In Vitro and *In Vivo* Disposition of PA-457, a Novel Inhibitor of HIV-1 Maturation

D. E. Martin[1,1], P. Smith[2], C. Wild[1], and G. Allaway[1]
[1]*Panacos Pharmaceuticals, Gaithersburg, MD and* [2]*School of Pharmacy, University of North Carolina at Chapel Hill, NC*

15th Annual International AIDs Conference, June 14, 2004, Bangkok Thailand

Background: PA-457 is the first in a new class of antiretrovirals called Maturation Inhibitors. PA-457 blocks a late step in HIV-1 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.

Methods: PA-457 was tested in a variety of in vitro test systems to characterize the metabolic profile of the compound. PA-457 was administered orally (PO) and intravenously (IV) to mice, rats, marmosets, and dogs to characterize its in vivo disposition. A single dose, double-blind, placebo-controlled, dose escalation study was conducted in normal, uninfected volunteers. PA103001-01 (salt form of PA-457) was administered as an oral solution to 4 groups (6 active:2 placebo) of healthy, male subjects. The doses studied were 25, 50, 100, and 250 mg.

Results: Studies with microsomes from mouse, rat, marmoset, dog, and human liver indicated that only liver microsomes from the rat caused significant metabolism. Inhibition of cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) was evaluated. The IC50 for inhibition for all isoforms was >100 µM except for CYP2C9 which was ~10 µM. Studies with human UGTs indicated that 1A3 was primarily responsible for glucuronidation of PA-457. PA-457 exhibited weak to moderate inhibition of 1A1, 1A3, 1A4, 1A8, 1A10, and 2B7. Following IV and PO administration the oral bioavailability was greatest in marmosets (~60%) and lowest in the dog (~10%). The half-life was longest in marmosets (~14 hrs). Administration of single oral doses of PA103001-01 to healthy volunteers was safe and well tolerated. Peak plasma concentrations occurred between 1.0 and 2.5 hours post-dose, were roughly proportional to dose and, at doses above 25mg, exceeded the 4 µM (2.5 µg/ml) target trough plasma concentration at 24 hours post dosing. The T1/2 averaged 57.9 to 79.9 hours.

Conclusions: PA-457 appears to undergo glucuronidation mediated primarily by 1A3. It does not inhibit the cytochrome P450 system but exhibits weak inhibition of glucuronidation by a subset of UGT isoforms. These data suggest that PA-457 will not exhibit significant drug-drug interactions when used in combination with other HIV drugs. PA-457 exhibits good oral bioavailability and a long half-life in rats and marmosets with moderate oral bioavailability in mice and dogs. Single, oral doses of PA103001-01 were safe and well tolerated in healthy volunteers. The long half-life suggests that therapeutic concentrations should be achievable with once daily dosing.