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**Structural Basis for Broad Neutralization by Anti-HIV-1 Antibody 447-52D.** R.L. Stanfield<sup>1</sup>, M.K. Gorny<sup>3</sup>, C. Williams<sup>3</sup>, S. Zolla-Pazner<sup>3</sup>, I.A. Wilson<sup>1,2</sup>, <sup>1</sup>Dept. of Molecular Biology and <sup>2</sup>Skaggs Inst. for Chemical Biology, The Scripps Research Inst., La Jolla, CA, USA, <sup>3</sup>New York VA Medical Center and New York Univ. School of Medicine, New York, NY, USA.

447-52D is an anti-HIV-1 monoclonal antibody isolated from a heterohybridoma derived from an HIV-1 infected individual. The antibody recognizes the third hypervariable (V3) loop of the viral envelope glycoprotein gp120. Most antibodies that target this hypervariable loop are viral type specific, neutralizing only a small number of highly related viral isolates. 447-52D is unique in that it can neutralize over 50% of the clade B viral isolates common to North America. To better understand how 447-52D differs from other, less effective anti-V3 antibodies, we determined the structure for the Fab-V3 peptide complex at 2.5Å resolution. Data were collected from a flash-cooled crystal at SSRL beamline 11-1 and the structure was determined by molecular replacement with final  $R_{\text{crist}}=24.9\%$  and  $R_{\text{free}}=28.5\%$ . The crystal structure reveals an unusual mode of binding for the V3 peptide to the antibody. The antibody contacts three highly conserved residues (GPxR) at the tip of the V3 loop, and forms additional hydrogen bonds with V3 main-chain atoms, resulting in a three-stranded, mixed  $\beta$ -sheet made from the antibody CDR H3 loop and the gp120 V3 loop. This binding mode allows for side-chain substitution at most positions in the V3 loop, thus allowing the antibody to recognize many different V3 sequences, as long as the GPxR epitope sequence is maintained.

