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Crystal Structures of Multi-Drug Resistant HIV-1 Protease Mutants Define a New Target For Protease Inhibitor Design. R.S. Yedidi, G. Proteasa, J.L. Martinez, J.F. Vickrey, P. Martin, L.C. Kovari, Dept. of Biochemistry and Molecular Biology, School of Medicine, Wayne State Univ., Detroit, MI.

Life cycle of HIV-1 reveals that the protease is critical for viral maturation and a very important target for designing inhibitors as a part of the highly active antiretroviral therapy (HAART). Accumulation of mutations causes the clinical failure of most protease inhibitors. The high resolution (1.3 Å) “wide open” structure of MDR769HIV-1 protease, recently solved by our group, has a set of mutations (L10I, M36V, M46L, I54V, I62V, L63P, A71V, V82A, I84V, L90M). Structural analysis indicated an expanded active site cavity and wide open flaps. We examined the impact of the drug resistance mutations at codon 82 and we report the MDR crystal structures of A82S, A82T and A82F at 1.85-2.25 Å resolution. All of these structures support the active site expansion hypothesis regarding the development of drug resistance. We are employing solvent mapping techniques to identify cavities for the design of small molecule inhibitors against the MDR HIV-1 protease. This work is supported by NIH grant AI 065294 to LCK.