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Induction of Antibodies with Long Variable Heavy Third Complementarity Determining Regions by Repetitive Boosting with AIDSVAX® B/E in RV144 Vaccinees

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Background: The Env $gp120_{AE.A244}$ used for boosting in the ALVAC/AIDSVAX® B/E RV144 trial expressed a dominant V2 linear epitope centered on lysine (K) at position 169, and a subdominant peptide-glycan epitope recognized by V1V2 broad neutralizing antibodies (bnAbs) CH01 and PG9 and the unmutated ancestor antibody (Ab) of CH01. V2-specific Abs isolated from RV144 vaccinees displayed tier-1 strain-specific neutralization (AE.92TH023) and bound K169-containing linear epitopes. The RV305 trial recruited 90 RV144 participants to return after 6 years for two boosts with either ALVAC + AIDSVAX® B/E or AIDSVAX® B/E alone to evaluate the effect of this boost on vaccine-induced immunity.

Methods: B-cell repertoires of 4 RV305 vaccinees with the greatest breadth of serum neutralization (A3R5 assay) were studied by antigen-specific memory B-cell sorting and recombinant Ab generation. Two vaccinees received ALVAC + AIDSVAX® B/E and two were boosted with AIDSVAX® B/E protein in alum. PCR-amplified monoclonal Abs (mAbs) were characterized in binding, neutralization, and ADCC assays.

Results: The boosts increased V_H mutation frequency from that seen following the initial RV144 vaccine regimen (RV305 mean 5.50%, 258 mAbs, 4 vaccinees; RV144 mean 2.60%, 105 mAbs, 12 vaccinees) and expanded a population of Abs with heavy third complementarity determining regions (HCDR3s) > 22 amino acids (RV305 30/258; RV144 1/105). Similar to V1V2 bnAbs- and other neutralizing Abs with long HCDR3s, these mAbs principally used D2/D3 and J_H6. Moreover, 35.2% of mAbs were sensitive to PNGase F native deglycosylation of Env $gp120_{AE.A244}$, including 9 mAbs with long HCDR3s. Four vaccine-induced N156QN160Q-sensitive V2 mAbs were isolated that are being characterized for neutralization capacity.

Conclusions: Repetitive boosting of RV144 vaccinees expanded a pool of Abs with many of the characteristics of V1V2 bnAbs. Expansion of this subdominant group of antibodies by vaccination may represent a step forward in the quest to induce bnAbs.