Structural basis of V2 apex recognition by rapidly developed broadly neutralizing HIV antibodies

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A major obstacle toward an effective antibody-based HIV-1 vaccine is the oftentimes long and complex maturation pathway required to develop potent broadly neutralizing antibodies (bNAbs). We recently published the design of a V2 apex germline-targeting HIV-1 envelope (Env), CAP256.OPT4, which elicited neutralization breadth in nonhuman primates (NHPs) when administered as a persistently replicating simian-human immunodeficiency virus (SHIV), with 90% of infected NHPs developing potent heterologous neutralization in serum by 16-28 weeks post-infection (Marchitto et al, Nature 2026). To determine the basis for rapid acquisition of breadth, we solved cryogenic electron microscopy (cryo-EM) structures of the most potent and broad V2 apex bNAbs elicited by SHIV-CAP256.OPT4 in complex with Env trimers.

The monoclonal bNAbs A19X008-1895 and A19X045-755 are members of distinct lineages isolated from two different NHPs at week 28 that each neutralized 81% of viruses on a heterologous 21-virus panel. Cryo-EM structures revealed A19X008-1895 to utilize an axe-like CDRH3 and A19X045-755 to utilize a needle-like CDRH3, both engaging the V2 apex C-strand epitope with similar binding modes to previously described human and NHP V2 apex bNAbs. A19X008-1895 shares high structural similarity with the NHP bNAb 41328-a.01 but achieves greater breadth and potency; structural analysis demonstrated A19X008-1895 and 41328-a.01 to exhibit different angles of engagement, with A19X008-1895 adopting an orientation that extensively interacts with N160 glycans while leaving only the CDRH3 to contact the C-strand. A19X045-755 shares high structural similarity with the NHP bNAb 44715-a.01 but achieves significantly greater breadth and potency; structural analysis demonstrated 44715-a.01 contacts two N160 glycans whereas A19X045-755 simultaneously contacts three, a feature common to human-derived needle-type bNAbs. Furthermore, the CDRH3 of A19X045-755 exhibits higher somatic hypermutation compared to previous SHIV-CAP256.OPT4-elicited needle-like lineages with markedly lower breadth, suggesting this to be a critical developmental feature. Overall, A19X008-1895 and A19X045-755 both displayed exceptional breadth and potency resulting from their extensive N160 glycan interactions, optimized C-strand-binding paratopes, and minimal engagement with the V2 loop. We demonstrate that CAP256.OPT4 can elicit distinct classes of V2 apex bNAbs and define the structural features compatible with the rapid development of breadth that should be rationally targeted by vaccination.