



**Presentations at the 48th Interscience Conference on
Antimicrobial Agents and Chemotherapy (ICAAC) /
46th Annual Infectious Disease Society of America
(IDSA) Joint Meeting**



Washington DC
October 25-28, 2008

Executive Summary

Monogram Biosciences and its collaborators presented the following 8 abstracts at the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) / 46th Annual Infectious Disease Society of America (IDSA) joint meeting in Washington DC:

- **Validation of an Enhanced Sensitivity Trofile™ HIV-1 Co-receptor Tropism Assay**
- **Response to Vicriviroc (VCV) in HIV-Infected Treatment-Experienced Subjects using an Enhanced Trofile HIV Co-receptor Tropism Assay: Reanalysis of ACTG 5211 Results**
- **Performance Characteristics and Validation of the PhenoSense® HIV Integrase Assay**
- **Weighted OBT Susceptibility Score (wOBTSS) is a Stronger Predictor of Virological Response at 48 Weeks than BL Tropism Result in MOTIVATE-1 and 2**
- **Reanalysis of the MERIT Study with the Enhanced Trofile Assay**
- **Clonal Analysis of HIV-1 Co-receptor Tropism Change Following Treatment with PRO 140, a CCR5 Monoclonal Antibody**
- **HIV Drug Resistance Profiles and Clinical Outcomes in Patients with Viremia Maintained at Very Low Levels**
- **Analysis of Resistance to the HIV-1 Integrase Inhibitor Raltegravir: Results from the Benchmrk 1 and 2**

Abstract Number: H-1219

Validation of an Enhanced Sensitivity Trofile™ HIV-1 Co-receptor Tropism Assay

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Background: Trofile is a clinically validated HIV-1 co-receptor tropism assay for selecting patients for therapy with entry inhibitors targeting CCR5. Trofile determines whether a patient virus population is CCR5 (R5), CXCR4 (X4) or dual (R5/X4)/mixed (D/M)-tropic and has demonstrated utility in clinical trials of CCR5 antagonists including maraviroc. Detection of CXCR4-using virus below the current sensitivity limit may further optimize patient selection. We therefore developed an enhanced sensitivity assay (Trofile (ES)) with improved ability to detect low levels of CXCR4-using virus.

Methods: Trofile (ES) was validated for patient management applications in compliance with CAP and CLIA regulations. Tropism of viral isolate and patient-derived HIV-1 envelopes (Envs) was evaluated to assess assay accuracy, precision and reproducibility. Sensitivity was determined using mixtures of patient-derived R5 and X4 *env* clones.

Results: Trofile enhancements increased detection sensitivity for X4 Envs by an average of 30-fold. X4 clones present at 0.3% were detected in 100% of assays. The lower limit of X4 detection was *env* clone pair (patient) dependent and ranged from 0.003-0.3%. Trofile (ES) accurately determined the tropism of 46 patient samples and isolates representing multiple subtypes including 14/18 with X4 variants below the detection limit of standard Trofile based on clonal analyses. Intra-assay precision (100%) and inter-assay reproducibility (99%) were demonstrated by concordant results for 135/135 and 228/230 pair-wise comparisons of R5, X4 and DM Envs and repeat testing of 46 patient *Env* populations, respectively.

Conclusions: Trofile (ES) has improved sensitivity to detect CXCR4-use in *env* clone mixtures and patient *env* populations compared to standard Trofile, while assay accuracy, precision and reproducibility are maintained. This increases the utility of Trofile for selecting patients for CCR5 antagonist therapy.

Session Number: 108

Session Title: *Antiretroviral Resistance and HIV Diagnostics*

Session Type: Poster Session

Session Start/End Time: Sunday, Oct 26, 2008, 11:15 AM -12:15 PM

Location: Hall C

Abstract Number: H-895

Response to Vicriviroc (VCV) in HIV-Infected Treatment-Experienced Subjects using an Enhanced Trofile HIV Co-receptor Tropism Assay: Reanalysis of ACTG 5211 Results

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Background: VCV demonstrated potent virologic suppression in treatment-experienced patients with R5 virus at study screen by the standard Trofile assay (Monogram Biosciences, San Francisco). An enhanced sensitivity Trofile assay [Trofile (ES)], with improved ability to detect CXCR4-using minor variants, could optimize selection of patients who may benefit from CCR5 antagonists.

Methods: We used Trofile (ES) to determine co-receptor usage at study screen and entry for the 118 subjects (90 and 28 randomized to receive VCV and Placebo, respectively; all had R5 virus by the standard assay at study screen) in ACTG 5211. We examined virologic and immunologic responses according to tropism results by Trofile (ES).

Results: Using Trofile (ES), 89 and 25 subjects were found to have R5 and dual/mixed (DM) virus, respectively, at screening; samples from 4 subjects were not available. Amongst VCV recipients, greater reductions in log₁₀ HIV-1 RNA were observed in 64 subjects with R5 virus at both screening and entry (group 1), compared to 5 subjects with R5 virus at screening but DM virus at study entry (group 2), and 15 subjects with DM virus at screening (group 3): at day 14, -1.15 vs. -0.66 vs. -0.09 and at week 24, -1.95 vs. -1.20 vs. -0.57 (P>0.05 comparing groups 1 and 2, 2 and 3; P<0.001 comparing groups 1 and 3 for both endpoints).

Conclusions: Reanalysis of key study endpoints demonstrated that Trofile (ES) had improved ability to predict antiretroviral response to VCV, indicating that Trofile (ES) may be a better screening tool for determining patient eligibility for CCR5 antagonist therapy.

Session Number: 80

Session Title: Antiretroviral Therapy

Session Type: Slide Session

Session Start/End Time: Sunday, Oct 26, 2008, 8:30 AM -11:00 AM

Location: Independence A (Grand Hyatt)

Abstract Number: H-1214

Performance Characteristics and Validation of the PhenoSense® HIV Integrase Assay

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Background: The PhenoSense HIV Integrase Assay is a rapid, recombinant virus assay capable of measuring the susceptibility of HIV-1 integrase inhibitors (INIs), such as Raltegravir (RAL) and Elvitegravir, and integrase (IN) associated changes in replication capacity (RC). Here we report on the technical validation of this assay in compliance with CAP (College of American Pathologists) and CLIA (Clinical Laboratories Improvement Act) regulations.

Methods: The PhenoSense PR-RT assay was modified to capture patient-derived C-terminal RT and IN *pol* gene sequences. IN RC is expressed as a percentage of viral infectivity (luciferase production) relative to a reference virus. Assay accuracy, precision, reproducibility, linearity, amplification sensitivity and specificity were assessed by testing RAL susceptibility of site-directed mutant (SDM) viruses, well-characterized laboratory strains, and patient plasma-derived viruses.

Results: RAL IC₅₀ fold change (FC) measures were consistent with published data for all SDMs. 100% of pair-wise FC comparisons were within 2-fold for precision, reproducibility and linearity experiments. For IN RC, 94%, 97% and 98% of pair-wise comparisons were within +/-0.25 log₁₀ for precision, reproducibility and linearity, respectively. Amplification sensitivity was successful for 95% of samples with viral loads above 500 copies/mL. The biological cutoff for RAL FC was determined to be 1.5 using 630 INI-naïve patient samples. In RAL treatment failure samples, reduced susceptibility (FC > 1.5) was detected in > 90% of samples with mixtures at positions known to confer resistance.

Conclusions: PhenoSense HIV Integrase is an accurate, precise, reproducible assay for assessing INI susceptibility and changes in RC associated with INI resistance. This assay is performed in the Monogram Clinical Reference Laboratory on samples with viral loads ≥500 copies/mL. The results may provide clinicians with a tool to aid in the selection and monitoring of potent antiretroviral combination therapy.

Session Number: 108

Session Title: *Antiretroviral Resistance and HIV Diagnostics*

Session Type: Poster Session

Session Start/End Time: Sunday, Oct 26, 2008, 11:15 AM -12:15 PM

Location: Hall C

Abstract Number: H-1221

Weighted OBT Susceptibility Score (wOBTSS) is a Stronger Predictor of Virological Response at 48 Weeks than BL Tropism Result in MOTIVATE-1 and 2

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Background: The objective of this post-hoc analysis was to understand the relative importance of different baseline (BL) variables in predicting week 48 virological response (VR, viral load <50 c/ml) in the Phase 3 MOTIVATE studies of maraviroc (MVC) + OBT in treatment experienced patients with R5 virus at screening.

Methods: Logistic regression analyses were performed on the 'Intent-To-Treat' population in the pooled MOTIVATE studies (N=1049). Since the objective was to ascertain predictors of virologic response we excluded patients (n=145) classified as non-virological failures (non-VF). The wOBTSS was calculated using phenotype for reverse transcriptase (RTI) and protease inhibitors (PI) and genotype for enfuvirtide (ENF). Any drug in continued use pre- and post-randomisation was scored as 0; active NRTIs as 0.5 and active NNRTI, PI or ENF as 1. BL variables included: CD4 (<50 vs. 50-100, 101-200, >200), VL (³100,000 vs. <100,000), tropism result at BL (R5 vs. D/M), treatment (MVC BID+QD vs. placebo) and wOBTSS (0 vs. 1, 2, ³3).

Results: The wOBTSS resulted in a better VR predictor and better fitting model than simply counting drugs reported as active by resistance testing in models that excluded non-VF patients. In these models a wOBTSS of 2 or ³3 was associated with an OR >8 for VR. A VL <100,000 c/ml or an R5 tropism result were significant predictors of VR, each with OR≈2. CD4 categories ³50 progressively increased the odds of VR. Of the 110 patients receiving MVC BID who had a wOBTSS ³2, 75% had a VR at 48 wks, compared to 47% on OBT alone. If BL CD4 was also ³50, 82% and 50% of patients achieved a VR in the MVC and placebo arms respectively.

Conclusion: The strongest predictors of VR were active drug availability and CD4. Earlier (CD4 ³ 50) initiation of therapy combining 2 or more potent active drugs (wOBTSS) with MVC was associated with a >80% VR rate at 48 wks.

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Session Title: *Antiretroviral Resistance and HIV Diagnostics*

Session Type: Poster Session

Session Start/End Time: Sunday, Oct 26, 2008, 11:15 AM -12:15 PM

Location: Hall C

Updated abstracts for the following posters / presentation will be available at the meeting:

Abstract Number: H-1232a

Reanalysis of the MERIT Study with the Enhanced Trofile Assay

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Session Number: 108

Session Title: *Antiretroviral Resistance and HIV Diagnostics*

Session Type: Poster Session

Session Start/End Time: Sunday, Oct 26, 2008, 11:15 AM -12:15 PM

Location: Hall C

Abstract Number: H-1218

Clonal Analysis of HIV-1 Co-receptor Tropism Change Following Treatment with PRO 140, a CCR5 Monoclonal Antibody

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Session Number: 108

Session Title: *Antiretroviral Resistance and HIV Diagnostics*

Session Type: Poster Session

Session Start/End Time: Sunday, Oct 26, 2008, 11:15 AM -12:15 PM

Location: Hall C

Abstract Number: H-1231

HIV Drug Resistance Profiles and Clinical Outcomes in Patients with Viremia Maintained at Very Low Levels

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Session Number: 108

Session Title: *Antiretroviral Resistance and HIV Diagnostics*

Session Type: Poster Session

Session Start/End Time: Sunday, Oct 26, 2008, 11:15 AM -12:15 PM

Location: Hall C

Abstract Number: H-898

Analysis of Resistance to the HIV-1 Integrase Inhibitor Raltegravir: Results from the Benchmrk 1 and 2

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Session Number: 80

Session Title: *Antiretroviral Therapy*

Session Type: Slide Session

Session Start/End Time: Sunday, Oct 26, 2008, 8:30 AM -11:00 AM

Location: Independence A (Grand Hyatt)