Modification of Antibody 10E8 To Improve HIV-1 Neutralization

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Background: Neutralization of HIV-1 by antibodies that target the membrane-proximal external region (MPER) of the gp41 subunit of the HIV-1 envelope glycoprotein has been shown to correlate with their capacity to recognize MPER in a membrane context. We sought to assess if modification of the broad and potent MPER-specific HIV-1 neutralizing antibody 10E8 could enhance its recognition of MPER in a membrane context and potentiate its neutralization of HIV-1.

Methodology: Antibody residue positions in the vicinity or co-planar with the gp41 contact interface, though not within it, were chosen for modification. Antibody variants were tested for HIV-1 neutralization and for MPER recognition in soluble and lipid contexts. Crystallization of the 10E8 variant with the greatest effect on virus neutralization was undertaken in complex with gp41 MPER to decipher its mechanism of action.

Results: Six residue positions within the 10E8 heavy chain were chosen for mutagenesis. Aromatic residues were introduced into these positions either individually or in combination. Up to 9-fold improvements in neutralization potency over wild-type 10E8 were observed against individual strains of a 5-isolate panel, and up to 4-fold mean improvements observed against all strains combined. Improvements in neutralization did not directly correlate with antibody recognition of MPER in a lipid context. The crystal structure of the most potent 10E8 variant was determined in complex with a peptide of gp41 MPER, though no additional contacts between the antibody and gp41 were observed.

Conclusions: We have defined residue modifications within the 10E8 heavy chain that improve antibody-mediated HIV-1 neutralization. Binding studies suggest improvements in neutralization were not associated with enhanced antibody recognition of MPER in a lipid context. The crystal structure of the most potent 10E8 variant in complex with gp41 MPER did not reveal additional contacts with the gp41 peptide, suggesting other mechanisms within the virion context are likely at play in the improved neutralization potency observed.