

# Chemokines Share Center Stage With Drug Therapies

VANCOUVER, BRITISH COLUMBIA—At the opening ceremony of the 11th International Conference on AIDS, the 14,137 delegates who came to this picturesque port city last week heard a message of optimism, springing from several studies showing that new drug cocktails are making unprecedented headway in combating HIV infections (see box). “Nobody can call AIDS an inevitably fatal, incurable disease any more,” said epidemiologist Peter Piot, head of the United Nations Programme on HIV/AIDS. The delegates also heard several speakers invoke the conference theme of “one world, one hope,” aimed at motivating developed countries to make sure their research advances benefit the less fortunate. They heard AIDS activists decry greed and indifference. They heard about behavioral change dramatically lowering infection rates in Uganda and Thailand. But one of the most significant topics discussed at subsequent sessions of the conference went entirely unmentioned in these



**Chemokine commotion.** Overflow crowds forced delegates into the hallways to hear talks.

opening remarks: chemokines.

Originally identified as pro-inflammatory chemicals made by the immune system, chemokines have become the topic du jour in the AIDS research world. The reason: The chemokines and the receptors through which they exert their effects provide a missing piece to the long-standing puzzle of how HIV infects cells—and how it might be

prevented from doing so. And the fact that chemokines did not even receive a nod at the opening ceremony—but attracted mobs of conferencegoers at sessions where they were discussed—reflects how they are still little appreciated outside of the basic research world, which they have taken by storm.

“This area is exploding,” said immunovirologist Guido Poli of the San Raffaele Scientific Institute in Milan, Italy, who co-chaired a session that involved chemokines. “There’s a chain reaction triggered by an incredible sequence of discoveries.” Yet, as also became clear at the 7 to 12 July meeting, adding to the drama is an intellectual rift between leading researchers about whether the chemokine work will ever bring improved HIV treatments or vaccines.

Interest in chemokines stems from studies of people who do not show evidence of harm from HIV, even 10 years after being infected. In work reported some 7 years ago, virologist Jay Levy of the University of California, San Francisco, discovered that certain white blood cells from these “long-term nonprogressors” (LTNPs) secrete a factor that potentially inhibits HIV replication. But neither Levy nor anyone else could isolate this factor from the cells, known as CD8 cells because of a particular type of receptor they carry. Last December, however, a team led by Robert Gallo of the Institute of Human Virology in Baltimore and Paolo Lusso of the San Raffaele Scientific Institute announced that they had found three factors, all chemokines, that together seemed to do the trick: MIP-1 $\alpha$ , MIP-1 $\beta$ , and RANTES (*Science*, 15 December 1995, p. 1811).

Although Levy argued that this troika does not have the powers of the factor he is hunting for (which he calls CD8<sup>+</sup> cell anti-viral factor, or CAF), chemokines solidified their place in the AIDS research world last month when no fewer than five research groups published evidence in *Science*, *Nature*, and *Cell* that a chemokine receptor also plays a critical role in HIV’s ability to infect cells. These results show that the virus must bind to this receptor, designated cysteine-cysteine chemokine receptor 5 (CCR5), in addition to another previously identified cell surface protein called CD4, in order to enter cells (*Science*, 21 June, p. 1740). This deluge of data also proved that the chemokines Gallo highlighted inhibit HIV infection of cells by blocking CCR5. Despite this evidence, all of which was obtained with cells in lab culture, researchers still disagree about whether the chemokines significantly suppress HIV infections in living patients.

In his talk at the meeting, Gallo made the case that the chemokines are clinically relevant. His argument rested in part on unpublished data from immunologist Daniel Zagury of the Pierre et Marie Curie Univer-

## Shooting for the Moon With Drugs

**Cure.** It’s a word that makes many AIDS researchers cringe. Still, there is one population in which drugs just might be able to eradicate the virus: people who have just become infected.

As revealed at the international AIDS conference held in Vancouver, Canada, last week, several studies are now under way with these so-called acute seroconverters to see whether potent cocktails of drugs can eradicate the virus from their systems. One such study, headed by Martin Markowitz at the Aaron Diamond AIDS Research Center in New York City, has followed eight acute seroconverters taking a triple combination of anti-HIV drugs for 8 to 10 months. To date, all have undetectable levels of virus in their blood, and several are even losing antibodies to HIV. During the next few months, Markowitz and co-workers plan to check for virus in the lymph nodes of these patients and, if they are clean, ask them whether they want to stop the drugs.

Molecular biologist Didier Trono of the Salk Institute for Biological Studies says in such cases, drugs may go beyond clearing the virus: They may provide what he calls “pharmacovaccination.” Trono’s thinking is that before the drugs clear out the virus, the infection may prime the immune system to defeat HIV should it ever invade again. Just such a smoldering infection with an artificially weakened version of SIV, HIV’s simian cousin, has led to the most powerful AIDS vaccine yet seen in monkey experiments (*Science*, 18 December 1992, pp. 1880 and 1938).

There’s a long road to proving this possibility in humans, though. The first step is showing that people can truly clear the virus, which Aaron Diamond director David Ho estimates will require anywhere from 30 to 120 weeks of potent drug treatment. And some researchers caution that even after seeing no evidence of virus for dozens of weeks, the odds are stacked high against a cure. Indeed, at the Vancouver meeting, molecular immunologist Bradford Saget and clinician Steve Scheibel, who share a private practice in San Francisco, reported a sobering case. The patient, whose lymph and blood appeared virus-free after 78 weeks of taking a drug combination, decided to stop the treatment. Within 1 week, high levels of virus could be found in his blood. —J.C.

sity in Paris, which suggest that infected people whose disease is not progressing have higher levels of these chemokines. Other unpublished data from Zagury, showing that hemophiliacs who were infused with infected blood but did not become infected had higher levels of all three chemokines, suggest that high concentrations of the proteins can even prevent infection. Gallo's hope is that this work might lead to the development of inexpensive, synthetic blockers of chemokine receptors that can be used for HIV treatment with "little or no toxicities."

Gallo also is anxious to determine whether vaccines that can increase levels of these chemokines—or down-regulate their receptors—might be protective. Further evidence for this idea comes from Nathaniel Landau and Richard Koup of the Aaron Diamond AIDS Research Center in New York City. These researchers have found that CC CKR5 is defective in a handful of exposed, uninfected people. This suggests that they are resistant to HIV because their receptors are genetically incapable of binding the virus, although that remains to be shown.

For his part, Levy counters that "compelling evidence" argues against the chemokines

being clinically relevant. In direct contrast to Zagury's data, Levy says he finds no correlation between clinical progression and chemokine levels. This point was underscored by immunologist Michael Ascher of the California Department of Health Services, who compared levels of these chemokines in eight LTNP to those in eight rapid progressors and found no difference. Levy did, however, find evidence for high levels of the elusive CAF in 16 of 28 uninfected people who have been repeatedly exposed to HIV by their infected partners. This means, Levy suggests, that CAF might be a better bet for treating or preventing AIDS.

Adding to Levy's skepticism about the chemokines is his firm belief that they differ markedly from the CAF he has been trying to unmask. Levy's test-tube experiments show that CAF inhibits HIV not by blocking the entry of the virus into CD4<sup>+</sup> cells—which is what the chemokines do—but by suppressing the ability of an infected cell to make more virus. Levy, and, separately, Otto Yang and co-workers at Massachusetts General Hospital in Boston, further show that CAF's suppressive powers remain intact even in the presence of antibodies directed against

this trio of chemokines.

The enormous chasm separating the chemokine crowd from the CAF enthusiasts might be bridged if someone could isolate the elusive CAF. "Unfortunately, we can say more about what it isn't than what it is," says Levy, who contends that he has had trouble isolating CAF because it's produced in small amounts. Still, Levy has the strong support of colleagues that his observations are real. "Jay Levy is so correct [about CAF's unique effects] it's ridiculous," says Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases.

The work on chemokines and the immune system's behavior is clearly not as advanced as that on the drug combinations (*Science*, 28 June, pp. 1882, 1884, and 1886). But while HIV drugs will likely go down in history as the stars of the Vancouver conference, for many basic researchers, the meeting will be remembered as a point in time when CD8<sup>+</sup> cells finally got their due. "Before the meeting, someone called me and said, 'Why are you going? It's all over because of anti-retrovirals,'" says Levy. "Well, that hasn't captured the meeting. This is terrific. I'm relieved."

—Jon Cohen

## '97 BUDGET

### Congress Targets Fusion, Favors NIH

Congress delivered a double punch to the U.S. fusion program last week when House and Senate panels voted separately to chop its budget well below the amount researchers agree is necessary to keep even a modest effort on track. The proposed cuts are a significant blow to the fusion community's attempts to maintain U.S. capability in a field increasingly dominated by Europe and Japan.

These votes were part of a flurry of budget activity in Congress, as lawmakers raced to complete as much work as possible on 1997 funding bills before the August recess and the political conventions that will usher in the campaign season. So far, science and technology programs are generally faring better in the Senate, where the Appropriations Committee voted last week to give the National Science Foundation (NSF) an amount close to the Administration's request and restored cuts made by the House in a NASA Earth observation program and a controversial life sciences project that would put monkeys into orbit. Biomedical research also scored a major victory: The House approved a 6.9% increase for the National Institutes of Health (NIH); the Senate is likely to follow suit with a smaller boost.

The big loser in both chambers was fusion. While a Senate panel voted \$240 million for the effort, a House subcommittee

allocated only \$225 million—well below the \$264 million request and the \$244 million budget for 1996. Any cut would come on top of the one-third reduction the program suffered last year. The House bill in particular dismayed Department of Energy officials, for it included language that would force DOE to keep facilities open at the expense of university research. "It's unbearable," says Martha Krebs, director of DOE's energy research. "They clearly want to destroy the program."

A DOE fusion advisory panel in March urged the government to spend at least \$250 million annually on the effort (not counting almost \$8 million for computer costs included in the budget). It said anything less would risk unraveling a program that funds three large facilities, a bevy of researchers scattered around the country, and the U.S. portion of an international effort to design a machine to test fusion on a large scale (*Science*, 22 March, p. 1660). The cuts now being planned by Congress "will make it difficult, if not impossible, to keep the program on track," says Michael Knotek, the Pacific Northwest Laboratory manager who led the review. The advisory panel planned to send a letter to DOE Secretary Hazel O'Leary this week protesting the proposed reductions, he added. But given the lack of political support for the program, House and Senate staffers

said fusion proponents should be thankful that the cuts did not go deeper.

Biomedical research, in contrast, continues to win broad support. The House voted on 12 July to provide a 6.9% increase for NIH, bolster support for extramural grants, and provide \$90 million to start building a new intramural hospital. The House did vote, however, for one provision researchers will find onerous: a ban on government funding of any research on human embryo material, including "spare" embryos likely to be discarded at private clinics. An amendment to lift the ban lost 167 to 256. The House also approved an amendment restricting the use of controlled substances such as marijuana in federal projects. NIH staffers worried last week that this could hurt investigation of some AIDS-therapy studies.

The Senate is expected to begin marking up its version of the bill containing NIH funding on 23 July. But Senator Arlen Specter (R-PA), who chairs the appropriations subcommittee that oversees NIH, says that the increase will be more modest. NIH's good fiscal fortune in the House comes at the expense of other items in the bill—especially education and jobs programs—and White House staffers warn that the president will veto this bill if it doesn't contain more money for social programs. That puts pressure on the Senate to limit NIH's windfall.

NASA also got some good news last week. The Senate Appropriations Committee voted