873140 Exhibits Potent Antiviral Activity Against A Broad Panel of HIV-1 Envelopes From Treatment Naive and Experienced Subjects

Introduction

873140 is a novel α4β7 integrin antagonist that demonstrates high potency and selectivity in vitro (Ref 1) and in vivo (Ref 2). Previous in vitro studies using PBMC infected with a limited panel of HIV clinical isolates showed broad-spectrum antiviral activity for 873140 (Ref 3). The current study assessed the antiviral activity of 873140 when tested against a broad panel of HIV-1 isolates from clinical samples.

Methods

- **Susceptibility** (IC50 (nM) of each HIV isolate) was determined using the ViroLogic PhenoSense HIV Entry assay. 
  - A new assay was used as an engineered cell line that expresses CCR5 and only CCR5.
  - Samples were from treatment experienced (still on the failing regimen at sample collection) and naive subjects (Table 1).
  - Used Analysis of Variance (ANOVA) and linear regression methods to describe IC50 to 873140 in terms of baseline characteristics (p<0.0002 with IC50 data).

Results

- Median IC50 for R5-tropic (n=296) is 8.81 nM (range: 0.89-33.19).
- The CCR5-using components of R54-tropic (n=44) samples were sensitive with a median IC50 of 3.61 nM (1.07-14.2).
- 85% of all samples had IC50 values <15.6 nM.
- Samples from treatment experienced subjects were more susceptible to 873140 than naive patients (p=0.0042), with median IC50s of 3.83 nM (6.61-37.33) vs 8.71 nM (0.84-33.19), respectively.

In the following figures, the box represents the 25th to 75th percentile, middle line of box is median. "+" means extended line represents minimum and maximum values.

**Figure 1. Distribution of IC50 (nM) by Tropism**

**Figure 2. Distribution of IC50 (nM) by ART Experience**

**Discussion**

- 873140 is active against R5-tropic envelopes derived from both naïve and experienced patients representing a range of CD4 count and plasma HIV-1 RNA levels.
  - The IC50 range is higher than previously observed using a PBMC assay system.
  - May relate to differences in CCR5 expression and/or the assay system (pseudotype vs replication-competent virus).
  - Previous studies have shown that 873140 is also active against HIV resistant to enfuvirtide (Ref 3).

- The mean is lower IC50 values with envelopes from experienced patients that naïve envelopes are unknown.

- R54-tropic samples have lower IC50 values than R5-tropic.
- These samples:
  - May contain a mixture of R5-, dual- and/or X4-tropic viruses.
  - May be sensitive to CCR5 antagonists in vitro when tested in PBMC that express both CCR5 and CXCR4.
  - Are sensitive to CCR5 antagonists in assays using cells that only express CCR5.

- The lower IC50 values may be due to the relative tropism mixture in the R54 samples or to decreased efficiency of entry for R54-tropic envelopes.

- Previous clinical analysis showed dual-tropic envelopes were more sensitive to 873140 than are R5-tropic Env (Ref 4).
- Tropon, treatment history, and CD4 count were associated with IC50 values.
- The CD4 count effect was more pronounced with R54-tropic samples.

**Conclusion**

- 873140 is active against a broad array of HIV-1 envelopes from both naïve and experienced subjects from geographic regions representing different HIV-1 clades.
- The CCR5-using components of R54-tropic envelopes were susceptible in this assay using a CCR4+ cell line that only expresses CCR5.
- Plasma concentrations of 873140 achieved in clinical studies exceed by 3-5 fold the IC50 for most HIV-1 envelopes.

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**References**