MEETING BRIEFS

AIDS Researchers Negotiate Tricky Slopes of Science

PARK CITY, UTAH—Outdoors, the air was bracing, the powder fine, and the skiing sublime. Indoors, 500 AIDS researchers, fortified with coffee and hot cocoa, discussed and debated the latest research on HIV and SIV, the viruses that cause AIDS in humans and other primates. The recent Keystone meeting* at this well-known ski resort served as a reminder that, like the white mountain slopes, AIDS research has its share of both fast schusses and mogul fields.

Cornucopia of Coreceptors

In 1996, everything seemed clear and simple. After a decade-long search, AIDS researchers had found two elusive "coreceptors," cell surface proteins that HIV uses to dock onto its target cells. The discoveries solved a puzzle posed by earlier experiments, which showed that HIV's primary receptor, known as CD4 and found plentifully on some T lymphocyte immune cells, was not sufficient to unlock the door for viral entry into the cell. The first coreceptor identified, a protein called CXCR4 that normally serves as a receptor for an immune-system molecule called a chemokine, appeared to be used by viruses from patients in later stages of the disease; the second, a chemokine receptor called CCR5, seemed to dominate in early stages of HIV infection.

Pioneer. Ed Berger identified first HIV coreceptor.

These discoveries led to an appealing model for how HIV-infected patients eventually progress to AIDS after years of harboring the virus. "Two years ago you could tell a beautiful story," says Dan Littman of New York University in New York City, a leading coreceptor researcher. Early in infection, mildly virulent viruses use CCR5 as an entry into cells, and these slowly evolve in the body into more highly virulent strains that prefer CXCR4. But as new work presented at Park City emphasized, the picture may not be quite so simple.

Today, more than a dozen coreceptors for HIV and SIV have been identified in the lab, and researchers are engaged in a lively debate about what role these new molecules might be playing in AIDS. Nor is the discussion merely academic: If the virus could easily gain entry to cells using one or more of these other coreceptors, researchers say, earlier hopes of developing drugs to block viral attachment to these molecules might prove more difficult to realize.

In a talk at the meeting, Edward Berger, whose team at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, first identified CXCR4, described his lab's work with two new members of the coreceptor stable—CCR8, which is abundant in the thymus gland, and CX3CR1, which is found in the brain as well as on the surfaces of immune cells called natural killer cells. In laboratory experiments, Berger and his coworkers found that both CCR8 and CX3CR1 could serve as coreceptors for a variety of HIV strains. Berger speculated that these coreceptors might be playing a role in HIV infection in babies and children, whose thymuses are still actively developing, as well as in viral infection of the brain and central nervous system, which occurs in more than a third of HIV-infected patients.

In spite of these laboratory results, researchers are divided over whether coreceptors other than CCR5 and CXCR4 play anything more than a minor role in actual patients. "I don't think there is any reason yet to think these other coreceptors are physiologically important," says molecular biologist Ned Landau at the Aaron Diamond AIDS Research Center in New York City. Landau notes that people with genetic mutations that cause production of defective CCR5 molecules are highly resistant to infection with HIV—implying that the virus cannot easily switch to other, even closely related, receptors, such as CCR3. "This is a natural experiment that tells us CCR5 is central," Landau says.

But some scientists are not so sure. "We don't really know what all these coreceptors mean," says Littman, adding, "I have a feeling it is important." He speculates that the binding of HIV to CCR5, CXCR4, and the other coreceptors might not only enable the virus to enter cells but also trigger signals that affect how easily the virus replicates in its target cells, as well as harm nontarget "bystander" cells. And although "none of us disputes" the key role of CCR5 in initial HIV infection, Littman says, "other receptors expressed on as yet undefined cell populations may hold the key to disease progression."

In spite of the proliferation of coreceptors, Littman, Berger, and others agree that therapeutic strategies to block CCR5, one of the two original coreceptors, are still worth pursuing. "A CCR5 antagonist continues to make sense despite this increasing repertoire," says hematologist James Hoxie of the University of Pennsylvania in Philadelphia. People with CCR5 mutations are not only resistant to HIV infection but seem to have normal immune systems, implying that blocking the receptor would not have serious side effects.

But the effects of blocking CXCR4, presumably the other major coreceptor, might be less benign. Littman and his co-workers created genetically engineered mice in which the gene coding for CXCR4 was deleted. These "knockout" mice did not survive long enough to be born, and their embryos showed serious developmental abnormalities, not only in their immune systems but also in their hearts and central nervous systems. This finding "has a lot of people worried," says Berger—as does recent work by Tadamitsu Kishimoto of Japan's Osaka University Medical School and his colleagues showing that knocking out the gene for SDF-1, the chemokine that naturally binds to CXCR4, causes similar developmental problems in mice.

On the other hand, Berger adds, "it is possible that you absolutely need [CXCR4] during development, but once the fetus is born it doesn't need it anymore." And the 10 March issue of *Current Biology* reported encouraging news: Nikolaus Heveker of the Cochin Institute in Paris, along with French and German colleagues, designed a modified version of SDF-1 that could block HIV bind-

KNOWN CORECEPTORS FOR HIV AND SIV

Coreceptor	Virus(es)	Known ligands
APJ	HIV	Unknown
CCR2b	HIV	MCP-1, -2, -3, -4
CCR3	HIV	Eotaxin, RANTES, MCP-2, -3, -4, -5
CCR5	HIV, SIV	MIP-1α, MIP-1β, RANTES
CCR8	HIV, SIV	I-309
CCR9	HIV	Many chemokines
CX3CR1	HIV	Fractalkine
CXCR4	HIV	SDF-1α, SDF-β
GPR1	SIV	Unknown
GPR15	HIV, SIV	Unknown
STRL33	HIV, SIV	Unknown
US28	HIV	Unknown
V28	HIV	Unknown

SOURCE: CRAIG GERARD *ET AL.*

* HIV Pathogenesis and Treatment, Park City, Utah, 13–19 March.

ing to CXCR4 without interfering with the chemokine's ability to trigger normal signaling through this receptor. So it might be possible to design drugs targeted at CXCR4 that would not have deleterious side effects.

But so far AIDS researchers are far from ready to predict such a happy ending to the coreceptor affair. "Right now there are a lot of observations, and we can ask a lot of questions," says Littman. "But there's no story yet."

Partners in Protection

In most HIV patients the infection appears to be under control for many years before it begins progressing to AIDS. Why they eventually lose control is one of the great riddles of AIDS research. Last fall, immunologist Bruce Walker and his team at Massachusetts General Hospital in Boston, including postdoc Eric Rosenberg, reported what looked like one piece of this puzzle: Patients whose immune systems still harbor CD4 T cells, also known as T helper cells, that specifically recognize HIV proteins seem able to control their infections, while patients who have lost these anti-HIV T helpers cannot (*Science*, 21 November 1997, pp. 1400 and 1447). At the time, Walker speculated that these T helpers keep the virus in check by ganging up with another breed of T cells, called cytotoxic T lymphocytes (CTLs), which home in on and destroy virus-infected cells.

At the Park City meeting, Walker reported new research from his group that seems to support this picture—and might help lift a barricade or two from the obstacle-strewn road to an effective AIDS vaccine. In a cohort of patients who had not yet been treated with antiviral therapy, immunologist Spyros Kalams and other members of Walker's team measured the relationship between virus levels in the blood and CTL and T helper responses against HIV. They found that patients who had strong T helper responses against an HIV protein called p24, which is found in the virus's inner core, had the highest levels of anti-HIV CTLs and the lowest virus concentrations in their blood.

Taking aim. Bruce Walker says one-two punch might knock out HIV.

"[Walker] has made an important contribution in showing the importance of T helpers in maintaining CTL activity," says Jay Berzofsky, an immunologist at the National Cancer Institute in Bethesda, Maryland, who adds that the findings "are right on target in terms of showing an important direction to take in maintaining the immune system of HIV-infected people." The finding that T helpers specific to p24 appear crucial to the CTL response is especially significant, Walker told the meeting, because most efforts at vaccine development have focused on the so-called envelope proteins that make up HIV's outer coat. "If patients respond to internal proteins rather than envelope proteins, that is very important to know," agrees immunologist Rodney Phillips of the University of Oxford.

By testing the HIV-infected patients for T helper responses against synthetic peptides corresponding to small segments of p24, the group homed in on four segments that were most responsible for triggering the immune response. The researchers have now teamed up with the Boston biotech company Peptimmune to see if some of these peptides could form the basis of a vaccine to boost the T helpers and CTLs—either in people already infected with HIV or in people at risk of infection. If T helpers and CTLs can indeed be provoked to gang up on the virus, nobody is going to root for the underdog.

–Michael Balter

ROBOTICS

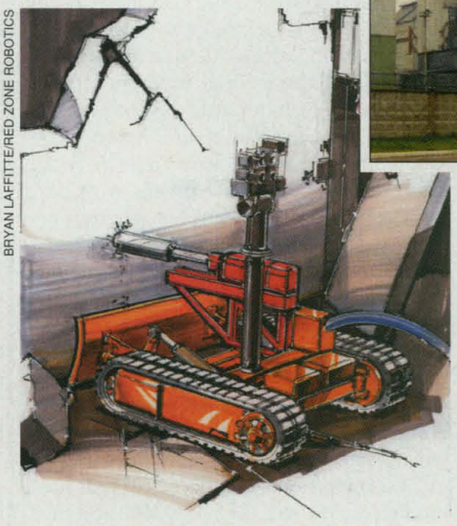
Navigating Chernobyl's Deadly Maze

In a serene forest in northeastern Ukraine is a room as forbidding as the lair of a folktale ogre. The room is in the bowels of the Chernobyl nuclear power plant—the scene of the world's worst nuclear accident when one of its reactors exploded on 26 April 1986. Filled with fiercely radioactive slag and detritus, room 305 has beaten back all comers, human and robot alike.

A new assault on 305 and other chambers in the ruined reactor is planned for this fall, when a U.S.–Ukrainian team will send in a robot fittingly named Pioneer to take samples and measure the environment. The goal of the $2.7 million effort is to map the guts of the damaged reactor building, now covered by a concrete sarcophagus that some experts fear could collapse in a moderate earthquake, sending radioactive dust into the air (*Science*, 19 April 1996, p. 352). Such a map would be invaluable to engineers attempting to stabilize the sarcophagus and prepare it for cleanup before a more sturdy covering can be built after the turn of the century.

But the foray into the sarcophagus may have other payoffs as well for the eight institutions taking part in the project. By testing the robot's ability to withstand radiation and navigate a complex environment, the mapping effort "is going to be a proving ground for many systems that we hope will have use in future planetary and asteroid exploration missions," as well as in nuclear weapons cleanup, says Pioneer project leader Maynard Holliday of Lawrence Livermore National Laboratory in California. "It's a real test and demonstration of the usefulness of robotics in situations where human activity is difficult," adds S. Venkat Shastri, robotics director at SRI International, a private research institute in Palo Alto, California, who is not involved in the project.

R. STONE



BRYAN LAFFITTE/RED ZONE ROBOTICS

Plumbing the depths. New robot will probe the radioactive guts of the Chernobyl sarcophagus *(inset)*, which covers a destroyed nuclear reactor.

After Chernobyl's number 4 reactor exploded, much of its core burned through the floor and into control rooms below. Molten uranium oxide fuel mixed with graphite rods and building materials—metal and concrete—then cooled into an amalgam called corium. Some 190 tons of this highly radioactive mineral is thought to lurk in the damaged building; its distribution has been roughly gauged by plucky Ukrainian physicists who have dashed through the dark, wet sarcophagus—even pausing for perilous seconds in room 305. But engineers need a complete, detailed look at the