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SELECTION FOR AND CHARACTERIZATION OF HIV-1 ISOLATES RESISTANT TO THE MATURATION INHIBITOR PA-457

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BACKGROUND: PA-457 is the first in a new class of antiretrovirals that inhibit HIV replication by disrupting virus maturation. PA-457 blocks a late step in *Gag* processing that results in defective core condensation and the release of non-infectious virus particles. Specifically, PA-457 disrupts the conversion of the capsid precursor, p25 (CA-SP1), to mature CA protein, p24. PA-457's mechanism of action (MOA) is distinct from that of protease inhibitors in that it appears to directly target the *Gag* precursor protein rather than the protease enzyme that is responsible for *Gag* processing.

METHODS: PA-457-resistant virus isolates were selected by continuous culture in the presence of increasing concentrations of compound. Genotyping of resistant virus and preparation of molecular clones with resistance-conferring mutations were carried out using standard methods. PA-457 resistance was characterized using cell-based activity assays and *in vitro* analysis of *Gag* processing.

RESULTS: *In vitro* selection generated PA-457-resistant virus. Genotypic analysis of these isolates revealed two independent patterns of resistance-conferring mutations. Consistent with our MOA studies these mutations mapped to residues flanking the *Gag* CA-SP1 cleavage site. An A to V change at either the first or third residues at the N-terminus of SP1 (A1V or A3V) resulted in a resistant phenotype. Both the A1V and A3V mutants exhibited reduced replicative fitness compared to WT, however, for the A3V virus a second point change in the C-terminus of capsid restored near-WT levels of replication. While these mutations resulted in a decrease in PA-457 activity, these viruses remained sensitive to all classes of approved HIV drugs.

CONCLUSIONS: These results support and extend previous observations that PA-457 is a specific inhibitor of CA-SP1 cleavage, with no activity against other *Gag* processing events. Characterizing the determinants of PA-457 activity is the first step in defining the molecular target for this novel HIV maturation inhibitor.

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