Drug Resistance Mutations Superimposed on the Structures of HIV-1 Protease and Reverse Transcriptase

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The 3-D structure of HIV-1 protease and reverse transcriptase and the mutable positions that confer drug resistance, as summarized by Mellors, et al., [1] are presented here in a companion piece to the Hammond et al. drug resistance table for 1997 (pages xx-xx, this volume) [2]. These figures are intended to provide a quick reference indicating the location of resistance mutations on the folded protein, and facilitate the comparison of different active compounds.

The figure depicting the protease protein was based on the structure found in the Protein Data Bank (PDB) database (http://molbio.info.nih.gov/cgi-bin/moldraw?1HVK) under accession number 1hvk. This crystal structure was originally determined by Hosur, et al., [3], and is based on an X-ray crystal structure of HIV-1 protease complexed with the inhibitor A76928 (S,S) at a resolution of 1.8 Å. A total of 26 mutations found to confer resistance to any of the compounds directed against protease as summarized by Mellors et al., [1], are indicated on the folded structure. Single mutations at positions 10, 20, 24, 32, 36, 46, 47, 48, 50, 54, 63, 71, 82, 84, 88, 90 conferred resistance to more than one drug. Only one monomer is labeled in the figure, as they are identical in the dimer. The active sites of HIV-1 protease are also indicated; in particular Asp 25, in a deep cleft formed in the protease dimer, is shown in red [4].

The figure depicting the HIV-1 reverse transcriptase (RT) protein was based on the structure found in PDB (http://molbio.info.nih.gov/cgi-bin/moldraw?1HNV) under accession number 1hnv. This crystal structure was originally determined by Ding et al., [5], and is based on an X-ray crystal structure of HIV-1 RT complexed with the inhibitor R 86183 at a resolution of 3.0 Å. A total of 35 mutations found to confer resistance to any of the compounds directed against RT [1] are indicated on the folded structure. Single mutations at positions 65, 70, 74, 75, 88, 89, 98, 100, 101, 103, 106, 108, 138, 179, 181, 184, 188, 190, 215, 219, 236, conferred resistance to more than one drug. Two subunits of HIV-1 RT are labeled in the figure, as they aren't identical in the dimer. The active sites of HIV-1 RT are also indicated; in particular Asp 110, Asp 186, and Asp 186, in a deep cleft formed in the p66 POL, are shown in red [6].

References

[1] Mellors, J.W., Schinazi, R.F.; Larder, B.A.; Mutations in Retroviral Genes Associated with Drug Resistance, in Myers, et al. Eds., *Human Retroviruses and AIDS 1996*, III-206, Los Alamos National Laboratory, Los Alamos, NM.

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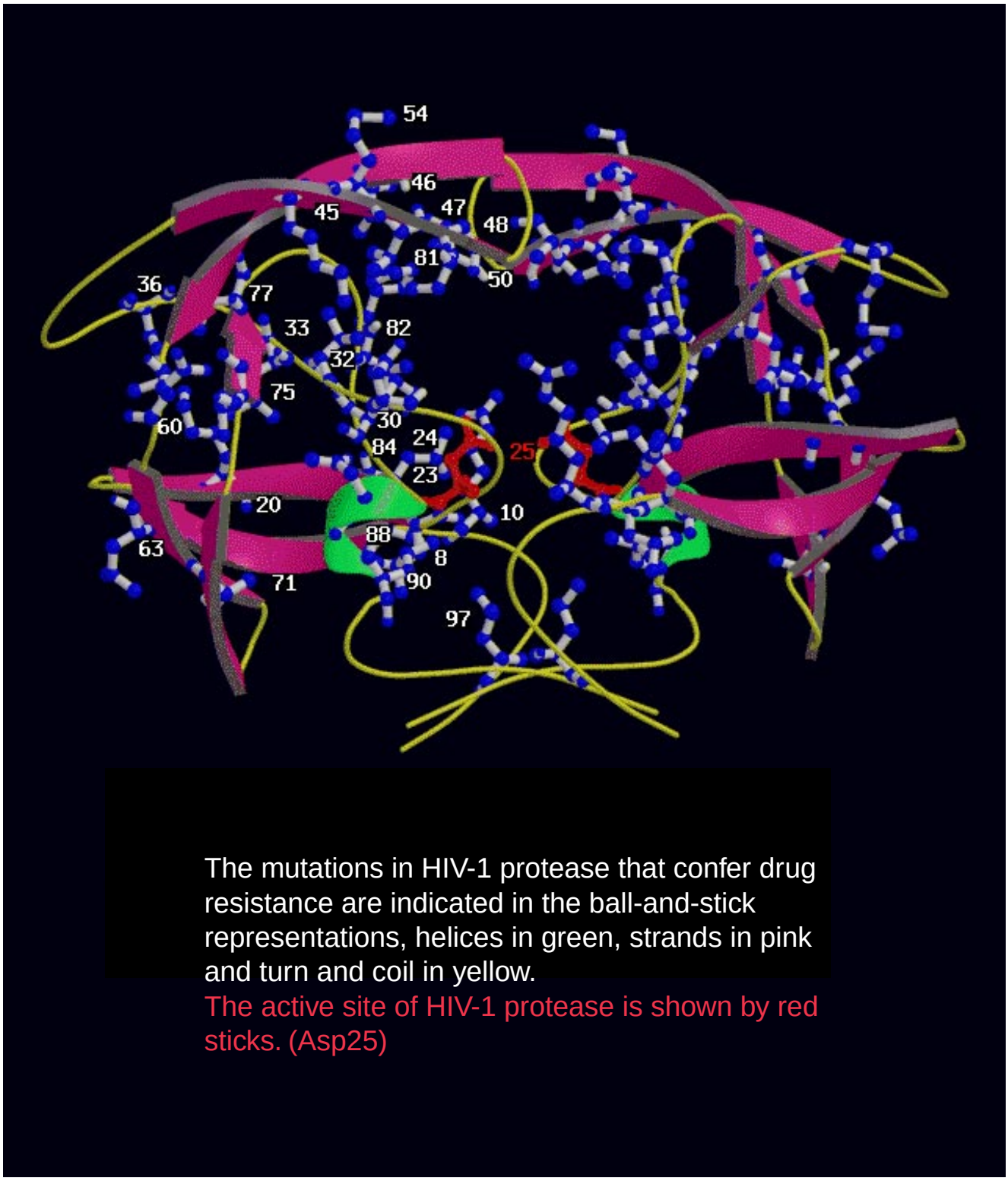
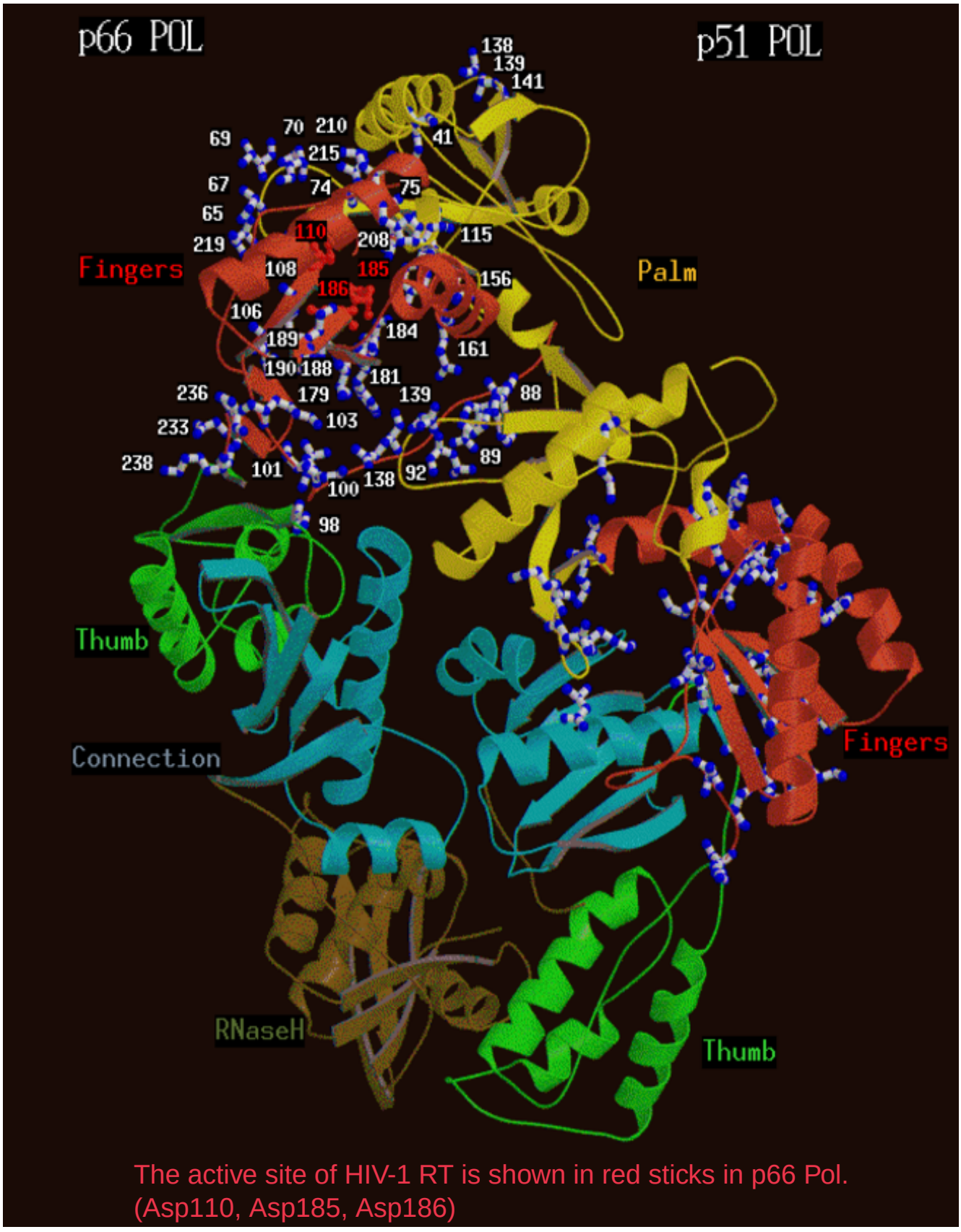


The mutations in HIV-1 protease that confer drug resistance are indicated in the ball-and-stick representations, helices in green, strands in pink and turn and coil in yellow.

The active site of HIV-1 protease is shown by red sticks. (Asp25)

Structure of Protease and RT



The active site of HIV-1 RT is shown in red sticks in p66 Pol. (Asp110, Asp185, Asp186)