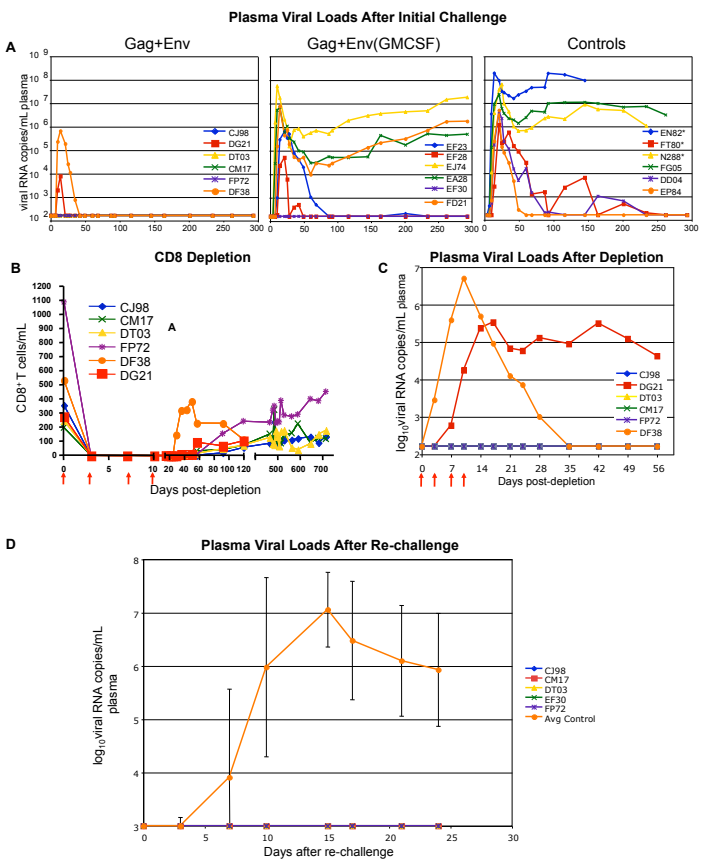

Figure 1. A) Viral load data (Schell et al., J. Virol. 85: 5764-5772; Schell et al., Vaccine. 30(28):4233-9.) are shown. Four out of six macaques in the vaccine group (Gag+Env) were completely protected from infection by high-dose rectal challenge with SIVsmE660. Only one out of six animals was completely protected in a second group of animals that received a VSV vector expressing GMCSF at the time of prime (GMCSF). All control animals became infected and three developed high viral load and AIDS. B) CD8+ T cell levels in animals treated with four doses of anti-rhesus CD8 antibody are shown at times after depletion. The CD8 cell depletion was complete in all animals by day 3 following the initial treatment. C) Viral RNA levels at times after depletion. Viral loads returned only in the two animals that showed initial viral loads. Red arrows indicate days when anti-CD8 antibody was administered. D) Five protected animals were re-challenged with a second intrarectal high-dose ($TCID_{50}$=4000) of SIVsmE660. No viral RNA was detected in any of the animals. Average loads of control animals challenged with the same stock are presented for comparison.

References and Acknowledgements

Schell JB, Rose NF, Bahl K, Diller K, Buonocore L, Hunter M, Marx PA, Gambhira R, Tang H, Montefiori DC, Johnson WE, Rose JK. 2011. Significant protection against high-dose simian immunodeficiency virus challenge conferred by a new prime-boost vaccine regimen. *J Virol* **85:**5764-72.

Schell JB, Bahl K, Rose NF, Buonocore L, Hunter M, Marx PA, LaBranche CC, Montefiori DC, Rose JK. Viral vectored granulocyte-macrophage colony stimulating factor inhibits vaccine protection in an SIV challenge model: protection correlates with neutralizing antibody. *Vaccine.* 2012 Jun 13;30(28):4233-9.

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Figure 2. Env-only vaccine regimen fails to prevent SIVsmE660 infection.

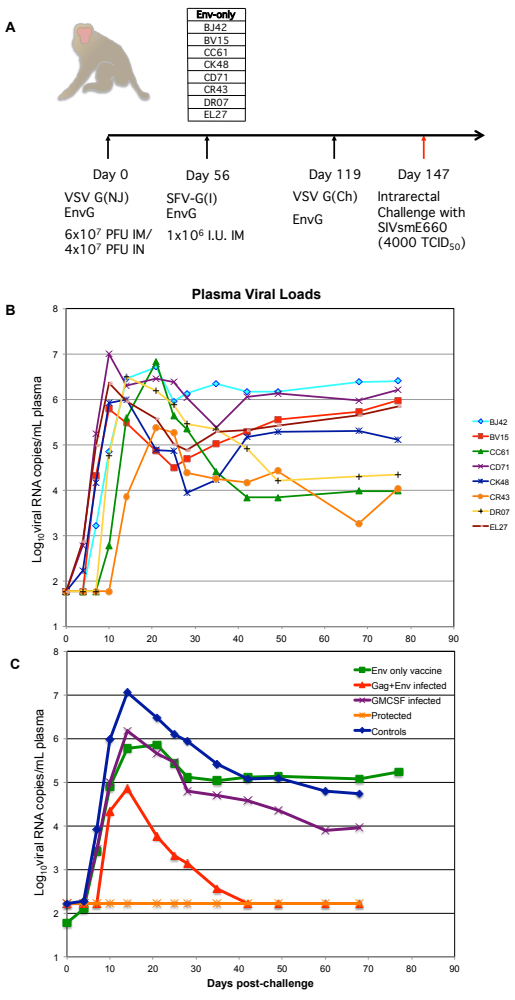

Figure 2. A) Vaccine schedule and dosing for Env-only vaccine group. B) Viral loads are shown. Upon high-dose intrarectal challenge (4000 $TCID_{50}$), all vaccinated animals became infected. C) Average viral loads from the Env-only vaccine group are compared to the protected and infected Gag+Env vaccine, and control groups.

Figure 3. Cell mediated IFN-γ production does not correlate with protection.

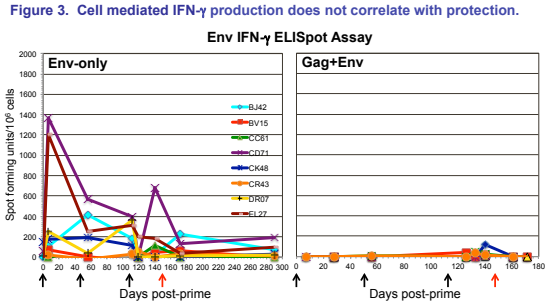

Figure 3. Graphs show IFN-γ production by PBMCs in response to Env antigen. The Env-only vaccine group (left panel) made greater numbers of Env-specific IFN-γ producing cells throughout the course of the vaccine regimen, as compared to the previous Gag+Env vaccine group (right panel). Arrows show the days of vaccination (black) and challenge (red).

Conclusions

VSV-based vectors combined with SFVG propagating replicons expressing SIV Env and Gag proteins can provide apparently sterilizing protection against high-dose mucosal challenge with an SIVsmE660 quasispecies. Despite generating comparable levels of antibodies with similar neutralization capabilities, and stronger cell-mediated responses to Env antigen, our Env-only vaccine strategy failed to protect any of the animals against high-dose SIVsmE660 challenge. We also did not see a correlation between Env V2-loop binding and protection. We think protection is most likely mediated through a combination of antibodies and resident cellular responses in the mucosa. Future experiments will be conducted to determine if our vaccine vectors expressing Gag-only can provide protection against high dose mucosal challenge with SIV, and to determine the immune correlates of this mucosal protection.

Figure 4. Serum anti-gp140 IgG and neutralizing antibody concentrations similar between groups prior to challenge.

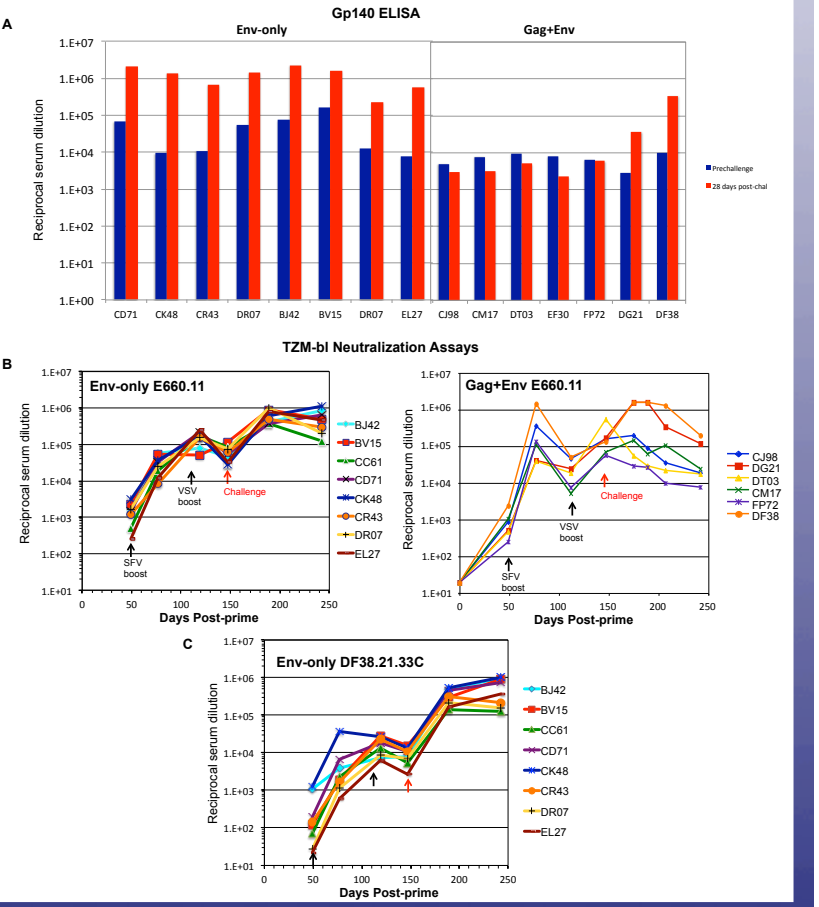

Figure 4. A) gp140 ELISA using pre-challenge (blue bars) or 1 month post-challenge (red bars) sera. Anamnestic antibody production seen in only those animals that became infected. This included all animals in the Env-only group, but only DF38 and DG21 in Gag+Env group. B) The ability of sera from animals in Env-only and Gag+Env groups to neutralize E660.11 envelope pseudotyped HIV in a TZM-bl assay. Arrows mark the time of boosts and challenge. Again anamnestic Ab responses were seen only in animals that were infected. C) Env-only group neutralizing antibody concentrations against a founder virus Env (DF38.21.33C) isolated from an infected animal from the Gag+Env group (DF38) by single genome amplification.

Figure 5. SPR shows IgG binding to cyclized V2 peptide does not correlate with protection.

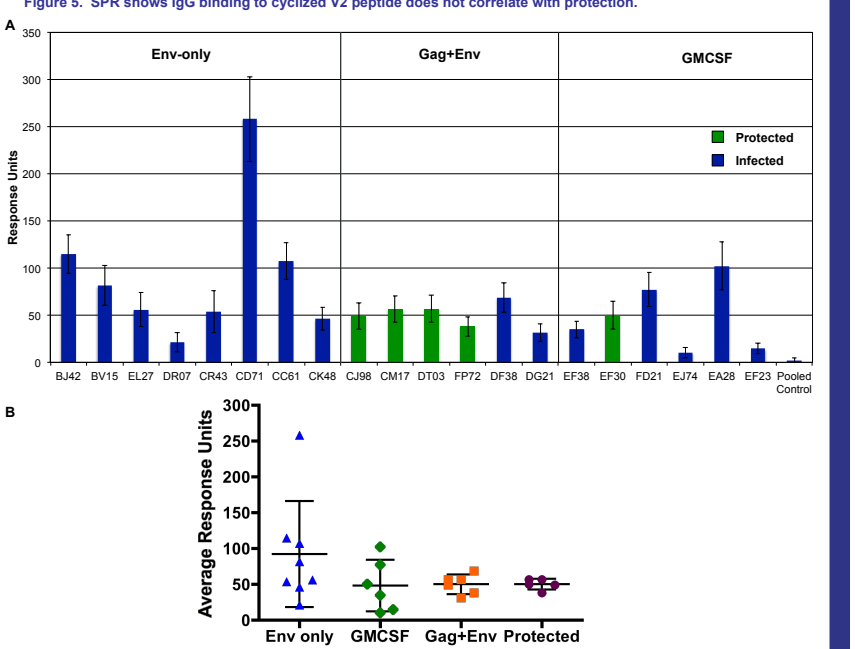

Figure 5. Surface plasmon resonance was used to measure the specific binding of IgG to a cyclized V2 peptide from the vaccine envelope (Biotin-CIKNNSCAGLEQEPMIGCKFNMTGLKRDKRIEYNETWYSRDLICEQSANESESKCY). A) The specific IgG binding of the V2 loop by each animals pre-challenge sera is shown (n=4). Pooled control animal sera did not recognize the V2 peptide. Infected and protected animals are represented by blue and green bars, respectively. B) Average binding of IgG antibodies to the V2 peptide are shown by group. V2-specific Ab binding does not correlate with protection in the SIVsmE660 challenge model.