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OA02.05LB Vaccine-induced Gene Signature Correlates with Protection against Acquisition in Three Independent Vaccine Efficacy Trials Including RV144

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Background: Two independent SIV and SHIV preclinical non-human primate (NHP) challenge studies showed partial efficacy with a mosaic Ad26-based HIV-1 vaccine candidate. Although the study design, vaccine strategy, and challenge virus differed between studies, both elicited strong antibody responses. We performed next-generation RNA-sequencing (RNA-Seq) at time points after vaccination but prior to challenge to identify gene signatures that could predict protection.

Methods: In both studies whole transcriptome data was generated from 10 rhesus monkeys, 20 weeks after last vaccination in the SIV challenge model, from sorted CD4 T cell, CD8 T cell, NK cell and B cell populations. RNASeq was also performed on sorted cells from 23 rhesus monkeys, 2 weeks after last vaccination in a SHIV challenge model. Reads were aligned against reference genome and differential gene expression was computed. Gene set analysis was performed to test significant association of gene sets with phenotypes.

Results: We obtained on average 58 million paired-end reads and identified 11,276 expressed protein-coding genes. Gene set enrichment analyses that differentiate phenotypes identified a transcriptional signature in B cells that associated with protection from acquisition in both studies. Next we tested if this gene signature could predict acquisition in the RV144 trial, and observed a significant enrichment in the protected vaccinees (p< 0.001, q< 0.05). Enriched genes in this signature are involved in B cell development and TLR signaling, and associate with higher magnitude of antibody dependent cellular phagocytosis responses.

Conclusions: This B cell gene signature may be a broad indicator of effective vaccination, as it was previously seen to associate with higher antibody responses to influenza and yellow fever vaccination. This report represents a powerful orthogonal approach that intersects both transcriptomic and correlates analyses to identify genes that correlate with acquisition and vaccine function in NHP and humans.
OA02.06LB Primary Analysis of TRAVERSE: A Phase 1/2a Study to Assess Safety/Tolerability and Immunogenicity of 2 Different Prime/Boost HIV Vaccine Regimens

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Background: Mosaic antigens are designed to induce broad immune responses which could provide protection against globally diverse HIV-1 strains. Heterologous Ad26/gp140 prime-boost regimens confer significant protection from SHIV challenge in non-human primates (NHP) and appear safe and immunogenic in human phase 1/2a trials.

Methods: A 4-valent Ad26.Mos4.HIV vaccine was created by adding Mos2S.Env to a 3-valent vaccine comprising Mos1.gag-pol, Mos2.gag-pol and Mos1.Env, aiming to enhance immune response breadth. TRAVERSE is a phase 1/2a, safety and immunogenicity study in 198 participants from the USA and East Africa. This study compares 2 regimens: two prime vaccinations at Month (M) 0&3 with either 3- or 4-valent Ad26 vaccine, both boosted at M6&12 with the same Ad26 vaccine as in the prime with adjuvanted clade C gp140. Here we report results of the primary analysis, performed 4 weeks after the first boost.

Results: Both vaccines were well tolerated, and most adverse events were mild or moderate. Use of the 4-valent vaccine significantly enhanced ELISA responses to the protein in the boost (3.1-fold Geometric Mean Titer increase; 95%CI 2.1-4.6, p<0.0001), previously identified as a correlate of protection in NHP challenge studies. Nearly 100% humoral immune response rates were observed in binding and functional humoral assays in the 4-valent group, with the magnitude of responses to Env clades A, B, C and Consensus significantly enhanced relative to 3-valent (GMT increase: ELISA 1.4-2.9-fold, ADCP 1.1-1.9-fold p=0.03 to p<0.0001). Env ELISPOT responses were also significantly increased (450 v 255 SFU p<0.0001), and a 96% response rate was observed to homologous mosaic and PTE peptides in the 4-valent group. No immune interference was noted by addition of Ad26.Mos2S.Env.

Conclusions: The primary analysis compares favorably to the APPROACH study and supports use of 4-valent Ad26.Mos4.HIV in clinical trials globally. This 4-valent vaccine regimen is currently being evaluated for efficacy in southern Africa.
Identification of near pan-neutralizing antibodies against HIV-1 by deconvolution of plasma humoral responses

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Background: Anti-HIV-1 envelope broadly neutralizing monoclonal antibodies (bNAbs) isolated from memory B-cells may not fully represent HIV-1 neutralizing profiles measured in plasma.

Methods: We characterized near pan-neutralizing antibodies extracted directly from the plasma of two “elite neutralizers.” This was accomplished by coupling proteomics of the anti-gp120 plasma neutralizing antibody response with lineage analysis of bone marrow plasma cells.

Results: In both subjects, a single lineage of anti-CD4-binding site (CD4bs) antibodies explained the plasma neutralizing activity. Strikingly, the members of a single plasma cell lineage of one subject (N49) potently neutralized 100% of a validated multi-tier 117 pseudovirus panel, matching the specificity, sequence, and neutralization breadth of the circulating plasma neutralizing antibodies. X-ray crystallographic analysis of two monoclonals, N49P6 and N49P7, suggested a unique ability to bypass the CD4bs Phe43 cavity, while reaching deep into highly conserved residues of Layer 3 of the gp120 inner domain, likely explaining its extreme potency and breadth.

Conclusions: We propose that conjoint analysis of plasma neutralizing antibodies by proteomics and bone marrow plasma cell derived lineages will improve understanding of how anti-HIV-1 neutralizing antibody responses evolve and improve antibody prophylaxis against this virus.
OA07.04 Structure-based Network Analysis of HIV-1 Defines Protective CD8+ T Cell Epitopes Across Diverse HLA: Implications for Global Immunogen Design

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Background: Mutationally constrained regions of the HIV-1 proteome represent optimal targets for T cell-based vaccines, but sequence based methods such as amino acid conservation have not reliably identified these sites. Here we employ an alternative approach-structure-based network analysis (SNA)-that applies network theory to protein structure data to better define amino acids critical to viral structure and function.

Methods: Relying on structural rather than sequence data, SNA builds networks of non-covalent interactions between amino acid (AA) side chains and then quantitates the sum contribution of each residue to the protein's overall structure (i.e. network score). Applying this approach to available HIV-1 structural data allowed us to calculate network scores for 71% of the viral proteome and 86% of reported optimal T cell epitopes.

Results: Network scores across the entire HIV proteome exhibited a strong inverse correlation with viral sequence entropy (P< 0.001), but also revealed numerous sequence-conserved residues that were poorly networked. In vitro mutagenesis of conserved residues with high and low network scores revealed a striking difference in mutational sensitivity (P< 0.0001), with only mutation of highly networked residues leading to impaired HIV infectivity. Assessment of CD8+ T cell responses in 134 HIV+ individuals also revealed that persons who successfully control HIV disproportionately targeted epitopes comprised of highly networked residues (P< 0.001), irrespective of HLA allele. Moreover, plasma viral sequencing revealed markedly reduced mutation rates in networked epitopes, despite robust CD8+ T cell targeting.

Conclusions: These findings demonstrate the superior ability of SNA to define residues critical to viral structure and function and implicate targeting of highly networked epitopes by T cells as a putative mechanism of viral control across diverse HLA. Application of this approach provides the rational framework for the design of a broad T cell-based HIV vaccine.
OA11.02 Fusion Peptide-Directed Antibodies Elicited in Immunized Rhesus Macaques Neutralized 59% of 208 Wildtype HIV-1 Strains

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Background: The N-terminal eight amino acids of HIV-1 fusion peptide (FP) is the target of several neutralizing monoclonal antibodies (mAb) isolated from HIV-1 infected individuals.

Methods: We immunized 15 rhesus macaques with FP linked to keyhole limpet hemocyanin (FP-KLH), BG505.DS.SOSIP.664 trimer and 426c.DS.SOSIP.664 trimer. Group 1 (N=5) received 2 FP-KLH prime and 6 trimer boost. Group 2 (N=5) received 2 trimer prime, 3 FP-KLH boost and 3 trimer boost. Group 3 (N=5) received 3 trimer prime, 2 FP-KLH boost and 3 trimer boost.

Results: After a series of 8 immunizations, plasma from most animals bound to FP and neutralized the BG505 Env-pseudovirus that lacked the N611 glycan shielding the FP region, with the strongest binding and neutralization in group 1 animals receiving FP-KLH followed by BG505 and 426c trimer boost. Week 72 plasma from group 1 animals were tested on 58 wildtype HIV-1 Env-pseudotyped viruses, which included all FP sequence-matched viruses from a multi-clade panel of 208 strains. Using ID50 of 1:20 as a cut-off, the broadest plasma neutralized 42 (72%) of 58 viruses, while the pre-immune and week 8 plasma from the same animal did not neutralize any viruses. By sorting antigen-specific B-cells, multiple lineages of FP binding mAbs were isolated from this animal, with one lineage showing broad neutralization. Using 50 μg/ml as a cut-off, the best representative mAb 110D12 neutralized 57 (98%) out of the 58 FP-matched viruses. On a panel of 208 wildtype viruses, 110D12 neutralized 123 (59%) with geometric mean IC50 of 3.1 μg/ml, and 110 (53%) viruses with geometric mean IC80 of 10.6 μg/ml. Structural characterization of mAbs is currently in progress. However, not all animals developed similar cross-reactive neutralization. Additional work is ongoing to attempt to improve the consistency and potency of FP-directed neutralization.

Conclusions: In summary, FP-KLH prime and heterologous trimer boost elicited FP-directed broadly neutralizing antibodies in rhesus macaques.