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Crystallographic Studies of HTLV-1 Protease. Mi Li^{1,2}, Alla Gustchina¹, Gary Laco³, Jan Rozycki³, Jerry Alexandratos¹, Mariusz Jaskolski⁴, and Alexander Wlodawer¹, ¹MCL, NCI at Frederick, Frederick, MD USA; ²Basic Research Program, SAIC-Frederick, Frederick, MD USA; ³National Cancer Inst., Bethesda, MD, USA; ⁴Dept. of Crystallography, A. Mickiewicz University, Poznan, Poland.

The success of structure-assisted drug design targeting HIV-1 protease (PR) has changed the clinical outcome of AIDS and validated the approach of targeting retroviral enzymes for the purpose of designing and improving therapeutic agents. HTLV-1 is a retrovirus clinically associated with diseases such as adult T-cell leukemia. HTLV-1 encodes a 125-amino acid long protease that shares 24% identity with HIV-1 PR, and thus provides an appealing new drug target. We have solved the structure of a truncated version of HTLV-1 PR consisting of residues 1-116 in complex with a statine-based inhibitor extending from subsites P5 to P5'. Significant structural differences are found in several loop areas, which include the functionally important flaps, previously considered to be structurally highly conserved. Potential key residues responsible for the resistance of HTLV-1 PR to anti-HIV drugs are identified. The extensive interactions between the inhibitor and the enzyme provide sufficient data to describe the substrate binding sites and elucidate the specificity of HTLV-1 PR.