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**MD Reveals the Binding Conformation of HIV Protease With the MAC4A Binding Domain of GAG.** Philip D. Martin, Ladislau Kovari, Wayne State Univ., Biochemistry and Molecular Biology, Detroit, MI 48201.



There are three basic crystallographic conformations for HIV protease. A “closed” form (1MUI with Lopinavir, 1KJ4 with an octapeptide), an “open” form (wild type HIV protease, 3PHV), and a “wide open” form (multidrug resistant mutant MDR-769, 1TW7).

The N-terminus of AVC4A contains the wild type HIV binding peptide (SQNYPIV). If one tries to dock this natural substrate, the AVC4A substructure of the GAG protein, into the HIV protease active site, numerous disastrous collisions occur. None of the HIV protease crystal structures can bind this “native” format without major conformational changes.

These crystal structures were subjected to 5-ns of molecular dynamics (MD) with GROMACS. We found that all the structures opened up even further (the “fully open” form). We could then dock the AVC4A polypeptide into the active site of HIV protease with only minor VDW contacts. The RMS delta CA for the middle four substrate residues (NYPI) start out at only 0.4 Å relative to that found in the 1KJ4 structure. We will present the results of the MD simulations on the various HIV protease crystal structures and of the complex.

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