Peptide Prodrugs: An Approach to Enhance Oral Absorption of HIV Protease Inhibitor, Lopinavir
M. Patel, N. Mandava, A. K. Mitra
University of Missouri, Kansas City

**Purpose**
Lopinavir (LPV) is a protease inhibitors (PIs) indicated in HAART for the treatment of HIV infections. Inclusion of PIs in HAART has significantly ameliorated clinical outcomes in HIV infected patients. However, the major problem associated with PIs is poor bioavailability following oral administration. Presence of efflux proteins i.e. P-gp and MRPs on the intestinal epithelial cells has been the major factor resulting in poor oral absorption. Peptide prodrugs of LPV can be a viable strategy where, prodrugs can circumvent efflux process by becoming substrates of peptide transporters (influx transporters) expressed on intestinal cells.

**Methods**
Peptide prodrug (Val-ile-LPV) of LPV was investigated for its potential in evading efflux proteins. Interaction of Val-ile-LPV was performed in P-gp and MRP2 overexpressing cells (MDCK-MDR1, MDCK-MRP2). Oral absorption in rats was performed to investigate the effect of peptide prodrugs in improving oral LPV bioavailability.

**Results**
Val-ile-LPV exhibited greater solubility compared to LPV. Val-ile-LPV was stable at acidic pH and degraded rapidly at basic pH. Transmembrane permeability of Val-ile-LPV across MDCK-MDR1 and MDCK-MRP2 was significantly higher relative to LPV. Permeability in MDCK-MDR1 cells for Val-ile-LPV and LPV was $10 \times 10^{-6}$ and $2 \times 10^{-6}$ cm/s, respectively. Permeability in MDCK-MRP2 cells for Val-ile-LPV and LPV was $10.9 \times 10^{-6}$ and $2.7 \times 10^{-6}$ cm/s, respectively. [3H]-Gly-Sar uptake was significantly reduced in presence of Val-ile-LPV suggesting that Val-ile-LPV was recognized by peptide transporter. Val-ile-LPV demonstrated higher plasma profiles in Male Sprague Dawley rats compared to LPV. AUC for Val-ile-LPV and LPV was 1440 and 170 umol*min/L, respectively. Cmax for Val-ile-LPV and LPV was 16.2 and 1.2 umol/L, respectively. Tmax for Val-ile-LPV and LPV was 45 and 35 min, respectively.

**Conclusion**
Results from this study clearly indicated that peptide prodrugs of LPV can overcome P-gp and MRP2-mediated efflux. Transporter-targeted peptide prodrug derivatization seems to be a viable strategy for improving oral LPV bioavailability.