



CCR5 Inhibitors: Up and Coming New Agents

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A new class of antiretroviral drugs came on the scene in 2003 with the approval of the first entry inhibitor, enfuvirtide (T-20, Fuzeon). Considerable research has been directed toward discovery of additional drugs that target the cell-entry stage of HIV replication, and CCR5 inhibitors—agents that block viral entry via a novel mechanism of action—are poised to join the antiretroviral armamentarium this year.

New Targets: Chemokine Receptors

In 1995, Fiorenza Cocchi, PhD, and Robert Gallo, PhD, then at the National Cancer Institute, and colleagues reported the discovery that three chemokines—proteins secreted by T-cells that carry the CD8 surface marker (known as CD8 cells)—prevent HIV from entering cells *in vitro*. Within months, other research teams reported that two chemokine receptors, CCR5 and CXCR4, play a critical role in HIV entry. (For a detailed history of early chemokine research, see “Chemokines and HIV” in the March 1997 issue of *BETA*.)

In the cell-entry stage of HIV replication, a protein called gp120 on the envelope of the virus binds to CD4, a protein found on the surface of some white blood cells. (T-cells that express the CD4 protein are known as CD4 cells.) The CD4 protein acts as a receptor for gp120, “unlocking” the cell and allowing the virus to enter. HIV also needs a second receptor in order to enter cells: CCR5 and CXCR4, two proteins expressed on the surface of some immune cells, are the key coreceptors for HIV entry. The chemokines described by Drs. Cocchi and Gallo—RANTES, MIP-1 α , and MIP-1 β —are believed to be capable of occupying these coreceptors’ binding sites or chemically altering the coreceptor proteins, thereby blocking HIV entry.

CCR5 and CXCR4 function as coreceptors for different HIV strains. When sexually transmitted, HIV typically establishes itself in the body as a non-syncytium-inducing (NSI) strain that preferentially binds to macrophages, immune cells that ingest and process pathogens in the blood and other tissues. For this reason, such strains are sometimes called “macrophage-tropic,” or “M-tropic.” CCR5 appears to be the key coreceptor for these strains of HIV; hence, they are also referred to as “CCR5-tropic.”

In some individuals, however, NSI strains transform into syncytium-inducing (SI) virus, which preferentially infects T-cells and relies on CXCR4 (also called fusin) for cell entry. These so-called “T-tropic” or “CXCR4-tropic” SI strains are more aggressive than NSI strains and are associated with more rapid disease progression and poorer response to antiretroviral therapy. It is unclear why NSI strains sometimes convert to SI virus.

SYNCYTIUM: an abnormal “clump” of fused cells; syncytium-inducing HIV strains cause T-cells to fuse and die.

Some individuals simultaneously harbor both CCR5-tropic NSI strains and CXCR4-tropic SI strains of HIV; this kind of infection is called “mixed-tropic” or “dual-tropic” infection. Although CXCR4-tropic strains are most often seen in individuals with advanced HIV disease, more than half of people with advanced disease still harbor only CCR5-tropic virus. Since HIV can potentially use either coreceptor, there is concern that preventing the virus from using one coreceptor could select for strains that are able to use the other.

The *CCR5Δ32* Mutation

The CCR5 coreceptor was shown to play a role in HIV replication with the discovery that people who are homozygous for a genetic mutation that prevents the expression of functional CCR5 on their cells appear to have resistance to infection with HIV-1, the most common form of the virus worldwide. (The other form, HIV-2, is rare outside of West Africa.)

In August 1996, Rong Liu, PhD, of the Aaron Diamond AIDS Research Center in New York and colleagues reported that this *CCR5Δ32* mutation—so named because 32 base pairs are deleted from the CCR5-expressing gene—conferred resistance to HIV-1 infection in individuals with a history of multiple high-risk sexual exposures. Other research teams subsequently reported similar findings, and also observed that individuals heterozygous for the mutation experienced partial protection against HIV infection.

Individuals homozygous for the mutant allele are not entirely protected from HIV infection, since they can acquire virus that uses the CXCR4 coreceptor. In such cases, CD4 cell counts decline rapidly, but HIV viral load does not increase with corresponding speed, and disease progression is slow. Although only 40% of non-progressors carry the *CCR5Δ32* mutation, researchers speculate that variations in the expression and/or function of the CCR5

HOMOZYGOUS: possessing two copies of the same allele, or gene variant, at a given site on a chromosome, the structure that carries a cell’s genetic information.

HETEROZYGOUS: possessing two different alleles at a given site on a chromosome.

CCR5Δ32: Who, When, and Why?

CCR5Δ32 is seen primarily in people of Northern European descent and is infrequent or absent in people of Asian or African ancestry, suggesting that the mutation appeared after these populations diverged; one recent analysis dates the gene to the Bronze Age. The high prevalence of the mutation in some populations suggests that it offered a significant advantage to its carriers at some fairly recent point in human history.

Current theories suggest that the defective gene conferred resistance to the bubonic plague or smallpox—diseases that were widespread in Europe about 700 to 1000 years ago, when the mutation is believed to have increased in prevalence. People with the normal gene enjoyed no such protection and died, the theory suggests, and hence did not pass the gene on to further generations. Those with the defective gene survived, and their descendants inherited the *CCR5Δ32* mutation.

gene may be one of many factors in the continued health of non-progressing individuals.

CCR5 Inhibitors in the Clinical Development Pipeline

The benefit conferred by the *CCR5Δ32* mutation and the fact that CCR5 is the coreceptor most commonly used by HIV in early infection make it a highly attractive target for antiretroviral therapy. Five experimental CCR5 inhibitors are currently in the clinical pipeline, and several more are in preclinical trials.

However, many challenges have hindered the development of a viable CCR5 inhibitor. Some early candidates were found to bind to chemokine receptors other than CCR5, while other experimental drugs showed little antiretroviral activity or had limited bioavailability in human trials. One agent that appeared promising, GlaxoSmithKline’s *aplaviroc*, reached Phase III clinical

development before trials were halted due to severe liver toxicity (which resolved after the drug was discontinued).

Two types of CCR5 inhibitor are now progressing through the clinical trials pipeline: small-molecule antagonists and monoclonal antibodies (mAbs). (See “Open Clinical Trials,” page 50.)

Small-molecule antagonists are thought to “lock” the coreceptor into a conformation that does not permit binding by the HIV envelope protein. These CCR5 inhibitors are orally bioavailable and can therefore be taken in pill form; in the clinical pipeline, these include Pfizer’s maraviroc (UK-427,857), Schering-Plough’s vicriviroc (SCH-D), and Incyte’s INCB9471.

In contrast, mAbs are believed to block HIV attachment to CCR5 by binding to distinct sites on the coreceptor. As proteins, mAbs are not orally bioavailable and must be injected. These agents include PRO-140, made by Progenics Pharmaceuticals, and CCR5mAb004, from Human Genome Sciences; both are in Phase I/II clinical trials.

In the Lead: Maraviroc

The first CCR5 inhibitor likely to become available is Pfizer’s small-molecule inhibitor, maraviroc. The drug was the first CCR5 inhibitor to enter clinical trials and received fast-track status from the Food and Drug Administration (FDA) in 2006; it is now undergoing Phase III trials. An

international expanded access program (EAP) for maraviroc is currently in the works (see “News Briefs,” page 5). Pfizer expects to file for licensing approval in early 2007; given the FDA’s six-month review period, the company anticipates that maraviroc may be approved mid-year.

In a late-breaker session at the 16th International AIDS Conference in August 2006, researchers presented 24-week results of a Phase IIb trial of maraviroc. One purpose of this double-blind, placebo-controlled trial was to assess the safety and efficacy of the investigational drug in treatment-experienced individuals with dual-tropic HIV infection: how would such participants respond to a drug that specifically targets the CCR5 coreceptor?

To enroll, participants had to be on stable antiretroviral regimens, have HIV viral loads greater than 5000 copies/mL, and have triple-class antiretroviral experience and/or harbor dual-class-resistant virus. The median baseline CD4 count was less than 50 cells/mm³. Of 186 enrollees, 70% were white and 26% black; 13% were women. Participants were randomly assigned to one of three groups: placebo, 150 mg maraviroc once daily, or 150 mg maraviroc twice daily; all groups also received optimized background therapy. Safety was assessed based on participant-reported adverse events, physical examinations, and lab tests. The primary endpoint was the change in viral load over 24 weeks for patients with dual-tropic virus at screening (n = 167).

The decrease in viral load from baseline through week 24 was similar for the placebo group and the group receiving once-daily dosing of the study drug (0.97 log and 0.91 log, respectively), but was slightly greater for the twice-daily dosing group (1.20 logs). Both maraviroc groups experienced larger mean CD4 cell increases (60 and 62 cells/mm³ in the once-daily and twice-daily dose groups, respectively) compared with the placebo group (35 cells/mm³). Similar frequencies of grade 3–4 adverse events, drug discontinuations, and deaths occurred in all three groups. The study investigators concluded that maraviroc was safe and well tolerated in this population with advanced HIV disease, despite the prevalence of CXCR4-tropic virus.

Several previous safety and efficacy trials evaluated maraviroc as monotherapy at doses of up to 300 mg twice daily (for one week to ten days) and 1200 mg once daily (for up to 28 days). Virological response to the study drug was encouraging; for example, a ten-day monotherapy study with doses of 300 mg once daily and twice daily demonstrated mean maximum viral load reductions of 1.60 logs and 1.84 logs, respectively. The most common treatment-related adverse events were headache, dizziness, nausea, asthenia (loss of strength), flatulence, and rhinitis

CCR5 Inhibitors in the Clinical Development Pipeline

Agent	Company	Status
Maraviroc (UK-427,857)	Pfizer	Phase II/III; granted fast-track status in 2006; EAP in development
Vicriviroc (SCH-D)	Schering-Plough	Phase II in treatment-experienced patients; discontinued in treatment-naïve patients
INCB9471	Incyte	Phase II
PRO-140	Progenics Pharmaceuticals	Phase I/II; granted fast-track status in 2006
CCR5mAb004	Human Genome Sciences	Phase I/II

(inflamed nasal passages); most of these were graded as mild or moderate, and no serious adverse events were reported.

Five subjects did, however, discontinue maraviroc in these studies: three due to postural hypotension (including one in the placebo group), one with elevated liver enzymes, and one with skin rash (in the placebo group). Liver function tests showed clinically significant increases in liver enzyme levels in seven patients taking various doses of the study drug, but no clear dose/frequency relationship was seen. Mild-to-moderate elevations in creatinine were observed in one study at 1200 mg once daily and in the placebo group. Investigators concluded that maraviroc is well tolerated at doses up to and including 300 mg twice daily.

Vicriviroc: Next in Line?

Following maraviroc, Schering-Plough's vicriviroc appears to be next in line in the clinical development pipeline. The drug has shown potent antiretroviral activity in clinical trials, and its long half-life may permit once-daily dosing. Vicriviroc's development has been rocky, however. The drug initially showed promise in a Phase II trial in treatment-naive participants, but Schering-Plough halted the study when subjects experienced early virological rebound (see "News Briefs," *BETA*, Winter 2006).

Similarly, a Phase II trial in heavily treatment experienced participants saw encouraging results by week 24: the three dosing arms (5, 10, or 15 mg vicriviroc daily) experienced mean HIV RNA decreases of 1.51, 1.86 and 1.68 logs (vs 0.29 log in the placebo group) and mean CD4 cell increases of 84, 142, and 142 cells/mm³ (compared with a decrease of 9 cells/mm³ in the placebo arm). However, the study was unblinded in March 2006 after five subjects in the vicriviroc arms developed malignancies. Study investigators and an independent safety monitoring committee concluded that no causal link between the study drug and the cancers could be determined, and the trial continued at the 10-mg and 15-mg doses.

Questions and Concerns

The science of chemokines and chemokine receptors is still young. In addition to the usual concerns that accompany any new antiretroviral drug—including potential side effects, toxicities, drug interactions, and resistance—CCR5 inhibitors come with a unique set of questions and cautions.

Tropism-Switching

First, an obvious concern is how patients with CXCR4-tropic or dual-tropic HIV will respond to long-term use of a CCR5-inhibiting drug. Will treatment with a drug that

Tropism, Sex, and Race

As part of ACTG Study 5211, researchers examined coreceptor tropism in a population with fairly advanced HIV disease and triple-class antiretroviral treatment experience.

The prevalence of CCR5-tropic virus was similar in women and men (52% and 51%, respectively), but racial differences approached statistical significance: CCR5-tropic HIV was found in 67% of Latino participants, 52% of whites, and 42% of blacks. The investigators concluded that "the potential relationship of race/ethnicity to coreceptor tropism deserves further study."

prevents the use of one coreceptor promote the evolution of virus that can use the other?

Evidence that drug pressure may indeed lead to "tropism-switching" comes from an AIDS Clinical Trials Group (ACTG) study described at the 13th Conference on Retroviruses and Opportunistic Infections, held in February 2006. In ACTG Study 5211, CXCR4-using virus emerged in 13 participants by the 14th day of vicriviroc monotherapy (eight subjects receiving 5 mg, three in the 10-mg group, two in the 15-mg arm, and one taking placebo).

Contrasting results come from a study by Mike Westby of Pfizer Global Research and Development and colleagues, published in the May 2006 issue of the *Journal of Virology*. Sixty of 62 patients who entered the study with CCR5-tropic HIV retained only CCR5-tropic virus after ten days of maraviroc monotherapy. CXCR4-tropic virus was detected at day 11 in two participants, but based on the genetic makeup of these strains, the authors concluded that these had emerged from a pre-treatment viral reservoir and did not arise in response to treatment with maraviroc.

Immune Function

Second, the role of chemokines and chemokine receptors in immune response is still being explored. For example, a 2001 *Lancet* article reported an association between the CCR5Δ32 mutation and decreased risk of tissue rejection in kidney transplant patients. This may be good news for CCR5Δ32-carrying organ recipients, but it raises an important question: What unintended effects on immune response might arise from mimicking this mutation?

A recent study published in the January 2006 issue of the *Journal of Experimental Medicine* showed that individuals homozygous for the CCR5Δ32 mutation were overrepresented among cases of West Nile virus (WNV) in Arizona and Colorado. The authors concluded that

“CCR5 mediates resistance to symptomatic WNV infection,” and added that “these findings have important implications for the safety of CCR5-blocking agents under development for HIV/AIDS.”

While individuals with the defective CCR5 gene generally appear to have normal life spans, continued research is clearly warranted to elucidate possible consequences of pharmacologically inhibiting the immunoregulatory function of chemokine receptors.

Conclusion: Caution and Hope

A decade ago, *BETA* featured an article on “a new field of biomedical research: the study of chemokines” (“Chemokines and HIV,” March 1997). The author speculated on the potential new therapeutic strategies that the study of chemokine coreceptors might yield.

Today, a new antiretroviral drug with an entirely novel—and not entirely understood—mechanism of action is just around the corner, and more than a dozen other CCR5 and CXCR4 inhibitors are in the clinical and preclinical pipelines. Existing data on maraviroc and other members of its class give cause for both caution and hope. Ongoing trials will need to address questions about CCR5 inhibition and its effects—both intended and unintended—but a more robust class of entry-inhibitor drugs is an exciting prospect.

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