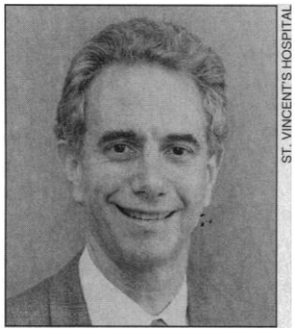
Cancer Vaccines Get a Shot in the Arm

New genetically engineered compounds designed to combat human tumors are bringing respect to a maligned field. But older vaccines may deliver the goods first

Twenty years ago, says Michael Mastrangelo, everyone working on vaccines as a way to treat cancer could have fit around his dining room table. And outside that tiny clan, recalls Mastrangelo, an oncologist at Jefferson Medical College, it was not easy to be taken seriously. "People working on cancer vaccines for all of the '70s were not very well thought of," he says. The idea that an injection of a vaccine made from a tumor could keep the disease at bay was assumed by mainstream cancer researchers to be rather farfetched. "The cancer vaccine business was black magic," Mastrangelo says.



ST. VINCENT'S HOSPITAL

Antigen stew. Mark Wallack will soon get results from the first large, well-controlled trial of a "crude" cancer vaccine.

Today the dining room table has given way to packed conference halls, where cancer vaccine developers elbow for space alongside representatives from biotechnology companies, as several hundred such developers did in San Francisco from 30 September to 2 October for the First International Conference on Engineered Vaccines for Cancer and AIDS. "This is *the* technology of the '90s," says conference organizer Lynn Spitler, who recently launched Jenner Technologies, a vaccine company devoted to cloned tumor antigens.

The surge of interest is based on advances in genetic engineering and immunology, which offer developers new powers to direct immunologic assaults precisely against obstinate tumor cells. Unlike the earlier vaccines, whose mode of action against tumors couldn't be precisely defined, these rationally designed therapeutic vaccines attempt to provoke highly specific immune reactions. Though it's much too soon to say how effective or safe these approaches are for people, initial animal data are encouraging, as are early results from human trials.

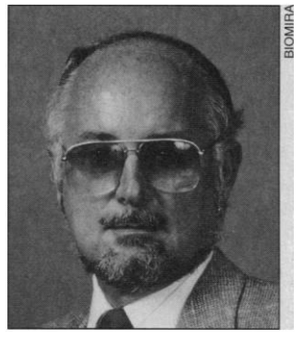
Yet the field still faces some hurdles. The low-tech vaccines haven't gone away, and some have also shown promise clinically, but the veteran vaccine makers are worried about being shoved to the side by regulatory agencies and biotech companies solely interested in newer technology. In addition, there is still a lingering distrust of vaccines in the research community, and it will take a lot more than "promising leads" before cancer vaccines take a place in the therapeutic arsenal.

The current limitations of that arsenal, however, are driving the new push for cancer vaccines. "[Cancer vaccines] are the types of things we ought to be trying because certainly, surgery, chemotherapies, and radiotherapies have not led to striking advances over the past 10 years," says Daniel Ihde, deputy director of the National Cancer Institute (NCI).

Making it a science

That isn't the only reason the field looks attractive now. Another is that, in the past 5 years, biotechnology has begun to reshape it. Before then, most cancer vaccines were made from crude preparations of whole tumor cells spiced with immune-stimulating chemicals known as adjuvants; some vaccines attempted to further grab the immune system's attention by adding harmless pieces of viruses or bacteria. The hypothesis was that tumor cells have antigens, characteristic proteins on their surfaces, that the immune system can recognize as foreign and eliminate. By presenting these antigens in an immunogenic stew, the early cancer vaccines attempted to teach the immune system how to attack tumors more vigorously (*Science*, 25 August 1989, p. 813).

Several of these vaccines moved forward in trials, yet even the best results only showed benefits for about 25% of treated patients. Even then, the trials were loosely controlled —leading to the skepticism that has been the field's hallmark.



BIOMIRA

Antigens à la carte. Biomira's Michael Longenecker is developing a cloned antigen vaccine.

But today, says Jeffrey Schlom, chief of NCI's Laboratory of Tumor Immunology and Biology, researchers have a much finer understanding of cancer immunology. For example, 2 years ago, Thierry Boon and colleagues at Belgium's Ludwig Institute for Cancer Research identified the first gene family, *MAGE*, that codes for antigens found on melanoma cells and nowhere else in the body. "Now it's a matter of making a science out of this and making the immune system work for you," says Schlom. "The key is finding the right antigens and using some tricks to turn it on."

That sounds simple enough, but there's a hot debate among cancer vaccine makers about which of the two arms of the immune system to turn on for the best results—the one that relies on T lymphocytes, which directly or indirectly kill tumor cells, or the one that banks on antibodies to block and inhibit metastasis. Schlom's work leads him to believe that, for fighting tumors, T lymphocytes are the goal. In mouse experiments with vaccines made from carcinoembryonic antigen (CEA)—which often is found on colorectal, gastric, pancreatic, and breast tumors—Schlom has found that antibody strategies against CEA pale next to ones that elicit the lymphocytes. "The odds are 10 to 1" that the cell-killing arm of the immune system is more important than antibodies, he says. Schlom now is testing a vaccine in humans that has the CEA gene stitched into vaccinia virus, the smallpox vaccine.

NCI's Steven Rosenberg also has put his chips on the cell-killing arm of the immune system. Rosenberg has been testing a gene-therapy vaccine on five cancer patients made from their tumor cells that have been engineered to contain genes for either interferon or interleukin-2. These immune system messengers can both boost the cell-mediated immune response.

While most researchers share Schlom and Rosenberg's faith in cell-mediated immunity, a substantial number of scientists are genetically engineering vaccines that primarily produce an antibody response. A leading proponent of this strategy is Philip Livingston of the Memorial Sloan-Kettering Cancer Center, who maintains that antibodies are a potent weapon. Livingston has been testing vaccines that contain the ganglioside antigens GM2, GD2, and GD3. Found on the surfaces of many melanoma cells, gangliosides are carbohydrates that stimulate antibody production. "If you get high titers [of antibodies], you almost sterilize the blood so it's very difficult to get new metastases," suggests Livingston, who has been making cancer vaccines for 18 years.

Another sect of antibody acolytes is testing carbohydrates derived from mucin molecules, which are found on the surface of carcinoma cells. Pioneered by oncologist Georg Springer of the Chicago Medical School, these mucin-antigen cancer vaccines are now being developed by Michael Longenecker and co-workers at Canada's Biomira Inc. After showing that a mucin-antigen vaccine triggers a strong antibody response, inhibiting tumor growth and prolonging survival in mice, Biomira began testing a few different formulations in patients with ovarian and breast cancer. Their current vaccine contains sialyl-Tn antigen, a mucin derivative that is associated with poor prognosis in four different carcinomas. The vaccine is in human trials in Canada, England, and the United States.

While these vaccines all use antigens to prompt antibody production, some companies are attempting to fashion cancer vaccines directly from antibodies. Idec Pharmaceuticals in San Diego is testing an anti-idiotype vaccine, which contains a synthetic antibody that looks like a melanoma-associated antigen.

One of the most ambitious high-tech approaches under way is to turn both arms of the immune system on high by shining a spotlight on tumor cells with B7, a molecule on the surface of immune cells that helps launch an immune system attack. Several groups, including longtime cancer vaccine developers Ingegerd and Karl Erik Hellstrom at Bristol-Myers Squibb, are now exploring the effects of transfecting B7 into mouse tumor cells (*Science*, this issue, p. 844; see also 15 January, p. 310).

Ready for prime time?

The dazzle of new technological possibilities, however, isn't completely blinding vaccine researchers to the utility of cruder preparations. With genetically engineered vaccines, "you have to gamble that the antigen you pick is the right one," says Jean-Claude Bystryn, a New York University (NYU) researcher who has been working on cancer vaccines for 15 years. "If you take the crude approach, the right antigens are in there." The University of Southern California's Malcolm Mitchell, another cancer vaccine veteran, offers similar caveats. "If you start from the point of view that you want absolutely pure material, you could spend a lifetime trying to find out what works," he says. (Mitchell's own vaccine, which is made from melanoma cell lines, is being developed by Montana's Ribi ImmunoChem Research Inc.)

One crude vaccine-maker will find out what works in much sooner than a lifetime. Mark Wallack of St. Vincent's Hospital in New York plans to unblind the data in the next few months from a placebo-controlled, 2-year trial of a vaccine made from melanoma cells lysed by vaccinia virus. This promises to be the first data from a widescale controlled trial of a cancer vaccine, and positive results from earlier tests have raised hopes for this preparation. Wallack, for one, is already thinking about ways to scale up production of a crude preparation and retain a given potency; many researchers feel this is a major obstacle to the usefulness of crude vaccines as it will be difficult to produce consistently the same product from a cell line or whole tumor. "We feel we can do it, but it may take the Food and Drug Administration years to approve it," says Wallack.

Some investigators think that the opposition between new and old approaches is illusory—that the best solution will be one that combines elements of both ways of protecting patients from their own tumors. One such combination is being tried by Donald Morton of the John Wayne Cancer Institute in Santa Monica, California. Morton selected melanoma cell lines for a vaccine based on their expression of the gangliosides and known protein antigens. He says this vaccine is the

HUMAN CANCER VACCINES ON TRIAL

	Vaccine	Developer	Cancer	Trial Status
1.	GM2 with KLH carrier and QS-21 adjuvant	Phillip Livingston, Sloan Kettering	Melanoma	Phase 3 planned
2.	Cloned antigen, Jen CRG	Jenner Technologies	Colorectal and lung	Phase 1 planned for 1994
3.	Two proteoglycan anti-idiotypes, Syntex' SAF adjuvant	Idec Pharmaceuticals Corp.	Melanoma	Ongoing Phase 1/2, Phase 3 planned for late 1994
4.	CEA in vaccinia virus	Jeffrey Schlom, National Cancer Institute	Colorectal, gastric, pancreatic, and breast	Phase 1 under way
5.	Sialyl-Tn with KLH carrier, in Ribi's DETOX adjuvant	Biomira Inc.	Breast, ovarian, colon, and pancreatic	Phase 2 at 6 sites, Phase 3 planned for early 1995
6.	Synthetic peptides of immunoglobulin epitope from B cell malignancies	Thomas Kipps, University of California, San Diego	Clinical lymphocytic leukemia	Phase 1 under way
7.	Polyvalent lysate of melanoma cell lines, DETOX adjuvant	Malcolm Mitchell, USC and Ribi ImmunoChem Research Inc.	Melanoma	Ongoing national Phase 3 trial with 140 patients
8.	Multiple antigens shed from 4 melanoma cell lines, alum adjuvant	Jean-Claude Bystryn, NYU and MedVac	Melanoma	Accruing 200 patients for Phase 3 trial
9.	Plasma membrane from melanoma cell lines coated on Large Multivalent Immunogen	LIDAK Pharmaceuticals	Melanoma	Phase 1 planned for early 1994
10.	Autologous colon tumor cells with BCG as nonspecific stimulant	Michael Hanna, Organon–Teknika	Colon	3 ongoing Phase 3 trials with more than 500 patients
11.	Irradiated melanoma cell lines screened for specific antigens	Donald Morton, John Wayne Cancer Institute	Melanoma	Phase 3 planned in 1994
12.	Vaccinia viral lystates of melanoma cell lines	Mark Wallack, St. Vincent's Hospital	Melanoma	Phase 3 trial being unblinded
13.	Vaccinia viral lysates of melanoma cell lines	Peter Hersey, Royal Newcastle Hospital	Melanoma	Ongoing Phase 3

☐ **Purified antigen vaccines** ☐ **"Crude" vaccines**

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.

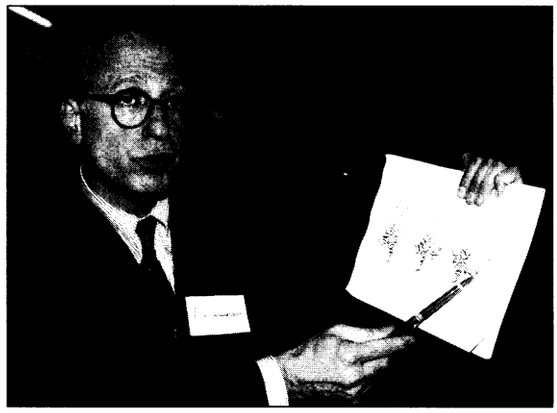
There would be good reason to be excited—if Hovanessian turns out to be right. If the molecule the Pasteur workers are studying, a cell surface protein known as CD26, does help HIV enter cells, CD26 could be an important new target for drugs aimed at halting the spread of HIV in the body. But when Hovanessian 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.



AP/WIDE WORLD

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.