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.

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

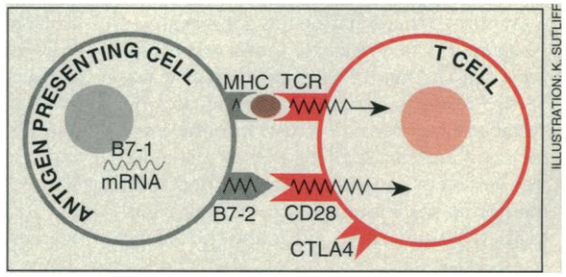
You might expect immunologists to be dismayed by this last-minute play doctoring. Instead, many immunologists are excited. "It's enriching our knowledge," says Yale University's Charles Janeway Jr. The University of Minnesota's Marc Jenkins, who is also studying T cell activation, agrees: "One of the 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



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

costimulatory molecule. To the Nadler group's delight, their fishing expedition was a success. In work described on page 909, they caught the cDNA for B7-2, which is 26% identical to B7-1. They then genetically engineered B7-2 into cells that do not normally send a costimulatory signal to show that it could perform that function.

The Boston group wasn't the only one hot on the B7-2 trail. Over at the National Institutes of Health, Richard Hodes and his colleagues were making monoclonal antibodies to activated mouse B cells, one type of cell that can present antigen to T cells. Sifting through these monoclonals, they found one that blocked T-cell activation, but did not bind B7-1. They then used this antibody to immunoprecipitate and characterize murine B7-2 (see p. 905).

The two groups now had evidence that B7-2, as well as B7-1, can costimulate T cells. But they couldn't tell which of the two molecules really was the star and which was the supporting actor. So the Nadler group looked at the times when B7-1 and B7-2 appeared on an active APC's surface. B7-1 didn't pop up until 24 to 48 hours after an APC sent its first signal to a T cell. This seemed too long, because many studies have shown that unless a T cell receives the costimulatory signal within 24 hours of the first, it will breed a population of cells that cannot respond to the specific antigen. In contrast, they found that messenger RNA for B7-2 was present in unstimulated APCs, suggesting that B7-2 could appear almost immediately after receiving the first signal. The researchers concluded from this that B7-2 deserved top billing as the molecule that sends the primary costimulatory signal.

Still more proof of B7-2's drawing power is reported in this week's *Nature*. Lewis Lanier's lab at Palo Alto's DNAX Research Institute has cloned a human B7-2 (called B-70). Lanier says his molecule is expressed all the time on the APCs called monocytes, indicating that it can provide a signal immediately.

The discovery of B7-2 could ultimately have important clinical implications. One possibility is that, as with CTLA4-Ig, antibodies to B7-2 might suppress transplant rejection by teaching cells to ignore foreign tissues that they would otherwise savage (*Science*, 7 August 1992, p. 751). Cancer is another target—because tumor cells often lack B7-1, perhaps creating a state that allows them to dodge immune attack. Mouse experiments have shown that tumor cells engineered to make B7-1 can potently stimulate anti-tumor immunity (*Science* , 15 January, p. 310 and 368). B7-2 might trigger an even stronger response. But right now, the only certainty is this: The B7 drama will continue to surprise.

–Jon Cohen

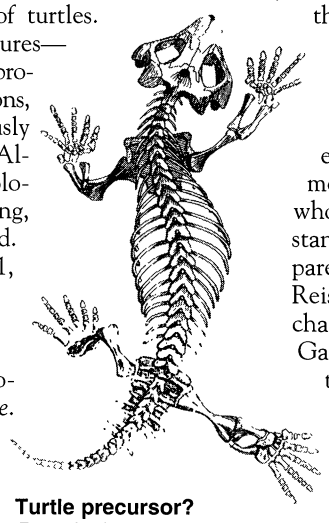
MEETING BRIEFS

Paleontologists Examine Old Bones and New Interpretations

The 53rd annual meeting of the Society of Vertebrate Paleontology took place in Albuquerque, New Mexico, from 13 to 16 October. As always in paleontology, many of the talks related to family matters—among them the search for the ancestors of living animals, and how to tell whether a *T. Rex* is a boy or a girl.

Turning Turtle

For most of this century, turtles have been paleontological orphans, the only living higher vertebrates whose lineage couldn't be traced all the way back to the earliest reptiles. Recently, however, turtles, like the winner of a lottery, have begun to find they have many relatives. In the past 3 years, two researchers have come up with two different groups of 250-million-year-old animals as candidates for the ancestors of turtles. Each group of four-legged creatures—one called pareiasaurs, the other procolophonids—has its champions, and the debate had previously seemed deadlocked. But at the Albuquerque meeting the procolophonids appeared to be crawling, slowly but steadily, into the lead.



Turtle precursor? *Procolophon*, a 250-million year-old animal, may be the closest thing to a turtle.

The debate began in 1991, when Robert Reisz and Michel Laurin, paleontologists at the University of Toronto, presented a case for the procolophonid connection in *Nature*. Michael Lee of the University of Cambridge presented the other side 2 months ago in the 24 September *Science*. The skeletal characteristics Reisz interpreted as exclusive to turtles and procolophonids, Lee argued, were actually widely shared among early reptiles. As a result, they can't be used to draw an especially close connection between any two groups. Lee identified 25 other features of turtles' skull, palate, and forelimbs and digits—among other parts of the anatomy—that, he said, resemble features found in pareiasaurs more than they resemble features of other early reptile groups. He also contended that the bony plates, called osteoderms, that sheathed pareiasaurs were the precursors of the armored shell seen even in the earliest turtles, which appeared 200 million years ago.

In Albuquerque, however, Reisz gave his case an even harder shell. Based on new examinations of procolophonid and pareiasaur specimens from Russia and South Africa, as well as other types of ancient reptiles, he listed a suite of other features that link turtles and procolophonids, including elements of the shoulder and upper limb bones, the shape of the stapes (a bone in the middle ear), as well as the shape of the lower jaw and its attachment point to the skull.

Many other paleontologists at the meeting found his ideas convincing. "Reisz's arguments are more sophisticated and better tested," says turtle expert Eugene Gaffney of the American Museum of Natural History. But these family disputes, ultimately resting on judgment calls about resemblances in skeletons, always have an element of subjectivity, and Lee, who wasn't at the meeting, stands by his 25 links between pareiasaurs and turtles. He says Reisz must "ferret out a lot more characters" to carry the day. But Gaffney thinks Reisz's characters are more specific and less open to variable interpretation than many of those used by Lee. "Some of Lee's characters are things like 'the basicranium [bottom of the skull] is thick.' What do you do with that?" he asks. In addition, paleontologist Kraig Derstler of the University of New Orleans points out that the dermal armor Lee cites looks quite different from turtle shells.

One important point of agreement in this dispute is that both ancestor candidates belong to an obscure group called "parareptiles." Previously thought to have died out 200 million years ago, their turtle relatives are now seen to be still crawling the earth.

Out of the Cold

In recent years, the Arctic has been a rich hunting ground for dinosaur fossils. Now the action is shifting to the south as the Antarctic gets a turn. At the meeting, paleontolo-