Background: An HIV-1 Env vaccine should induce broadly neutralizing antibodies (bNAbs). One approach is to create soluble mimics of the native Env trimer that expose multiple bNAb epitopes, while occluding non-NAbs epitopes. The cleaved SOSIP.664 gp140 trimers based on the subtype A founder virus, BG505, closely approximate the desired antigenicity properties. These trimers are also highly stable and homogeneous, closely resemble native virus spikes when viewed by negative stain EM, and their high-resolution X-ray diffraction and cryoEM structures have been determined.

Methodology: We immunized rabbits intramuscularly with native-like BG505 SOSIP.664 gp140 trimers (or, for comparison, gp120 monomers) in ISCOMATRIX™ adjuvant. The trimers were produced in 293T or 293S cells and with or without glycosidase digestion. We measured the autologous and heterologous NAb responses in the sera using the Tzm.bl cell assay, and assessed NAb epitope specificities using mutant viruses and specific competitors such as Env proteins and peptides.

Results: The trimers induced strong (titers of 50-3000) and consistent (16 of 16 animals) NAbs against the autologous, neutralization-resistant (Tier-2) BG505.T332N virus, much more so than the corresponding monomeric gp120. Heterologous Tier-1 NAbs were also induced efficiently, but other Tier-2 viruses were neutralized only weakly and inconsistently. The autologous NAb responses in the trimer-immunized rabbits were similar in magnitude to those found in the HIV-1 BG505 infected-infant, but over time the infant developed broader, heterologous responses not seen in the rabbits. The most immunogenic linear peptide epitope was V3, but anti-V3 Abs neutralized only Tier-1 viruses (from multiple subtypes) and did not contribute to the autologous, Tier-2 response. Neutralization-inhibition experiments with peptides and proteins indicate that the autologous neutralization is directed to conformational epitopes on gp120, but not to linear variable loop peptides. The glycan-variant trimers did not differ markedly in immunogenicity, and mutant virus studies suggest that the autologous NAbs are not directed against the N332- or N160-dependent sites. Complex, variable-loop dependent epitopes as well as elements near the CD4bs are now being evaluated as the most likely target of autologous NAbs.

Conclusions: A native-like trimer based on a founder virus induces a NAb response that mimics what is often seen in primary infection; the NAbs are strong against the autologous virus but lack breadth against Tier-2 strains. The challenge now is to combine knowledge of the BG505 SOSIP.664 trimer structure with a better understanding of the immunology of bNAb development during infection, to guide improvements to Env trimer-based immunogens.