Chemokine Receptors and Antagonists: Summary of Clinical Experience

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HIV Entry Inhibitors

Adapted from Moore JP, PNAS 2003;100:10598-10602.
• **Challenges** of developing R5 inhibitors in antiretroviral HIV-infected patients
  Deeks, Lancet 2006;367:711

• Oral CCR5 inhibitors: *will they make it through?*
  Biswas, Expert Opin Investig Drugs 2006;15:451

• **Serious doubts** on safety and efficacy of CCR5 antagonists: CCR5 antagonists teeter on a knife-edge
  Horster + Goebel, Infection 2006;34:110
CCR5 Issues in Development

- Entry tropism: determination and pathogenesis
- Co-receptor tropism changes
- Immunologic consequences (compound- vs. class-specific)
  - Malignancies
- Toxicities (compound- vs. class-specific)
  - QT prolongation
  - Hepatitis
- Antiretroviral activity: Rx-naïve and rx-experienced patients
- Resistance
- Long-term follow-up
Syncytium formation in MT-2 cells expressing CXCR4 only

Entry Tropism Assay

Transfection

pHIVlucΔU3 DNA

pHIVenv DNA

+ 

Infection

virus entry inhibitors added

CD4 + CCR5 + CXCR4 +

Courtesy of Monogram Biosciences
## Entry Tropism Assay Performance

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Current Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turnaround Time</td>
<td>14-18 days</td>
</tr>
<tr>
<td>Unscreenable Failure Rate</td>
<td>3-7%</td>
</tr>
<tr>
<td>Minimum HIV RNA</td>
<td>1000 copies/ml</td>
</tr>
<tr>
<td>(may amplify at lower levels)</td>
<td></td>
</tr>
<tr>
<td>Assay Sensitivity to Minor Populations (X4 or D/M)</td>
<td>100% at 10% mixture</td>
</tr>
<tr>
<td></td>
<td>83% at 5% mixture</td>
</tr>
</tbody>
</table>

*Courtesy of Monogram Biosciences*
# Chemokine Receptor Tropism

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>N</th>
<th>R5-only</th>
<th>D/M</th>
<th>X4-only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demarest(^1)</td>
<td>naïve</td>
<td>325</td>
<td>88%</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Homer Cohort(^2)</td>
<td>naïve</td>
<td>979</td>
<td>82%</td>
<td>18%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Moyle(^3)</td>
<td>naïve</td>
<td>402</td>
<td>81%</td>
<td>19%</td>
<td>n/a</td>
</tr>
<tr>
<td>Moyle(^3)</td>
<td>experienced</td>
<td>161</td>
<td>78%</td>
<td>22%</td>
<td>n/a</td>
</tr>
<tr>
<td>Demarest(^1)</td>
<td>experienced</td>
<td>117</td>
<td>67%</td>
<td>28%</td>
<td>5%</td>
</tr>
<tr>
<td>TORO(^4)</td>
<td>heavily experienced</td>
<td>627</td>
<td>50%</td>
<td>48%</td>
<td>2%</td>
</tr>
<tr>
<td>ACTG 5211(^5)</td>
<td>heavily experienced</td>
<td>391</td>
<td>49%</td>
<td>47%</td>
<td>4%</td>
</tr>
</tbody>
</table>

\(^1\)Demarest ICAAC 2004, #H-1136; \(^2\)Brumme JID 2005; \(^3\)Moyle JID 2005; 
\(^4\)Melby EI Workshop 2005; \(^5\)Wilkin CROI 2006, #655
Initial Questions

• Significance of dual/mixed tropism and minor viral variants?

• Co-receptor switching (and consequences)?

• Immunologic consequences of CCR5 inhibition?
Effect of SI Virus on CD4+ Cell Count: Amsterdam Cohort Study (N=188)

Koot et al Ann Intern Med 1993
Natural History of Chemokine Tropism

R5 infection  R5+X4 infection

Absolute Viral Load

weeks  years

Time

R5  X4

detection limit

Courtesy of John Moore, PhD
5%-14% of European Caucasians carry CCR5Δ32
1% are homozygotes
CCR5 Deletion Implications (1)

• Rheumatoid arthritis
  – CCR5Δ32 associated with less joint inflammation and morning stiffness
    Garred, J Rheumatol 1998

• Asthma
  – CCR5Δ32 less common in patients with asthma
    Hall, Lancet 1999
  – CCR5Δ32 not associated with asthma
    Mitchell, Lancet 2000

• Kawasaki Disease
  – CCR5Δ32 less common in patients with KD
    Burns, J Infect Dis 2005
CCR5 Deletion Implications (2)

• **Sclerosing cholangitis**
  - CCR5Δ32 more common in patients with PSC than in those with IBD or healthy controls
    - Eri, Genes Immun 2004
  - CCR5Δ32 less common in patients with PSC than in those with IBD or healthy controls
    - Henckaerts, Inflamm Bowel Dis 2006

• **Organ transplant survival**
  - CCR5Δ32 associated with longer graft survival of renal transplants
    - Fischereder, Lancet 2001
  - CCR5Δ32 not associated with graft survival of liver transplants
    - Schroppel, Am J Transpl 2002
  - CCR5Δ32 associated with Ischemic-type biliary lesions and decreased graft survival following liver transplant
    - Moench, Liver Transpl 2004
CCR5 Deletion Implications (3)

• HCV
  – CCR5Δ32 more common in HCV infection
    Woitas, Gastroenterology 2002
  – CCR5Δ32 associated with lower inflammation and fibrosis and clearance of viremia
    Hellier, Hepatology 2003
    Goulding, Gut 2005

• West Nile Virus infection
  – CCR5Δ32 associated with increased severity of disease and death
CCR5 Deletion Implications (4)

• Hepatitis (mice)
  – CCR5 knockout mice had fulminant liver failure following Con A administration by preventing NK cell apoptosis Ajuebor, J Immunol 2005
  – CCR5 knockout mice had exacerbation of T-cell mediated hepatitis Moreno, Hepatology 2006

• Non-Hodgkin’s Lymphoma
  – CCR5Δ32 associated with 3-fold lower risk of AIDS-related Non-Hodgkin’s lymphoma; no difference in KS or OIs Dean, Cancer Res 1999
CCR5 and HIV infection

- CCR5Δ32 homozygotes are relatively resistant to HIV infection.
- CCR5Δ32 heterozygotes have reduced HIV disease progression.

Combined Effect of CCR5 and CCL3L1 (MIP-1-α) Genotype on AIDS Progression

Structures of Small Molecule CCR5 Inhibitors

Schering C: Phase IB

Antiviral effect of Sch-C in humans; Phase 1B clinical trial

Antiviral Effect
25 mg BID (n = 12)

Log10 Change from Baseline

Dosing
Washout

Day 3

0 100 200 300 400 500 600 700

Hours

Laughlin, M.
Reynes, J. et al.
9th CR01, Feb 2002

Reynes, 9th CROI, 2002, abst. #1
Aplaviroc (873140): Phase I -- Median HIV RNA Change

Study pop: R5-tropic, CD4 nadir >200, VL >5K

GSK Statement to HIV Patient Community (9/05): aplaviroc rx-naïve studies stopped due to hepatotoxicity in a rx-naïve pt.

GSK Press Release (10/05): 3 additional cases of hepatotoxicity in rx-naïve pts; 1 case in rx-experienced pt – all aplaviroc studies stopped.

GW873140/005  Lalezari AIDS 2005;19:1443
Aplaviroc

• Discontinued due to drug induced hepatotoxicity (elevated AST/ALT and total bilirubin, Oct 2005) \(^1,^2\)
  – 10 treatment emergent cases in 282 (3.5%) subjects who received aplaviroc for a median of 13 wks\(^2\)
  – 4 clinically relevant cases in treatment-naïve subjects in Phase 2b clinical trials\(^2\)
  – 1 case in a Phase 3 trial in treatment experienced patients\(^1\)
  – No further clinical studies of the compound planned\(^1\)

\(^1\)GSK Press Release (10/26/05).
Maraviroc:
Phase 2a Monotherapy

Doses $\geq$100 mg BID resulted in HIV RNA reductions of $>1 \log_{10}$ c/mL in all patients.

Study population: asymptomatic, CD4 $>250$, R5-tropic (N=82); BL VL $\sim$42K

Maraviroc:
Safety Summary (Phase 1-2a)

• >500 HIV- and >65 HIV+ subjects treated
• Adverse events were similar to placebo at doses of <300 mg BID
• No orthostatic hypotension at daily doses <600 mg
• Clinically relevant elevations in transaminases occurred sporadically
  – No dose relationship and no associated elevation in bilirubin
• No evidence of clinically relevant prolongation of QTcF
Maraviroc: Recent Events

• Single case of hepatotoxicity reported in 11/05, complicated history and on other hepatotoxic meds
  Mayer, Viral Entry Inhibitor Workshop (12/2005)

• Phase IIb/III studies fully enrolled
  – 1026: Rx-naïve, R5 tropic (N=908)
  – 1027: Rx-exp, R5 tropic (N=601)
  – 1028: Rx-exp, R5 tropic (N=474)
  – 1029: Rx-exp, D/M tropic (N=190)

• >2100 subjects enrolled on MVC studies

• DSMB recommends stopping 300 mg qd MVC dose (and continuing 300 mg bid dose) on rx-naïve study.
  Pfizer Press Release 1/06

• DSMB notes incidence of malignancy consistent with known rates in population; recommends continuing phase 2b/3 studies.
  Pfizer Announcement 5/4/06
Vicriviroc:
Phase 2a Monotherapy Data

Study population: Off ART X 8 weeks, CD4 >200, VL 5-250K, R5 tropic (N=48, 16/cohort: 12 on study Rx, 4 on placebo); BL VL ~80-100K

Vicriviroc: Phase II in Rx-Naïve Pts.

- 17 sites in Europe and Canada
- Study population: rx-naïve; R5 tropic, VL >5K, CD4 >150, no baseline resistance mutations
- Baseline: VL ~60K, CD4 ~290 (N=92)
- Study treatment: vicriviroc at 25, 50, or 75 mg qd X 2 wks, then add ZDV/3TC vs. ZDV/3TC + EFV started at 2 wks
- Results:
  - HIV RNA change (log copies/ml) at day 14: -0.9 (25mg), -1.2 (50mg), -1.3 (75mg), -0.1 (placebo)
  - HIV RNA rebound to >50 cps/ml during follow-up: 13/23 (56%, 25mg); 9/22 (41%, 50mg); 4/23 (17%, 75mg); vs. 1/24 (4%, EFV)
- **DSMB recommended stopping the study**

Greaves, CROI 2006, abst. #161LB
Vicriviroc: Safety Summary

• Dose-limiting toxicity in animals was seizures
  – Seizure threshold 10- to 20-fold above clinical exposures
  – No seizures reported on vicriviroc studies

• Phase 2a trial
  – 3 serious adverse events
  – Mild-moderate headache, diarrhea, nausea
  – No changes in ECG or cardiac rhythm
  – No clinically significant changes in lab values

• No hepatotoxicity seen

Schuermann D, 3rd IAS Conference. 2005, abstract TuOa0205.
Greaves CROI 2006, abst. #161LB
ACTG 5211: Phase I/II

- **Study population:** Patients on failing RTV-containing regimen, VL >5K (N=118)
- **Study treatment:** Add vicriviroc at 3 doses (5, 10, 15 mg with RTV vs. placebo) X 2 weeks, then optimize background ART (with resistance testing) X 46 weeks
- **Study endpoints:** change in HIV RNA over first 14 days, 24 weeks; safety/tolerability; durability of HIV RNA response; resistance
- **10/14/05:** SMC recommends stopping 5 mg arm.
Vicriviroc and Malignancies

ACTG 5211

• 118 heavily treatment-experienced pts
• 5 malignancies reported in patients taking vicriviroc
  – 4 lymphomas: 2 HD, 2 NHL (2 with hx of HD)
  – 1 gastric adenocarcinoma
• Causality could not be established
• Virologic activity and CD4 responses seen with vicriviroc

Schering-Plough Press Release 3/3/06
Changes in co-receptor tropism during maraviroc (MVC) monotherapy

• 10-day dosing with MVC (25-300 mg QD or BID) in 63 patients with R5-only tropic virus (Monogram assay).

• In 60 of 62 patients, no change in phenotype.

• In the other 2 patients (on MVC 100 mg qd), X4 viruses detected at day 11.
  • One patient reverted to R5 at day 40.
  • One patient remained D/M and had a decline in CD4 (593 to 219) over a year and started ART at day 433 post-study.

• In a 3rd patient D/M virus was detected at baseline (due to a screening error) with a transient increase in the X4 component during therapy. No change in HIV RNA level.

• X4 variants emerged from a preexisting reservoir, not from a co-receptor change.

## Co-receptor Tropism Changes

<table>
<thead>
<tr>
<th>R5 inhibitor</th>
<th>Patient</th>
<th>Dose</th>
<th>VL change</th>
<th>Day 1 Tropism</th>
<th>Nature of X4 appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplaviroc</td>
<td>A</td>
<td>200 QD</td>
<td>-0.53 log</td>
<td>R5</td>
<td>pre-existing D/M</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>C</td>
<td>100 mg</td>
<td>None</td>
<td>D/M</td>
<td>pre-existing D/M and X4</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>100 mg</td>
<td>-0.71 log</td>
<td>R5</td>
<td>pre-existing D/M</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>100 mg</td>
<td>-1.26 log</td>
<td>R5</td>
<td>appearance of D/M and X4 on treatment</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>100 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>C</td>
<td>BID</td>
<td></td>
<td>D/M</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>QD</td>
<td></td>
<td>R5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>QD</td>
<td></td>
<td>R5</td>
<td></td>
</tr>
<tr>
<td>Vicriviroc</td>
<td>1</td>
<td>High Dose</td>
<td>-0.5 log</td>
<td>D/M</td>
<td>pre-existing D/M</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>High Dose</td>
<td>&gt;-1.5 log</td>
<td>R5</td>
<td>transient appearance of X4 on treatment</td>
</tr>
</tbody>
</table>


Courtesy of John Moore, PhD
Resistance – In vitro

• Resistance not associated with co-receptor change
  Trkola PNAS 2002

• HIV can bind CCR5-inhibitor complex
  Kuhmann J Virol 2004

• Resistance associated with increased affinity for CCR5
  Maroszan Virology 2005

• Resistance associated with changes in V3 loop that may differ among inhibitors
  Lewis Eur. Resistance Workshop 2005

• Resistance also associated with other gp 120 (or other ENV) changes
  Maroszan Virology 2005

• MVC-resistant isolates not cross-resistant to APL, VCV or SCH-C
  Westby Antiviral Therapy 2005, S72
Resistance -- Clinical

- Aplaviroc
- Maraviroc
- **Vicriviroc:** In rx-naïve study, changes in IC50 did not explain viral rebound.
  Greaves, CROI 2006, abst. #161LB
CCR5 inhibitors: Current Status (1)

- **Schering C**: Withdrawn (QT prolongation)
- **Aplaviroc**: Withdrawn (Hepatotoxicity)
- **Maraviroc**:
  - Phase 2-3 clinical trials in treatment-naïve and treatment experienced subjects with R5 tropic virus fully enrolled and in active follow-up
  - One trial in subjects with D/M virus fully enrolled and in active follow-up
  - 300 mg QD arm in naïve trial terminated due to suboptimal antiretroviral activity
  - One case of severe hepatotoxicity most likely not related to study drug
CCR5 inhibitors: Current Status (2)

• **Vicriviroc**
  – Phase 2 ACTG trial in rx-experienced subjects fully enrolled and in active follow-up
  – Rx-naïve study closed due to suboptimal antiretroviral activity compared to EFV
  – 4 lymphomas in ACTG A5211

• **TAK-652**
  – HIV- volunteer studies reported Baba AAC 2005;49:4584

• **PRO 140**
  – HIV- volunteer studies reported Olson CROI 2006
  – HIV+ phase I study begun 12/1/05 Progenics Press Release
  – Granted FDA Fast Track Status 2/22/06 Progenics Press Release
CCR5 Issues in Development

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- Toxicities (compound- vs. class-specific)
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- Antiretroviral activity: Rx-naïve and rx-experienced patients
- Resistance
- Long-term follow-up