

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

James Demarest¹, Tab Bonny¹, Cindy Vavro¹, Celia LaBranche¹, Kathryn Kitrinis¹, Charlene McDanal¹, Sara Sparks¹, Jeannette Whitcomb², Wei Huang², Chris Petropoulos², Stephen Piscitelli¹

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¹GlaxoSmithKline, Research Triangle Park, NC, United States of America; ²ViroLogic, San Francisco, CA, United States of America

Introduction

873140 is a novel spirodiketopiperazine CCR5 antagonist that demonstrates *in vivo* anti-HIV activity (mean 1.66 log₁₀ decrease at nadir) following 10 days of monotherapy (Ref 1). Previous *in vitro* studies using PBMC infected with a limited panel of HIV clinical isolates showed low/sub-nanomolar anti-HIV activity for 873140 (Ref 2). The current study assessed the anti-HIV activity of 873140 when tested against a broad panel of HIV-1 envelopes from clinical samples.

Methods

- **Susceptibility (IC₅₀ (nM)) of HIV envelopes in plasma (N=402) to 873140 was evaluated by the ViroLogic PhenoSense HIV Entry assay**
 - This assay uses an engineered cell line that expresses CD4 and only CCR5
- **Samples were from treatment experienced (still on the failing regimen at sample collection) and naïve subjects (Table 1)**
- **Used Analysis of Variance (ANOVA) and linear regression methods to describe IC₅₀ to 873140 in terms of baseline characteristics (n=402 with IC₅₀ data)**
 - IC₅₀ values were log₁₀ transformed in this analysis
 - Initial predictors were examined alone to screen variables to use in model selection

Table 1. Patient Demographics

	Median values (% or range)		
	Exp	Naïve	Total
Log₁₀ HIV-1 RNA PCR (copies/mL)	N=113 4.08 (2.70, 5.88)	N=299 4.69 (1.90, 5.88)	N=412 4.50 (1.90, 5.88)
Tropism	N=113	N=299	N=412
R5/X4	37 (33%)	36 (12%)	73 (18%)
R5	76 (67%)	263 (88%)	339 (82%)
CD4+ Count (cells/mm³)	N=110 308 (55, 1489)	N=290 308 (24, 1465)	N=400 308 (24, 1489)
CD8+ Count (cells/mm³)	N=106 1022 (316, 4331)	N=277 849 (202, 3360)	N=383 893 (202, 4331)
CD4/CD8 Ratio	N=106 .301 (.037, 2.15)	N=277 .341 (.044, 2.04)	N=383 .333 (.037, 2.15)
Age (yr)	N=111 39 (24, 78)	N=299 36 (20, 74)	N=410 37 (20, 78)
Race	N=111	N=299	N=410
White	80 (72%)	175 (59%)	255 (62%)
Black	22 (20%)	73 (24%)	95 (23%)
Other	9 (8%)	51 (17%)	60 (15%)
Sex	N=111	N=299	N=410
Female	25 (23%)	57 (19%)	82 (20%)
Male	86 (77%)	242 (81%)	328 (80%)
Geographic	N=111	N=299	N=410
EU	63 (57%)	0	63 (16%)
Latin America	0	26 (9%)	26 (6%)
US / Canada	48 (43%)	273 (91%)	321 (78%)
CDC Class	N=111	N=299	N=410
A, B	76 (68%)	285 (95%)	361 (88%)
C	35 (32%)	14 (5%)	49 (12%)

Results

- Median IC₅₀ for R5-tropic (n=338) samples was 6.81 nM (range: 0.89-33.19).
- The CCR5-using components of R5X4-tropic (n=64) samples were susceptible with a median IC₅₀ of 3.61 nM (0.67-14.72).
- 95% of all samples had IC₅₀ values < 16.5 nM.
- Samples from treatment experienced subjects were more susceptible to 873140 than naïve (p<0.0001), with median IC₅₀s of 5.83 nM (0.67-17.53) vs 6.71 nM (0.84-33.19), respectively.
- In the following figures, the box represents the 25th to 75th percentile, middle line of box is median, "+" is mean, extended line represents minimum and maximum values.

Figure 1. Distribution of IC₅₀ (nM) by Tropism

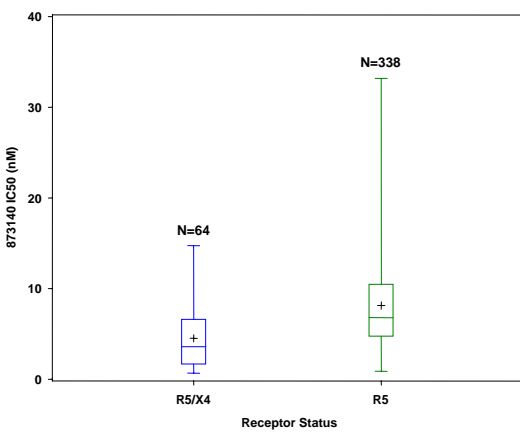


Figure 2. Distribution of IC₅₀ (nM) by ART Experience

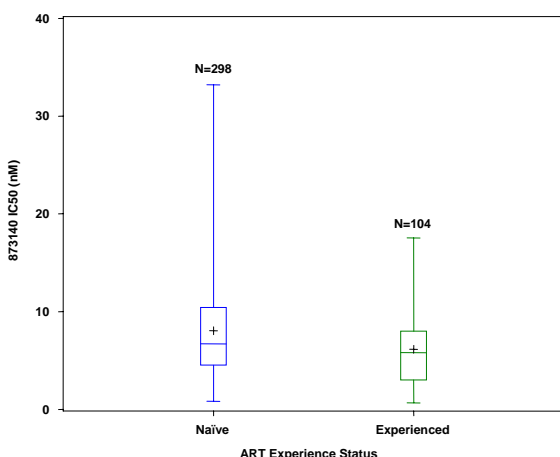
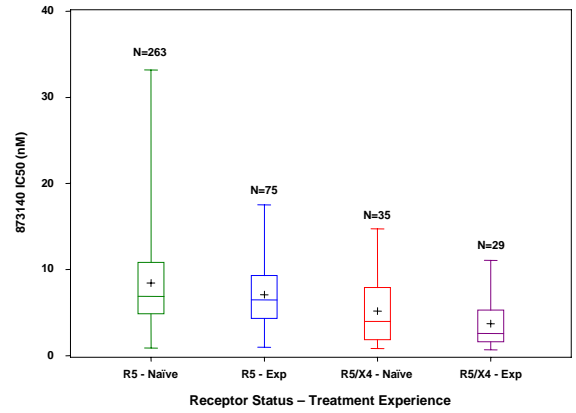


Figure 3. Distribution of IC₅₀ (nM) by Tropism and ART Experience



One Way ANOVA Results for Dependent Variables

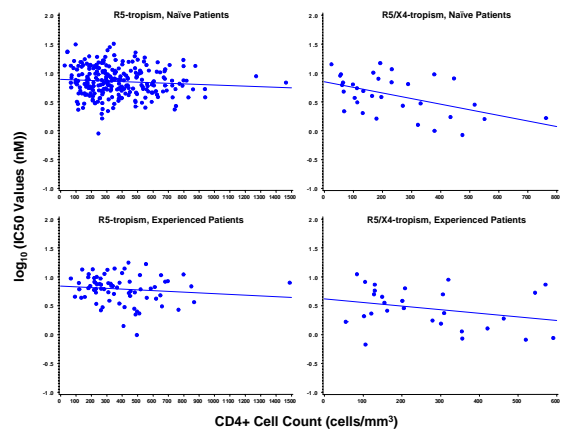
- **Plasma HIV-1 RNA PCR** (p=0.0407)
- **Tropism (R5 only vs R5/X4)** (p<0.0001)
- **CD4+ Cell Count**
- **CD8+ Cell Count**
- **CD4/CD8 ratio**
- **Age, ethnic origin (white vs other), gender**
- **Geographic region (EU vs NA + Latin Am)**
 - No naïve patient samples were from EU
- **CDC Category (C versus others)**
- **Prior antiretroviral treatment (naïve vs exp)** (p=0.0001)

P<0.05 in univariate models

Multiple Regression Analysis for Independent Variables

- Dependent variables were entered into a multiple regression selection procedure to identify independently significant predictors of IC₅₀ values. In this case, the final model contained the following terms:
 - Tropism (p<0.0001)
 - ART Naïve (p=0.0104)
 - CD4+ Cell Count (p=0.0065)
 - Plasma HIV-1 RNA fell out of significance in this analysis

Figure 4. Distribution of IC₅₀ (nM) by CD4 Count



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 reason(s) for lower IC₅₀ values with envelopes from experienced patients than naïves are unknown
- **R5X4-tropic samples have lower IC₅₀ values than R5-tropic**

These samples:

 - may contain a mixture of R5-, dual-, and/or X4-tropic viruses
 - may not 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 R5X4 samples or to decreased efficiency of entry for R5X4-tropic envelopes
 - Previous clonal analysis showed dual-tropic envelopes were more sensitive to 873140 than are R5-tropic Envs (Ref 4)
- **Tropism, treatment history, and CD4 count were associated with IC₅₀ values**
 - The CD4 count effect was more pronounced with R5X4-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 R5X4-tropic envelopes were susceptible in this assay using a CD4+ cell line that only expresses CCR5
- Plasma concentrations of 873140 achieved in clinical studies exceed by several fold the IC₅₀ values of viruses in clinical plasma samples, suggesting that 873140 should provide antiviral activity in HIV-1 infected individuals

References

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