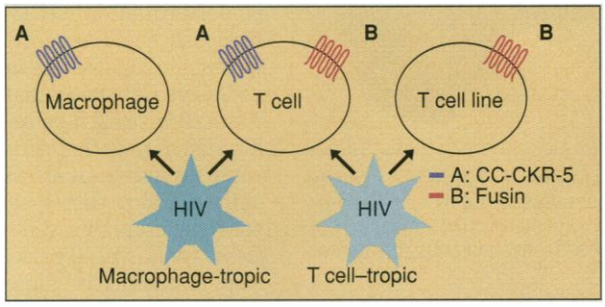
A Second Coreceptor for HIV In Early Stages of Infection

Despite more than a decade of research, many key questions about how HIV destroys the immune system have remained shrouded in mystery. But a recent series of breakthroughs has begun to lift the veil and point AIDS researchers in new and potentially rewarding directions. In the latest of these discoveries—reported in two papers published in this week's issue of *Nature* and a third that will appear in the 28 June issue of *Science* (with independent results from at least one other team reportedly about to be published)—several laboratories have identified an essential "coreceptor" for the HIV strains involved in the critical early stages of infection. All have fingered a cell membrane–bound protein called CC-CKR-5 as the elusive partner of HIV's primary receptor, CD4, in allowing these strains to enter their target cells.



SOURCE: *NATURE*, DENG *ET AL.*

Receptor swap. In a model proposed by Dan Littman and colleagues, macrophage-tropic HIV strains that predominate early in infection use CC-CKR-5 as a coreceptor; T cell–tropic strains found later in infection switch to fusin.

That makes CC-CKR-5 the second such coreceptor to be reported within the past 6 weeks. Last month, a team led by Edward Berger of the National Institute of Allergy and Infectious Diseases (NIAID) reported in *Science* that HIV strains that infect T cells maintained in laboratory culture—an experimental system with parallels to later stages of the disease—apparently interact with another cell-surface protein called "fusin" (*Science*, 10 May, pp. 809 and 872).

The discovery of these two coreceptors—and perhaps others yet to be identified—suggests that HIV may use different molecules to enter the cell at different stages of the disease. And that, in turn, may help explain why the body ultimately loses its battle with HIV after years of holding it at bay. "These are results we have been awaiting for 10 years," says immunologist Quentin Sattentau at the Centre d'Immunologie in Marseilles, France.

Researchers have known since 1986 that CD4 wasn't enough for HIV to gain entry to immune-system cells. In that year, Paul Maddon, then at Columbia University, and his colleagues showed that mouse cells genetically engineered to express human CD4 on their surfaces could not be infected with HIV. This finding launched a decade-long hunt for a "second receptor" that HIV uses in conjunction with CD4.

Now researchers have discovered not one, but two, second receptors. The identification of CC-CKR-5 as a coreceptor for so-called macrophage-tropic strains of HIV—those which predominate during the early stages of infection—was made almost simultaneously by at least three research teams. The two *Nature* papers come from a group at Rockefeller University's Aaron Diamond AIDS Research Center in New York led by John Moore and Richard Koup, and a second team headed by Dan Littman at New York University Medical Center as well as Nathaniel Landau, also at Aaron Diamond. And the *Science* paper comes from Berger's group at NIAID, fresh from nailing fusin as a coreceptor for so-called T cell line–tropic HIV strains.

The leaders of all three teams say they started focusing on CC-CKR-5 last December, when *Science* published a paper (15 December 1995, p. 1811) by a team led by Robert Gallo, director of the Institute of Human Virology at the University of Maryland, and Paolo Lusso, at the San Raffaele Scientific Institute in Milan, Italy. That paper reported that the three chemokines RANTES, MIP-1α, and MIP-1β—proteins involved in the immune system's inflammatory responses—are powerful suppressors of HIV infection, particularly for macrophage-tropic strains of the virus.

The discovery set researchers wondering whether these chemokines might suppress HIV by blocking or otherwise interfering with a coreceptor. And their suspicions fell on CC-CRK-5 because, out of some half-dozen chemokine receptors that had already been identified, it was the only one known to serve as a receptor for all three molecules. "Gallo's paper was the first thing that steered us in this direction," says Moore. Although the experimental approaches used by the three teams differed somewhat, in general they took cultures of human, mouse, or simian cells engineered to express CD4 and various candidate coreceptors. They then measured either viral entry or the degree of fusion between these cells and artificial "mock virus" cell preparations whose surfaces carry the viral proteins from different HIV strains.

Littman and his colleagues believe that the existence of more than one coreceptor may help to explain the "phenotypic switch" the AIDS virus undergoes as HIV-infected individuals progress from early asymptomatic stages to full-blown AIDS. Work from several labs has shown that small changes in the amino acid sequences of proteins in the virus's outer coat known to be involved in binding to target cells appear to correspond to progression of the disease. This raises the possibility, says Littman, that HIV uses CC-CKR-5 or a related coreceptor early in the course of infection, and then later switches to a fusinlike molecule, perhaps avoiding the suppressive activity of the chemokines and broadening the number of cell types it can attack.

The coreceptor discoveries may also help researchers understand how some individuals avoid becoming infected with HIV despite repeated exposure to the virus. For example, William Paxton, Koup, and other colleagues at Aaron Diamond have recently been working with a group of these so-called exposed-uninfected (EU) people. In their *Nature* paper, they present evidence that the T cells of some EUs are highly resistant to infection with HIV, possibly because of a genetic defect in their CC-CKR-5 receptors.

Littman notes that "if these people have [dysfunctional] CC-CKR-5 and yet have normal immune systems ... that would be terrific," implying that HIV infection could be combated by blocking the receptor without harming the patient. "In the early stages of the disease you might want something that blocks CC-CKR-5, and later in the disease you might want to block fusin or whatever the pathogenic receptor is at that point," Littman says.

The three teams—as well as other labs—are wasting no time following up on the new findings. The Aaron Diamond group is looking closely at its cohort of EUs to see what genetic defects in coreceptor function might be involved; Berger's team plans to explore how fusin and CC-CKR-5 function on the biochemical level to allow HIV to enter cells; and Littman and his colleagues are using the newly identified coreceptors to develop genetically engineered mice that could serve as a model system for human AIDS pathogenesis. Says Gallo: "We're going through a milestone period in AIDS research."

–Michael Balter