The first in class maturation inhibitor, PA-457, is a potent inhibitor of HIV drug-resistant isolates and acts synergistically with approved HIV drugs *in vitro*.

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Background: The product profile for new HIV therapies includes activity against drug resistant isolates and synergy with approved drugs. PA-457 represents a new class of anti-HIV compounds termed maturation inhibitors. Specifically, PA-457 blocks the cleavage of the capsid precursor (p25) to mature capsid protein (p24) resulting in the release of immature, non-infectious viral particles. Previously, we demonstrated that PA-457 is active against drug resistant HIV isolates and is synergistic when combined with approved HIV drugs. In this report, we extend the previous work to show PA-457 activity against additional drug resistant isolates (including multi-drug and fusion inhibitor resistant viruses) and characterize synergy with a more comprehensive panel of approved drugs.

Methods: We generated a panel of reverse transcriptase, protease, and fusion inhibitor-resistant HIV isolates (12, 5, and 10 isolates respectively). Inhibitory activity of PA-457 against this virus panel was determined using *in vitro* assays. Drug synergies were determined in assays employing PA-457 in combination with representatives of all approved classes of HIV inhibitors.

Results: PA-457 proved to be a potent *in vitro* inhibitor of drug resistant HIV-1 isolates. Against the panel of resistant viruses PA-457 retained wild-type activity while the approved drugs exhibited decreases in activity ranging from several fold to >100 fold. Synergy or additivity was observed with representatives of all classes of approved HIV drugs. At the 90% inhibitory concentrations, Combination Index (CI) values ranging from 1 (nearly additive) to 0.2 (strongly synergistic) were obtained.

Conclusion: PA-457 possesses the necessary product profile for a new anti-HIV therapy. PA-457 inhibits wild-type virus isolates with an IC_{50} comparable to currently approved drugs. Importantly, PA-457 is a potent inhibitor of drug resistant HIV strains, and exhibits synergy or additivity when combined with approved HIV drugs. These features, in addition to PA-457's potent *in vivo* activity (previously reported), suggest that this first in class maturation inhibitor can provide new options in HIV therapy.