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## NEXT GENERATION HIV PEPTIDE FUSION INHIBITOR CANDIDATES ACHIEVE POTENT, DURABLE SUPPRESSION OF VIRUS REPLICATION *IN VITRO* AND IMPROVED PHARMACOKINETIC PROPERTIES

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**BACKGROUND:** Enfuvirtide (ENF, Fuzeon™), the first approved entry inhibitor for HIV and an important therapeutic for treatment-experienced patients, is administered as a subcutaneous injection twice a day. The goal for the next-generation fusion inhibitor candidate is to maintain or improve upon the efficacy demonstrated by ENF while decreasing injection frequency. We have identified 2 candidates that demonstrate substantial improvements in potency, durability, and pharmacokinetics. These peptide candidates are being evaluated with sustained-release formulations targeting once/week administration.

**METHODS:** Candidate potency has been evaluated in a cMAGI assay against a range of laboratory and clinical isolates, having varying degrees of sensitivity to ENF. Durability of the peptides has been evaluated in *in vitro* passaging experiments. Intravenous and subcutaneous pharmacokinetic parameters have been obtained in cynomolgus monkeys.

**RESULTS:** TR-290999 and TR-291144 are peptides derived from a gp41 HR2 region partially overlapping the ENF sequence. Both peptides have been modified using independent strategies to optimize potency, durability, and pharmacokinetic properties. TR-291144 displays potent antiviral activity against a panel of 12 clinical isolates, with a 7-nM geometric mean IC<sub>50</sub>, equivalent to the performance of ENF. TR-290999 displays a 7-fold improvement over Fuzeon against this panel, with a geometric mean IC<sub>50</sub> of 1 nM. Both compounds have potent activity against an isolate panel resistant to Fuzeon, T-1249, and other peptide fusion inhibitors. Passaging experiments demonstrate superior *in vitro* durability of these compounds compared to other peptide fusion inhibitors. Cynomolgus monkey intravenous clearance values for TR-290999 and TR-291144 are 4 and 9

mL/Kg/hr, respectively, equal to 10- and 4-fold improvements over ENF. Subcutaneous bioavailability values for TR-290999 and TR-291144 are 100% and 87%, respectively.

**CONCLUSIONS:** TR-290999 and TR-291144 demonstrate: potent *in vitro* antiviral activity; durable *in vitro* control of virus replication; and slow, extended clearance properties in monkeys. The combination of potency, durability, and pharmacokinetic and appropriate physical properties enables the evaluation of sustained-release formulations to provide once/week dosing. Further study of these novel, next-generation fusion inhibitors is in progress.

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