Characterization of the HIV-1 epitope recognized by antibody Ab3

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An ideal HIV-1 vaccine would elicit broadly neutralizing antibodies (bnAbs) that recognize conserved sites on the HIV-1 envelope (Env) glycoprotein of many variants to block viral entry. However, immunization can elicit antibodies that target non-neutralizing epitopes, presenting a major challenge for vaccine development. Understanding how antibody specificity can be redirected from non-neutralizing to neutralizing epitopes may provide new strategies for overcoming this challenge. We are investigating the structural mechanisms underlying this process using a novel Ig knock-in (KI) mouse expressing Ab3, a nonhuman primate antibody that targets a non-neutralizing epitope at the base of HIV-1 Env. Preliminary immunization studies demonstrate that sequential immunization with Env immunogens can “rescue” this off-target antibody response and redirect its specificity toward the neutralizing V3-glycan epitope.

To characterize the structural basis of this epitope switching, we are using cryogenic electron microscopy (cryo-EM) to determine and compare structures of Ab3 and rescued antibodies in complex with Env. As an initial step, we analyzed cryo-EM data of Ab3 bound to Env and identified the region of the Env base recognized by Ab3. Our analysis also revealed that Ab3 destabilized the trimeric Env and can associate with a single Env protomer, suggesting that Ab3 binding may influence the structure or stability of the Env trimer. We are currently working to obtain a higher-resolution structure and identify key residues at the Ab3–Env interface through targeted mutagenesis and binding studies. These experiments will provide insight into the molecular determinants of Ab3 recognition and establish a structural framework for understanding how antibody specificity can be redirected toward a neutralizing epitope. Ultimately, this work may reveal new strategies for overcoming off-target antibody responses and inform the design of immunogens capable of eliciting protective anti-HIV-1 bnAbs.