Chemokine Receptors and Antagonists: Summary of Clinical Experience

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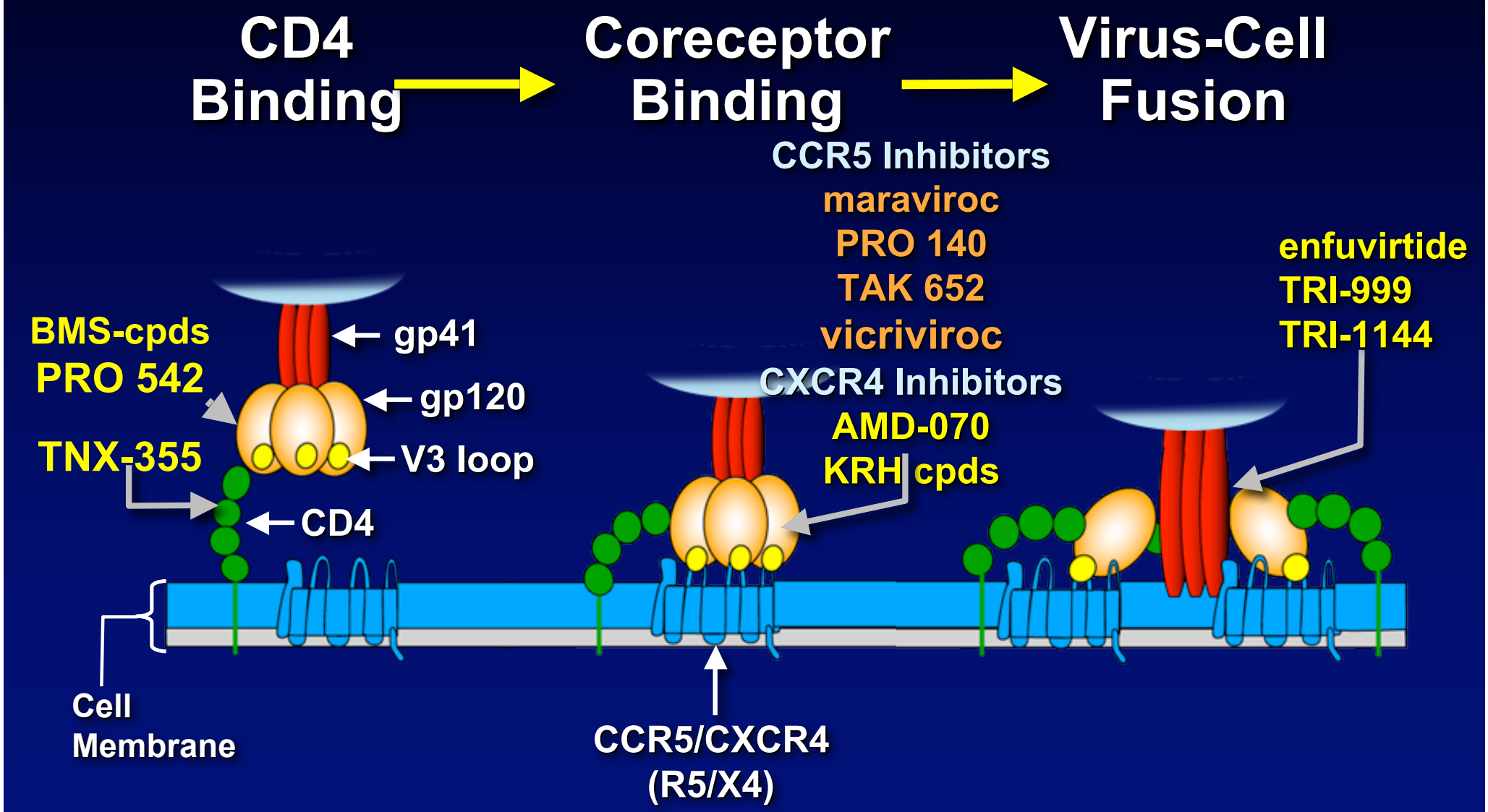
HIV Entry Inhibitors



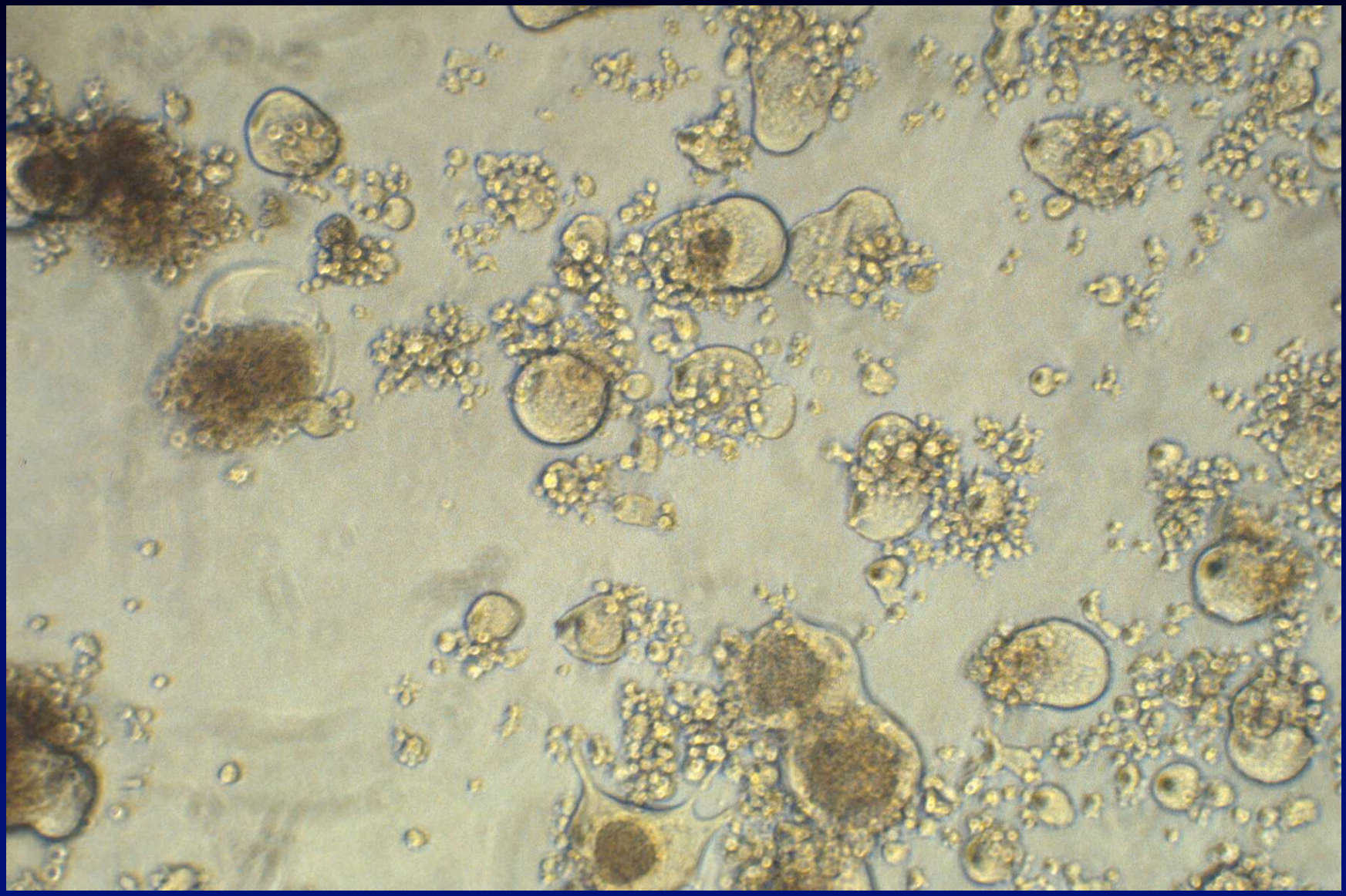
Adapted from Moore JP, *PNAS* 2003;100:10598-10602.

- **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

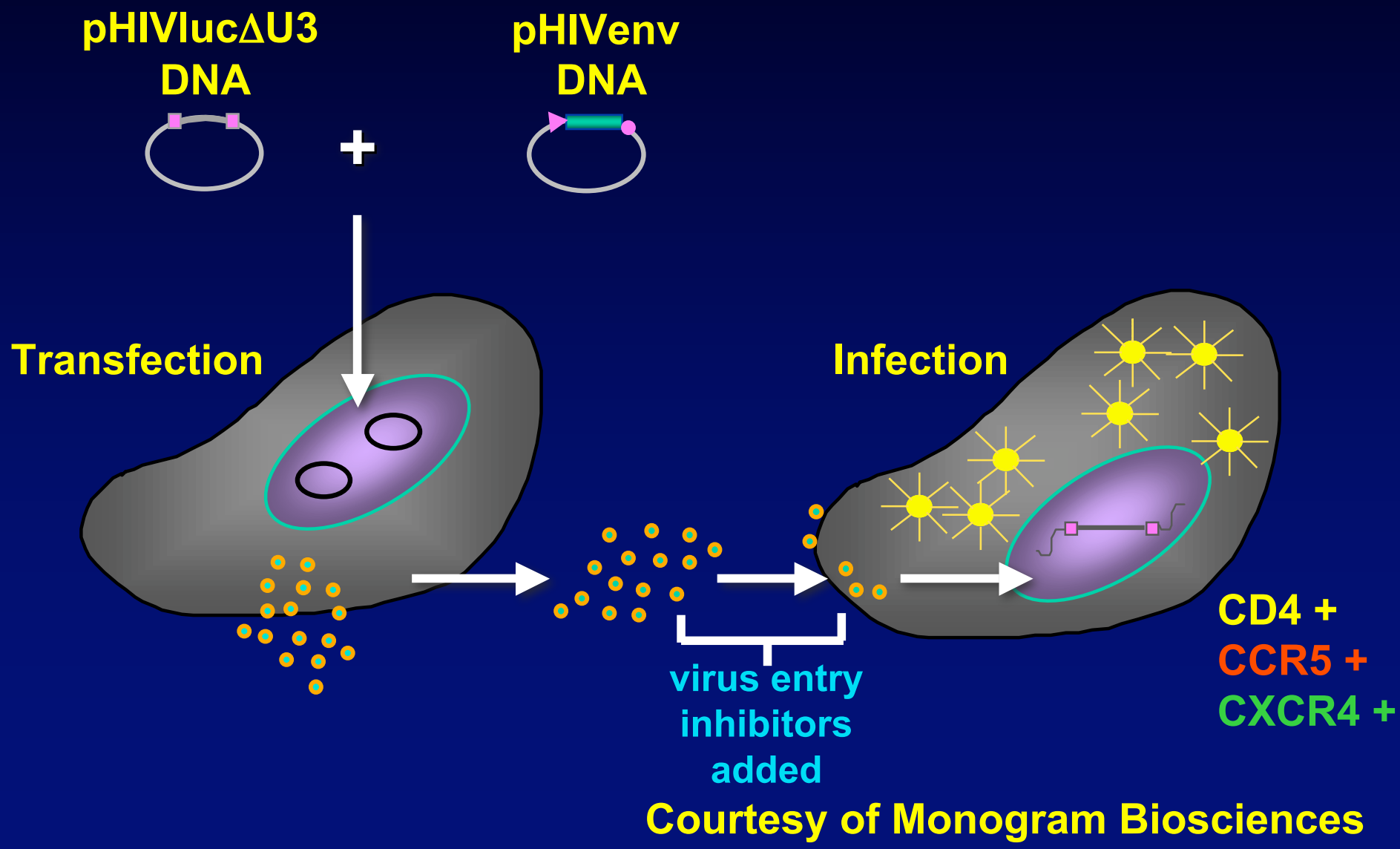
- Entry tropism: determination and pathogenesis
- Co-receptor tropism changes
- Immunologic consequences (compound- vs. class-specific)
  - Malignancies
- Toxicities (compound- vs. class-specific)
  - QT prolongation
  - Hepatitis
- Antiretroviral activity:
  Rx-naïve and rx-experienced patients
- Resistance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

Syncytium formation in MT-2 cells expressing CXCR4 only



Schuitemaker H, et al. *J Virol.* 1991;65:356-363.

Entry Tropism Assay



Courtesy of Monogram Biosciences

Entry Tropism Assay Performance

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

Courtesy of Monogram Biosciences

Chemokine Receptor Tropism

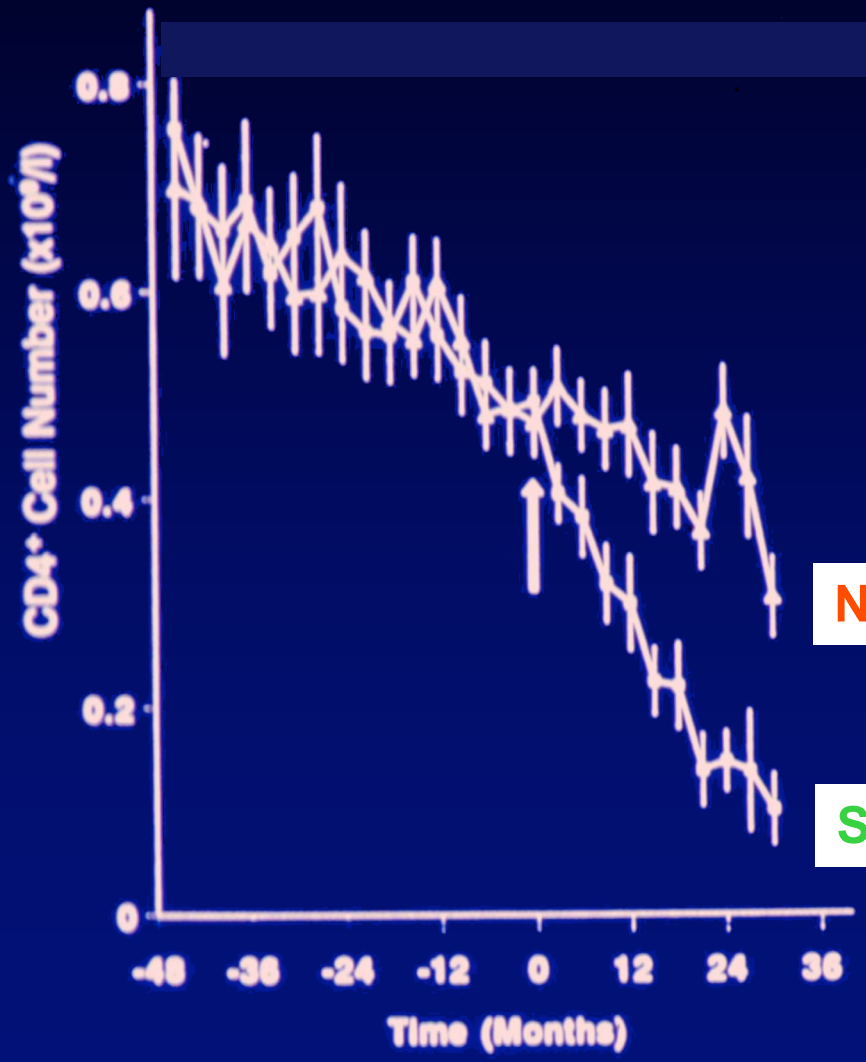
Study	Patient Population	N	R5-only	D/M	X4-only
Demarest[1]	naïve	325	88%	12%	0%
Homer Cohort[2]	naïve	979	82%	18%	0.1%
Moyle[3]	naïve	402	81%	19%	n/a
Moyle[3]	experienced	161	78%	22%	n/a
Demarest[1]	experienced	117	67%	28%	5%
TORO[4]	heavily experienced	627	50%	48%	2%
ACTG 5211[5]	heavily experienced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

[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)

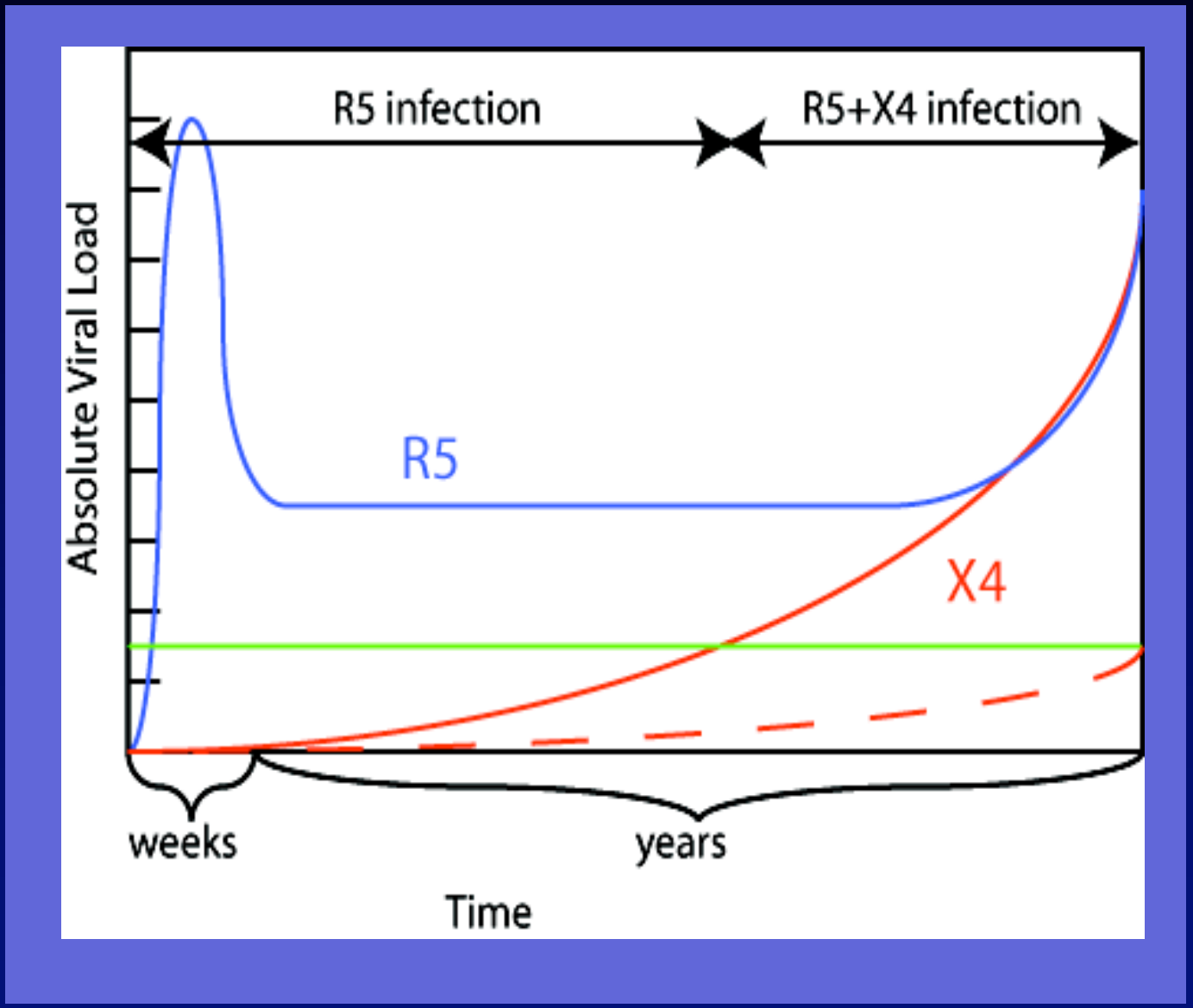


NSI (n=144)

SI (n=22)

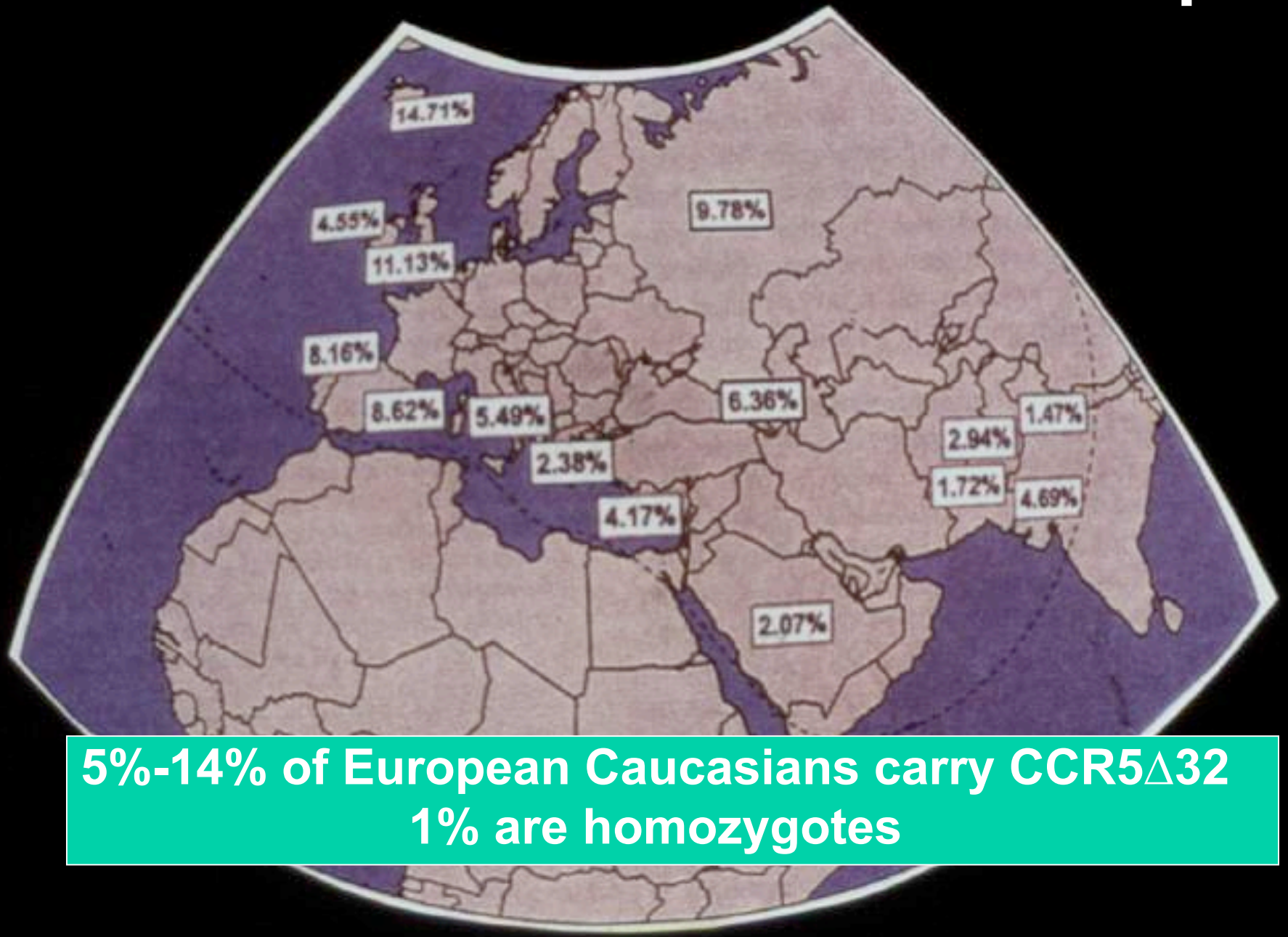
Koot et al Ann Intern Med 1993

Natural History of Chemokine Tropism



Courtesy of John Moore, PhD

Distribution of CCR5Δ32 in Europe



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
    Glass, J Exp Med 2006

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.

Lui R, et al. *Cell.* 1996;86:367-377.

Samson M, et al. *Nature.* 1996;382:722-725.

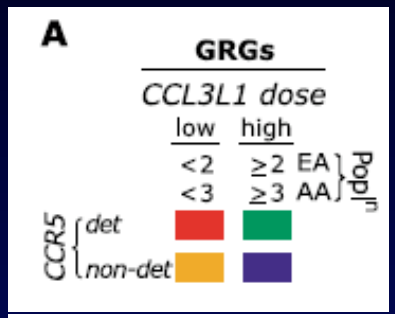
Dean M, et al. *Science*. 1996;273:1856-1862.

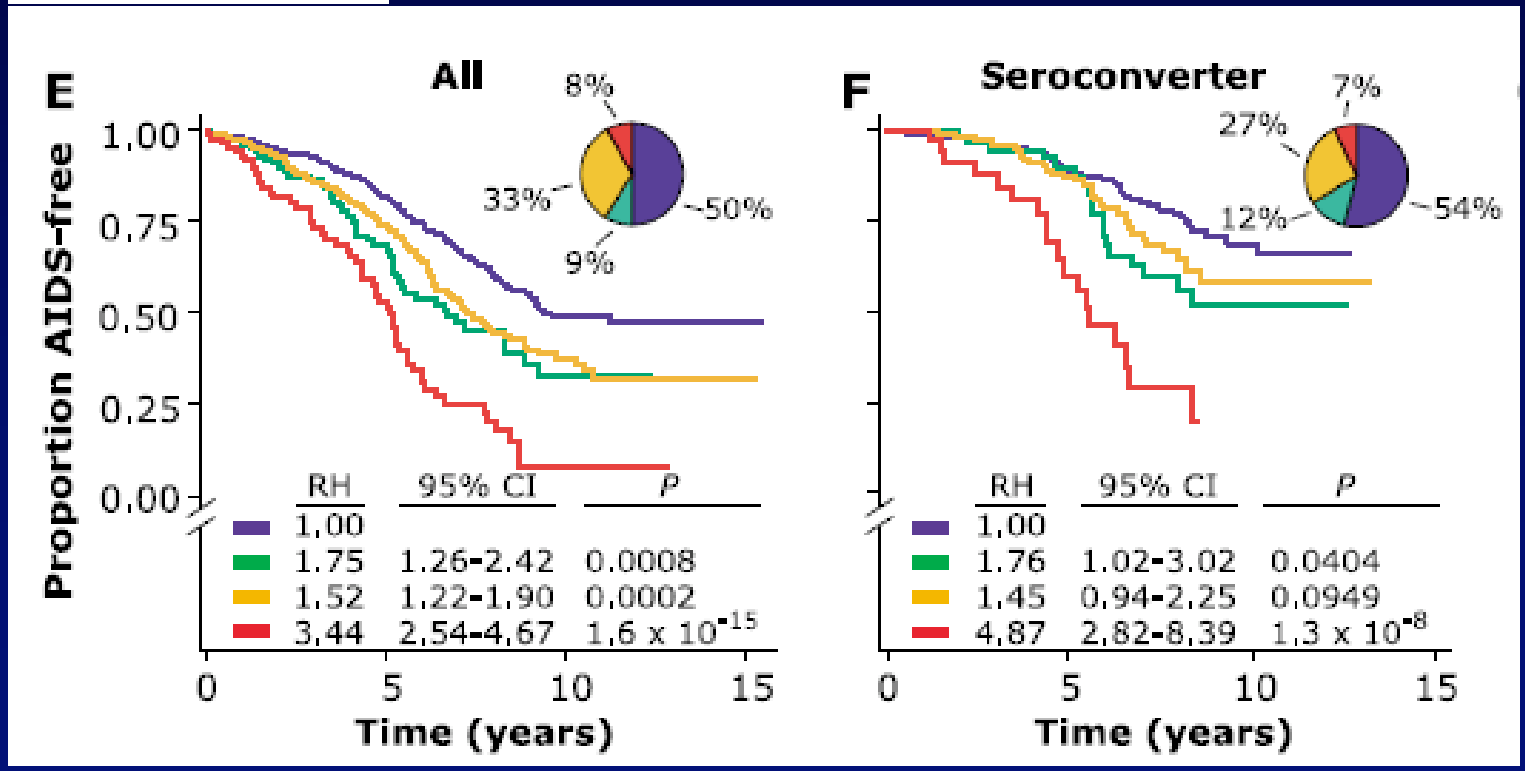
Huang Y, et al. *Nat Med.* 1996;2:1240-1243.

Michael NL, et al. *Nat Med.* 1997;3:1160-1162.

Eugen-Olsen J, et al. *AIDS*. 1997;11:305-310.

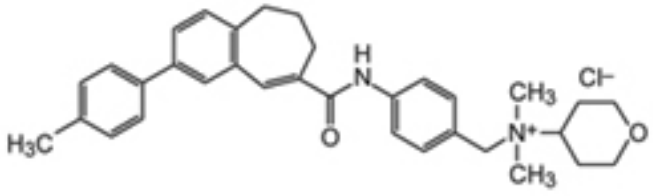
Combined Effect of *CCR5* and *CCL3L1* (MIP-1-α) Genotype on AIDS Progression



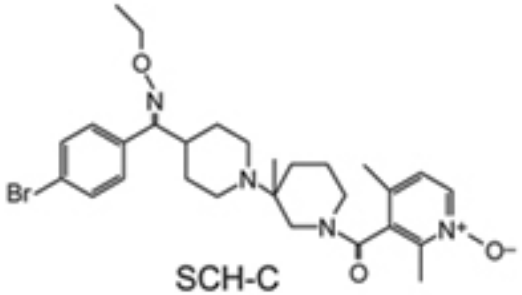


Gonzalez et al Science 2005; 307:1434-40.

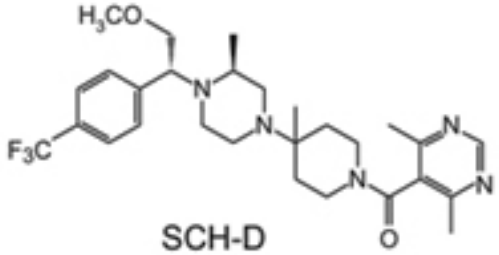
Structures of Small Molecule CCR5 Inhibitors



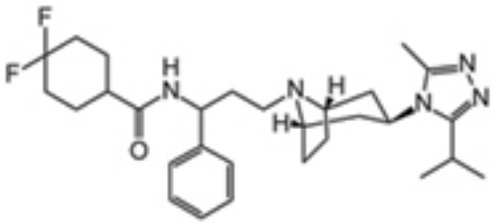
TAK779



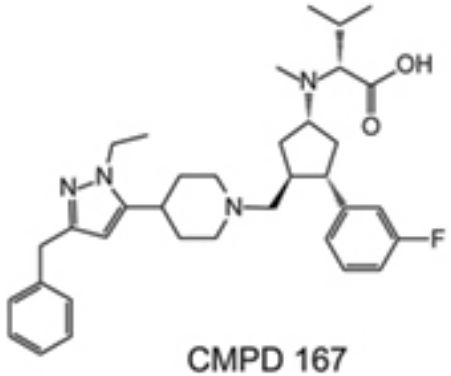
SCH-C



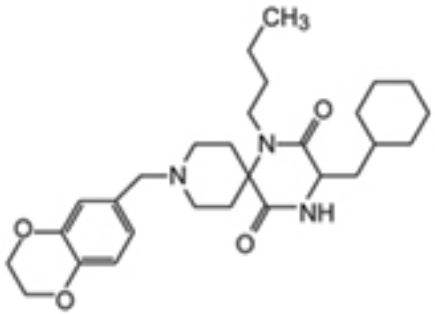
SCH-D



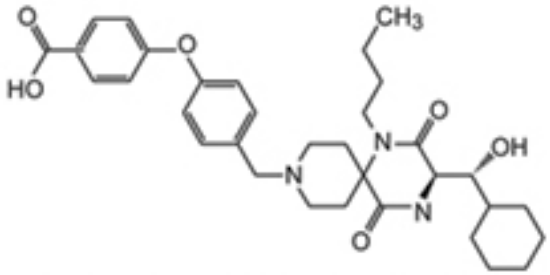
UK427,857



CMPD 167



E913

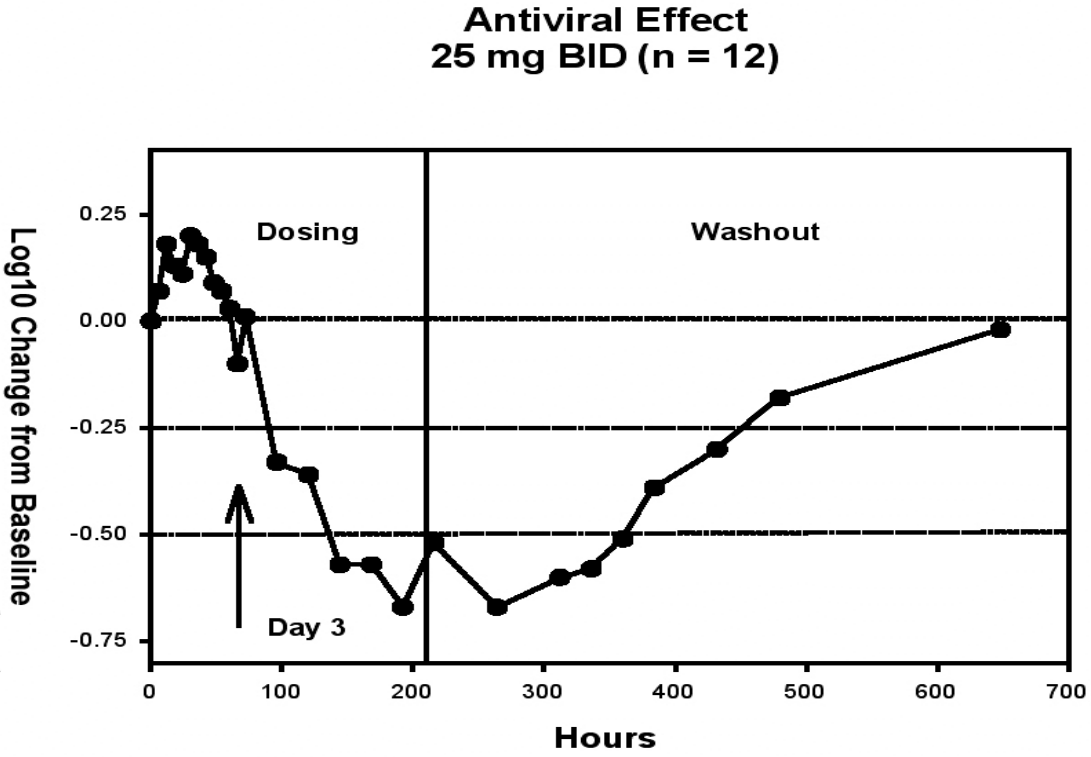


AK602/ONO4128/GW873140

Maeda, *Current Opinion in Pharmacology* 2004;4:447–452.

Schering C: Phase IB

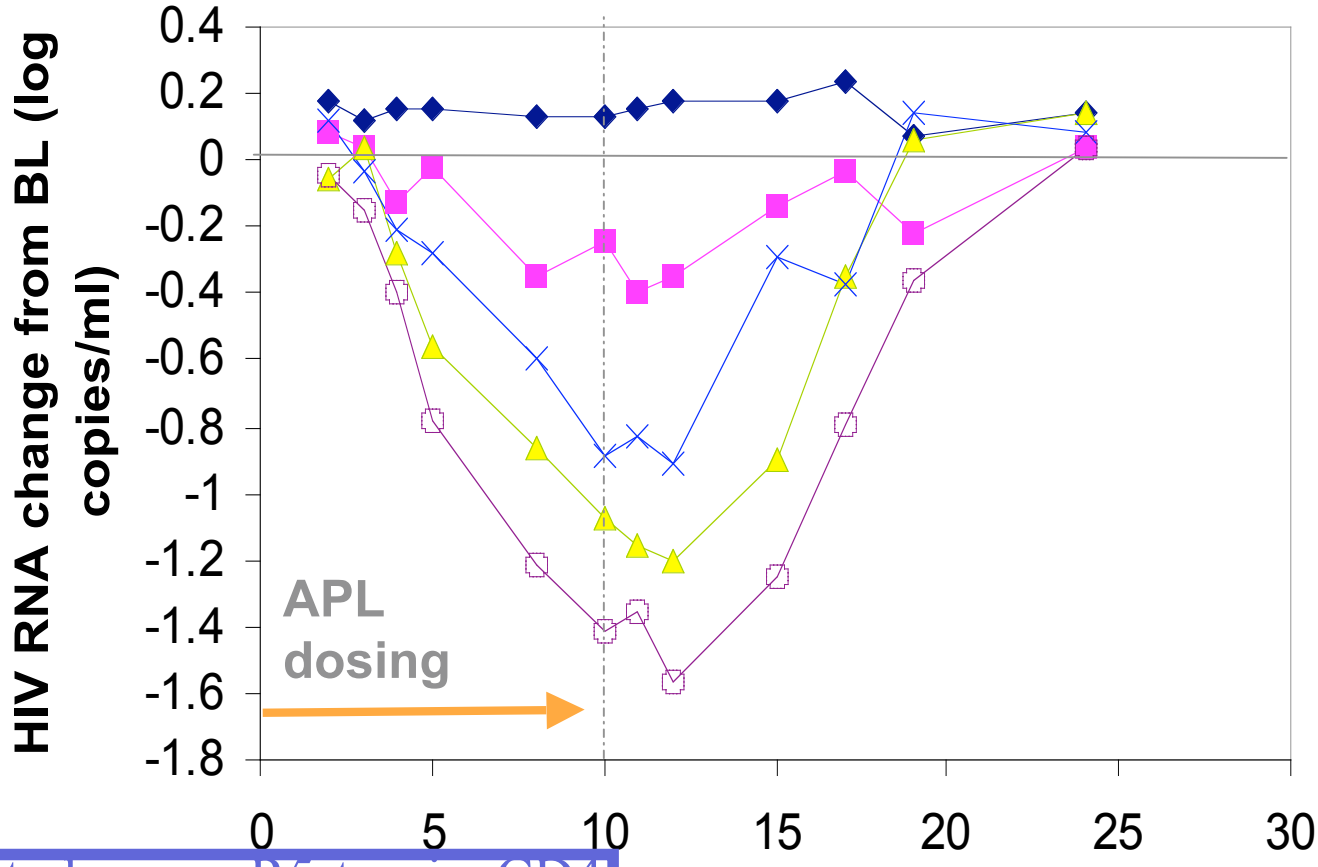
Antiviral effect of Sch-C in humans; Phase 1B clinical trial



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 hepatoxicity 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

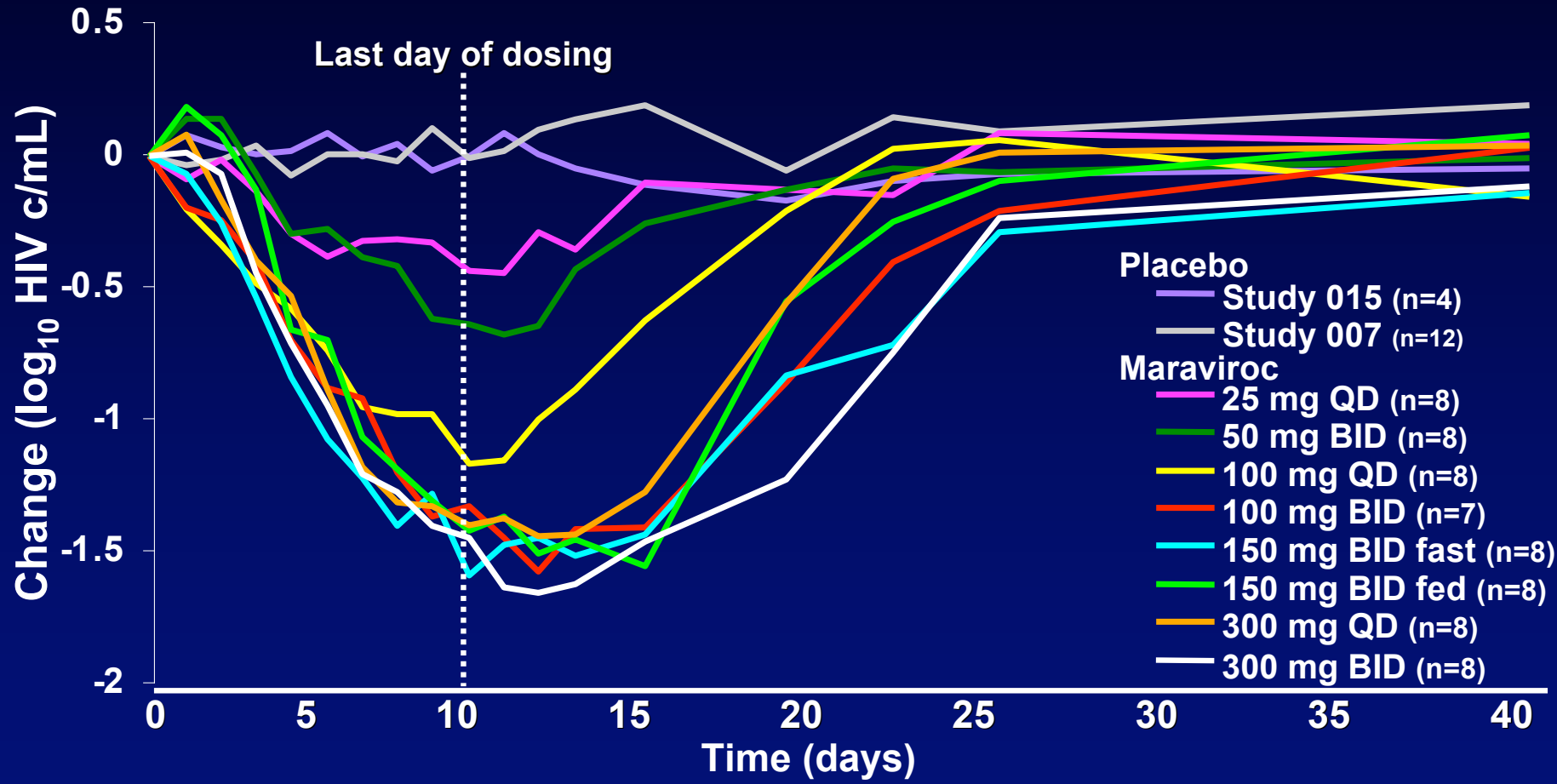
Lalezari AIDS 2005;19:1443

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).
[2] Nichols W, et al. HIV Entry Workshop, 2005, Abstract 26

Maraviroc: Phase 2a Monotherapy



Doses ≥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 ~42K

Fätkenheuer G, *Nat Med.* 2005;11:1170-1172.

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

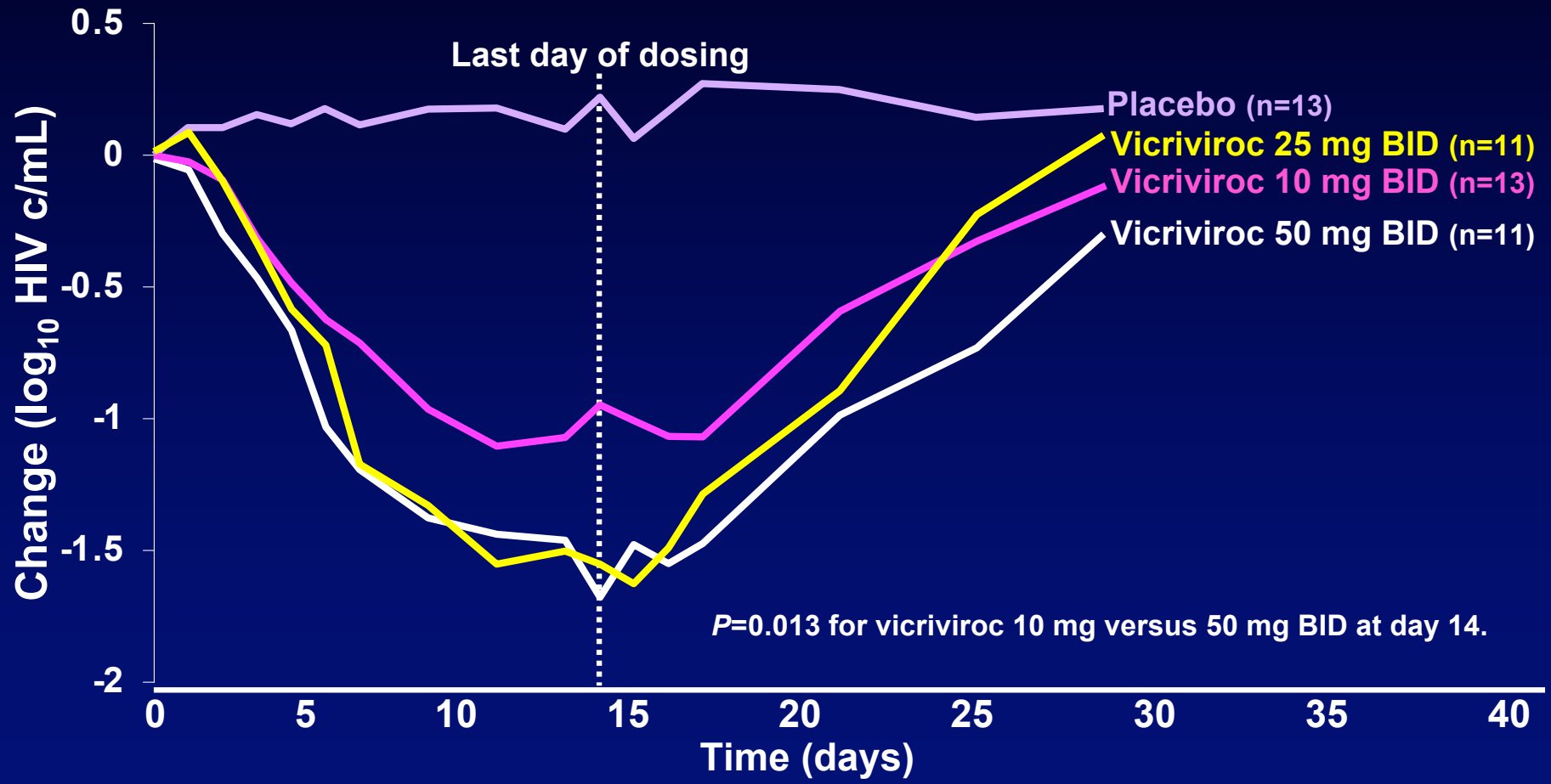
Maraviroc: Recent Events

- 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

Schuermann D, et al. 3rd IAS Conference. 2005. Abstract TuOa0205.

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.

Westby, J Virol 2006;80:4909-4920.

Co-receptor Tropism Changes

R5 inhbitor	Patient	Dose	VL change	Day 1 Tropism	Nature of X4 appearance
Aplaviroc	A	200 QD	-0.53 log	R5	pre-existing D/M
Maraviroc	C	100 mg BID	None	D/M	pre-existing D/M and X4
	A	100 mg QD	-0.71 log	R5	pre-existing D/M
	B	100 mg QD	-1.26 log	R5	appearance of D/M and X4 on treatment
Vicriviroc	1	High Dose	-0.5 log	D/M	pre-existing D/M
	2	High Dose	>-1.5 log	R5	transient appearance of X4 on treatment

Lalezari AIDS 2005;19:1443; Westby J Virol 2006;80:4909; Schurmann CROI 2004 #140LB

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 inhhibitors Strizki Int. Resistance Workshop 2005, Maroszan Virology 2005, Yusa J Biol Chem 2005, 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

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- 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