

## POSTER 27

### VIRAL RESISTANCE TO PA-457 (BEVIRIMAT), A NOVEL INHIBITOR OF HIV-1 MATURATION

Catherine S Adamson<sup>1</sup>, Kayoko Waki<sup>1</sup>, Sherimay Ablan<sup>1</sup>, Karl Salzwedel<sup>2</sup> and Eric O Freed<sup>1</sup>

<sup>1</sup>Virus-Cell Interaction Section, HIV Drug Resistance Program, National Cancer Institute, Frederick, MD;

<sup>2</sup>Panacos Pharmaceuticals, Gaithersburg, MD

**Background:** The maturation inhibitor PA-457 (bevrimat) potently inhibits HIV-1 replication by blocking Gag processing at the CA-SP1 cleavage site. We previously isolated a panel of six PA-457-resistant mutants *in vitro*. The mutations map to the CA/SP1 junction in CA or SP1 (CA-H226Y, L231M, L231F; SP1-A1V, A3V, A3T). Since PA-457 will likely be used clinically in PR-inhibitor (PI) experienced patients, we examined the impact of mutations that confer resistance to PIs on the evolution of PA-457 resistance.

**Methods:** We introduced all of our PA-457-resistance mutations into a molecular clone encoding a PI-resistant (PIR) PR and evaluated virus replication, Gag processing, and virus maturation both in the presence and absence of PA-457. *In vitro* selection experiments were performed in the presence of PA-457 using the PIR clone to examine acquisition of PA-457 resistance in the context of the mutant PR.

**Results:** Biochemical analysis demonstrated global defects in Gag processing in the presence of the PIR mutations independent of the sequence at the CA-SP1 junction or the presence of PA-457. As a likely consequence of the global processing defects, modest delays in virus replication were observed for the PIR clone in the context of WT Gag or fit PA-457-resistance mutations either in the presence or absence of PA-457. For replication-impaired PA-457-resistant Gag mutants, combination with the PIR PR abolished virus replication. PA-457 resistance in the PIR context took significantly longer to emerge than in the context of WT PR.

**Conclusions:** Understanding the evolution of resistance to PA-457 is highly significant as this compound is currently undergoing phase IIb clinical trials in HIV-1 infected patients. The nature of PA-457 resistance arising in the context of both WT and mutant PR elucidates the interplay between mutations in PR and the CA/SP1 cleavage site and may help to predict the types of mutations that are more likely to arise *in vivo*. The data presented in this study suggest that PIR mutants may be less likely than WT isolates to develop PA-457 resistance.