best one he's made in 25 years. "This is the first time we've had anything that worked," says Morton. "That's why we're so excited." As Morton reported last year in the *Annals of Surgery*, 26% of the vaccinated patients with late-stage disease survived for 5 years, as opposed to 6% of the historical controls.

Such claims of cancer vaccine efficacy, however, should be taken with a large chunk of salt, cautions oncologist Charles Moertel of the Mayo Clinic. "You can prove anything with selective controls," says Moertel, adding that he has yet to see any evidence from a properly controlled study that a cancer vaccine has had even the modest benefits that Morton reported (Morton hopes to launch a controlled trial in the next year to prove the vaccine's worth). "Cancer vaccines are highly experimental," adds Philip Greenberg, a tumor immunologist at the University of Washington and Seattle's Hutchinson Cancer Research Center. "Patients should not assume that there's a cancer vaccine that's effective and that they should abandon chemotherapy."

But even Greenberg's skepticism has its limits: He too has begun to work on engineering cancer vaccines, because he says science finally has the tools to build on successes logically—and learn from failures.

The clinical trials of old-style vaccines that are now under way should determine their merits—or lack of same—once and for all. But even if those vaccines fail to extend people's lives, the engineered therapies are entering trials right on their heels, and that is sure to attract continued interest from both basic researchers and industry—and to push the cancer vaccine field ever further from the days when all its practitioners could sit comfortably around a single table.

–Jon Cohen

AIDS RESEARCH

Skepticism Greets HIV Coreceptor

Few scientific discoveries stimulate a media feeding frenzy faster than those dealing with the AIDS virus—especially when there are hints that the new finding could lead to better treatments for the dread disease. And so it wasn't surprising that when Pasteur Institute biochemist Ara Hovanessian told a Paris press conference on October 25 that his team had found the long-sought "second receptor" that HIV uses to enter and infect cells, the news made headlines in some of the biggest newspapers on both sides of the Atlantic: *Le Monde* and *The New York Times*, among others.

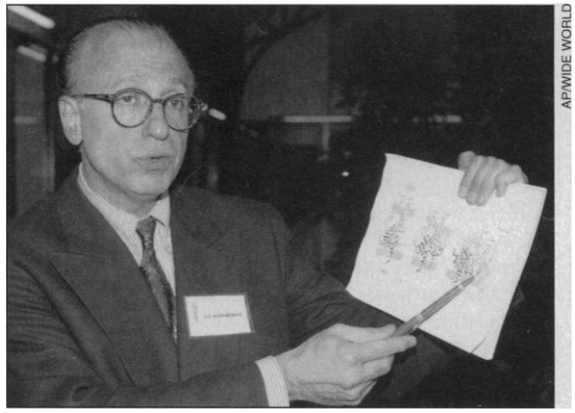
There would be good reason to be excited—if Hovanessian turns out to be right. If the molecule the Pasteur workers are studying, a cell surface protein known as CD26, does help HIV enter cells, CD26 could be an important new target for drugs aimed at halting the spread of HIV in the body. But when Hovanessian presented his results in more detail the day after the press conference at an invitation-only meeting of more than 300 AIDS experts in the Paris suburb of Marnes-la-Coquette,* they met with far more skepticism than was apparent from the accounts in the lay press. Many attendees expressed doubt that CD26 is in fact an HIV coreceptor. "I am surprised that a major announcement like this was made on such flimsy data," commented John Moore, an expert in HIV receptors who works at the Aaron Diamond AIDS Research Center in New York. "He has a lot of work to do to convince us that what he has got is real."

Some of the criticism, however, was directed at the media hype as much as it was at the research, and Hovanessian and his collaborators, Bernard Krust, Etienne Jacotot and Christian Callebaut, were defended by a variety of researchers, among them their mentor at the Pasteur Institute, Luc Montagnier. "I think they have found the second receptor," Montagnier told *Science*, adding that "the importance of this discovery is equal to the identification of the first receptor."

The "first receptor" is the cell surface glycoprotein called CD4. In 1984, researchers in France and the United Kingdom began accumulating evidence that HIV uses CD4 as a receptor for entering cells. But over the past several years, scientists studying the interaction between HIV and its host cells have found evidence indicating that CD4, while necessary, is not sufficient for HIV entry. For example, when mouse cells in culture are genetically engineered to produce human CD4 on their surfaces, HIV is able to bind to the cells but not actually enter them. This and other results suggested that the "second receptor" Montagnier referred to is also needed, although no one could come up with a convincing candidate.

Hovanessian first turned his attention to CD26 as the possible coreceptor more than a year ago. He thought it might be involved, he said, because the cell surface molecule, which is a protein-splitting enzyme, cleaves its targets at certain short amino acid sequences found in the "V3 loop" of gp120, an HIV coat protein that interacts with CD4. Those sequences are found in virtually all isolates of HIV-1 and the related viruses HIV-2 and SIV, and such a high degree of conservation usually means the sequences have an essential function."We thought that the V3 loop might play an important role [in virus penetration into cells] by interacting with CD26," Hovanessian said.

To test that idea, Hovanessian and his coworkers performed several experiments. They showed that a potent inhibitor of CD26's enzymatic activity could block HIV infection of cells; monoclonal antibodies directed against CD26 had a similar effect. Another key piece of evidence came from a series of transfection experiments in which the group introduced either the human CD4 gene or the human CD26 gene, or both, into mouse cells, which ordinarily can't be infected by HIV. The result: The virus entered and reproduced only in mouse cells expressing both human CD4 and human CD26 on their surfaces.



Point of interest. Pasteur researcher Ara Hovanessian describes his model for CD26's role in HIV infection.

That would seem to be powerful evidence, but in the discussion session after the paper was presented at the scientific meeting, and in subsequent conversations with *Science*, a number of scientists were critical. Some of the negative reaction was clearly fueled by annoyance at the advance publicity Hovanessian's finding received even before it was presented at a meeting—let alone published in a peer-reviewed journal. (The manuscript has been submitted to *Science* and is under review, but this article is based solely on discussions at the meeting.) "We don't need all this hype. If we do good science, some day we might be able to help people infected with HIV. But by playing to the press, you actually obscure things," said molecular biologist Simon Wain-Hobson, also of the Pasteur Institute. Pasteur officials insist they never intended to announce

*The Eighth Colloquium of the "Cent Gardes" was held from 25 to 27 October.

Hovanessian's results before his presentation, and did so only after they learned that the story had leaked out to the French press.

But in addition to irritation over advance publicity, many researchers were concerned that Hovanessian's experiments, particularly those involving the gene transfers into mouse cells, were technically flawed. Joseph Sodroski of the Dana-Farber Cancer Institute in Boston pointed out that the mouse cells only expressed CD4 and CD26 temporarily, making a clear comparison between infected cells and controls more difficult. "It would have been more convincing if he had used stable cell lines," said Sodroski. Pasteur Institute virologist Marc Girard, among others, commented that the use of a transient system, requiring virus production to be measured over a very short period of time, cast doubt on Hovanessian's assay for measuring virus production. "That's the biggest criticism," Girard said, "whether he is sure the virus he sees has been replicated inside the cell and is not just the virus put into the cell culture."

Montagnier rejects these arguments. "He didn't describe all the details [in his talk]," Montagnier told *Science*, "but he used a virus with a very high replication rate"—which would make it easier to detect significant virus reproduction in a short time. Hovanessian himself, who was taken aback by the intense criticism, said that even if there were problems with the transfection experiments, "all the other results are still there."

And in spite of the criticism from AIDS researchers, investigators whose own work focuses more closely on CD26 think that the molecule is at least a "strong candidate" to be an HIV receptor, as Chikao Morimoto of the Dana-Farber Cancer Institute put it. "And even if it isn't a second receptor," he adds, "it still may be involved in certain aspects of HIV infection." One line of evidence in favor of this idea comes from recent studies by groups in Belgium and Spain, which indicate that CD26-expressing T cells might be particularly susceptible to destruction by HIV, since their number begins to decline before the subsequent fall in CD4 cells classically associated with the later stages of AIDS. "There must be some relation," between the presence of CD26 and the immune cell destruction, said Ingrid De Meester of the University of Antwerp in Belgium, who was involved in some of these studies. "There is a very notable decrease in these cells."

But despite these hints at a possible role for CD26 in AIDS pathogenesis, some researchers remain quite skeptical that Hovanessian's results have closed the case on the coreceptor. "We've been looking for the second receptor for 7 years," says Aaron Diamond's Moore. "And we'll carry on looking."

–Michael Balter

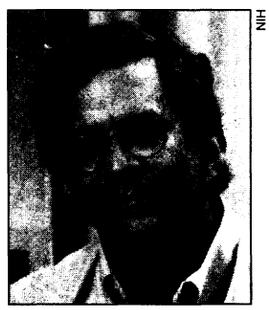
Michael Balter is a science journalist based in Paris.

IMMUNOLOGY

New Protein Steals the Show As 'Costimulator' of T Cells

Over the past few years, the cell surface protein known as B7 garnered some of the best reviews in all of immunology. The reason: a great deal of evidence indicated that this protein transmits a signal needed for immune cell activation, leading many researchers to believe that it holds the key to preventing everything from cancer to autoimmunity to graft rejection. But a flurry of papers, including three in this issue of *Science* and one in the 4 November *Nature*, suggests that B7 may actually be a supporting actor rather than the lead in this crucial immune-system scenario. The current work indicates that the true star of the show is a newly discovered protein called B7-2.

DANA-FARBER



NIH

B7-2's finders. Gordon Freeman *(top)* and Richard Hodes.

You might expect immunologists to be dismayed by this last-minute play doctoring. Instead, many immunologists are excited. "It's enriching our knowledge," says Yale University's Charles Janeway Jr. The University of Minnesota's Marc Jenkins, who is also studying T cell activation, agrees: "One of the partners in this dance has changed and that's highly significant." And oncologist Lee Nadler of Boston's Dana-Farber Cancer Institute, whose lab has two of the papers in this issue, expects that the findings may soon be applied in the clinic, possibly leading to better treatments for cancer and transplant rejection.

The original B7-1 storyline was proposed 3 years ago, when it was discovered that two signals are required to activate the immune system's T cells and set in motion the chain of events that generates the immune warriors that rid the body of invaders. One signal is transmitted by the foreign antigen itself, which must be "presented" to the responding T cell on the surface of another cell. But in addition to this first, specific signal, the antigen-presenting cell (APC) sends a second, nonspecific signal to the T cell. And this "costimulatory" signal was thought to be transmitted solely by an interaction between the original B7, which is present on the surface of APCs, and its receptor on T cells, a molecule known as CD28.

This was a neat little story, but it didn't have enough characters to really drive the plot home. Several groups found in mouse experiments, for example, that antibodies against the original B7, now known as B7-1, did a poor job of blocking the costimulatory signal. Nadler, Gordon Freeman and co-workers, in collaboration with Arlene Sharpe's lab at Brigham and Women's Hospital, performed an even more definitive experiment. As reported on page 907, they created a new mouse strain without the B7-1 gene. If B7-1 was solely responsible for the costimulatory signal, activation of the animals' T cells should have been impossible. Instead, the researchers found that activation was present—at about 30% of normal—implying that some other molecule can also transmit the signal.

The knockout mice also provided a major lead for identifying that other actor. CD28 has a cousin on the T cell surface known as CTLA-4, which binds B7-1 even better than CD28. When the Boston team gave the knockouts a soluble form of CTLA-4, CTLA4-Ig (developed by Peter Linsley and co-workers at Bristol-Myers Squibb), they found to their surprise that APCs from the knockouts bound CTLA4-Ig as strongly as APCs from mice with intact B7-1. Whatever was binding the CTLA4-Ig, they reasoned, likely was transmitting the costimulatory signal in the knockouts.

The researchers then went on to use CTLA4-Ig as a lure to fish for complementary DNAs (cDNAs) that make the putative

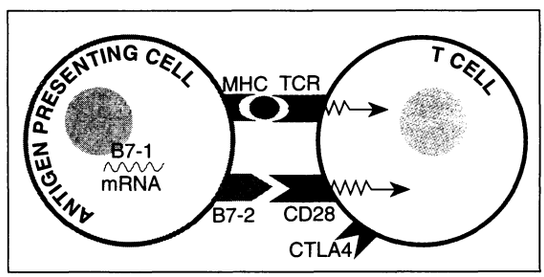


ILLUSTRATION: K. SUTLIFF

Getting together. The new model for T cell activation has B7-2 replacing B7-1.