Cancer Vaccines Show Promise at Last

In early clinical trials, tumor cell vaccines appear able to help cancer patients fight off metastases by stimulating immune responses to the patients' tumors

BY RIGHTS, MALCOLM MITCHELL'S patient should be dead by now. She had arrived at the University of Southern California School of Medicine in the spring of 1986 with an advanced case of melanoma, a very malignant form of skin cancer. The original tumor had been removed, but now the cancer had returned with a vengeance. "She had extensive disease on her right buttock and maybe hundreds of tumor nodules extending down her leg," Mitchell recalls. The melanoma had also spread to her left lung.

But the woman is alive today—more than 3 years after receiving injections of an experimental melanoma vaccine developed by Mitchell and his colleagues.

Even the USC researcher was astounded by the response of his patient, only the seventh or eighth he had treated with the new vaccine. "Her husband began to notice improvement in her lesions within a week," he says. "But I couldn't believe that those things would begin disappearing that soon." By the third week, however, it was apparent that the husband was correct. And by the seventh week, the tumors were gone, although the remains of the largest had to be removed surgically.

Mitchell's patient may be a harbinger of a dramatic turnaround in the fortunes of a line of cancer research that until now has resulted in a frustrating series of failures. Scientists have been trying for more than two decades to find therapies for cancer that employ the body's own immune system. The rationale for their efforts is simple enough. A great deal of evidence has suggested that the immune system is capable of recognizing cancer cells and suppressing their growth—although all too often it fails at this task.

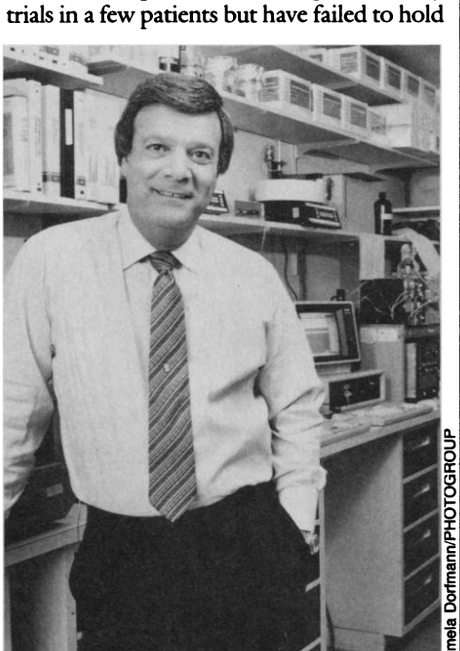
As Jean-Claude Bystryn of New York University Medical Center points out, "The growth of a malignant cancer depends not just on the cancer itself, but on the body's response to it." If a patient's immune responses could be bolstered, researchers hypothesized, then he or she might be able to fight off the cancer. Unfortunately, this has proved to be much easier said than done.

But that may all be changing. Mitchell's group is one of several that are beginning to see signs of success in their efforts to develop immune therapies against such previously intractable malignancies as melanoma and colon and kidney cancer.

The old therapies focused on nonspecific stimulators of the immune system, including bacteria such as Bacillus Calmette-Guerin (BCG) and, more recently, the interferons and interleukins. The new therapies are different: they use tumor cells—often prepared from the patient's own cancer—to elicit specific immune responses to the particular tumor from which the patient suffers.

The vaccine therapies also differ from the immune therapy pioneered by Steven Rosenberg of the National Cancer Institute, which uses activated lymphocytes to attack tumor cells and has also been producing encouraging results (*Science*, 23 June, p. 1430).

The clinical trials performed so far with the tumor cell vaccines have indicated that they are safe and may be effective in some circumstances, although the investigators are understandably cautious about their results in view of the poor previous track record of immunotherapy. Other potential immunotherapies have looked good in early trials in a few patients but have failed to hold up when tested more rigorously.



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Patient pioneer. *After 20 years, Michael Hanna is getting some encouraging results.*

One of the most advanced of the new vaccines was developed by Michael Hanna of Organon-Teknika's Bionetics Research Institute in Rockville, Maryland, and his colleagues. A just completed clinical trial that was headed by Herbert C. Hoover of Massachusetts General Hospital assessed the ability of the vaccine to prevent the development of metastases in patients who have undergone surgery for colon or rectal cancer but are at high risk of relapsing. "There was a greater than 50% reduction in recurrences," Hanna says. "I think that is very dramatic. We're very excited about it."

As a long time veteran of the immunotherapy campaigns, Hanna has particular reason to be excited. He began laying the foundation for the colon cancer vaccine more than 20 years ago when he was at Oak Ridge National Laboratory.

Hanna, like most of the researchers studying tumor cell vaccines, credits his current progress largely to information gleaned from studies of immunotherapy in an animal cancer model. In Hanna's case, it was work with guinea pigs, originally begun by the late Herbert Rapp of the National Cancer Institute, that set him on his present course.

In the early 1970s, Rapp, Hanna, and their colleagues discovered that BCG injections could induce the guinea pigs' tumors to regress. At the time, this finding achieved a certain amount of notoriety when some overzealous news reports hailed BCG as a "cancer cure." It wasn't. But Hanna made an observation that was eventually to prove very helpful.

He found that under appropriate conditions, the BCG cells could interact with the tumor cells in eliciting an immune attack directed against the guinea pig tumors, causing their regression. Hanna based his colon cancer vaccine on this observation. It consists of the patient's own tumor cells, which are irradiated to stop them from growing, mixed with BCG.

This vaccine will elicit an immune response to colon cancer cells, Hanna says, delaying or preventing colon cancer metastases. Moreover, it does this with minimal side effects, especially when compared to radiation and most chemotherapeutic re-

gimes. The main problem is the development of ulcer-like sores at the vaccine injection sites in the groin, although these heal. "I'm now of the frame of mind that you can treat cancer patients without knocking their socks off," Hanna says.

Although the vaccine seems to prevent metastases, not enough time has elapsed since the study began to establish whether it improves 5-year survival rates, the "gold standard" for a successful cancer therapy. It looks as if it may, Hanna says, but that cannot be confirmed yet. Meanwhile, a larger trial, conducted under the auspices of the Eastern Cooperative Oncology Group, is under way. Its results, which are not expected for another 5 to 6 years, should give a better idea of the vaccine's effectiveness in saving lives.

Researchers generally intend for their vaccines to be given to patients early in cancer therapy, usually just after their original surgery, to prevent metastases. Animal studies indicate that the vaccines will work best at this time, when the tumor burden is low.

For ethical reasons, however, unproven cancer therapies are usually tested first in patients with advanced disease—people who have nothing to lose but might gain something if the treatment works. So far, for example, Mitchell has tested his vaccine only in patients with metastatic melanoma.

Even so, he has been pleased with the results. About one-quarter responded with complete or partial remissions. "We're talking about billions of tumor cells going away. I didn't expect that," Mitchell says. He is currently setting up a large cooperative study to find out whether the vaccine can prevent metastases from developing.

Mitchell's response rate compares favorably with that being obtained by the NCI's Rosenberg, who has seen remissions in about 20% of the advanced cancer patients he has treated with infusions of "tumor-infiltrating lymphocytes" and the natural immune stimulant interleukin-2. The lymphocytes are immune cells that have been activated to attack the patients' tumor cells.

The vaccines apparently work by stimulating the patients' immune systems to make the activated lymphocytes themselves. Several investigators have noted that the tumors that regress after vaccine therapy contain lymphocyte infiltrates.

Getting the patients to produce the active immune cells may have the advantage of giving a much more persistent protective response. "The immune system has this wonder quality of memory," says Craig McCune of the University of Rochester Medical Center. "Once you have produced the sensitized [immune cell population] they are long-lived."

McCune and his colleagues are testing a vaccine that they developed to combat kidney cancer. And they, too, find that about one-fifth to one-quarter of the patients with metastatic disease respond with complete or partial tumor remissions.

Other researchers developing melanoma vaccines include NYU's Bystryn, who has preliminary evidence that his vaccine can delay the appearance of metastases, David Berd and Michael Mastrangelo of Thomas Jefferson University in Philadelphia, and Donald Morton and Anne Nizze of the University of California School of Medicine in Los Angeles.

The researchers have not detected any serious side effects in the patients they have treated. Inflammation at the injection site and mild fevers are about the worst reactions seen so far. Not all patients mount a strong immune response to their tumor cells after receiving the vaccines, however, and those that don't tend to do poorly.

Right now there are about as many ways of making the cancer vaccines as there are investigators doing the work. Where possible, as with the colon and kidney cancer vaccines, the researchers use cells prepared from the patient's own tumor. The cells are always irradiated to stop them from growing. "The advantage of using [the patient's] cells is that the antigen in the vaccine will match the tumor better," Bystryn says.

But this has the disadvantage of being logistically complicated. According to Hanna, it takes 4 to 6 hours to prepare the tumor cells for his vaccine, and the cells then have to be preserved until the vaccinations are given in three weekly installments, beginning about 3 weeks after surgery. The lag is needed to allow the patients' immune systems to recover from the suppression caused by the surgical trauma.

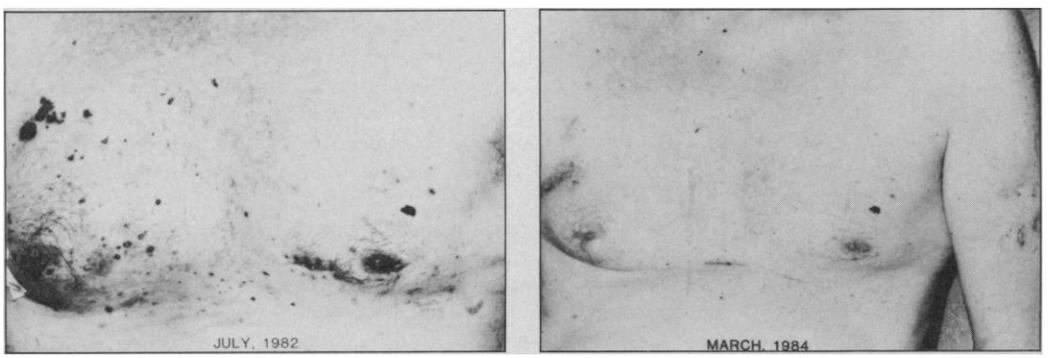
Hanna points out that community physicians perform most of the surgery to remove primary colon cancers and they will probably not have the facilities, and perhaps not the inclination, to do the necessary vaccine preparations. He wants to set up local centers that can do this, but concedes the problem is much more difficult than if he "just had something in a bottle" to give to cancer patients.

Melanomas present a different problem for vaccine development. One of the critical findings that came out of the animal work is that the vaccine injections must include 10 million tumor cells to be effective, and multiple doses are generally required. Primary melanoma tumors are often too small to provide so many cells. So Mitchell makes his with cultured melanoma cells, and Bystryn uses antigens shed by cells growing in culture.

A concern here is that the antigens from the cultured cells might not match those of the patients' tumors and therefore might be ineffective in stimulating the desired immune response. Cancer cells, even those within a single tumor, have highly heterogeneous properties, including their antigenic composition. That was one reason why some researchers scoffed at immunotherapy: If the immune system failed to recognize and destroy just a few metastatic cells, they could seed new tumors. And despite the promising results with the new vaccines, tumor heterogeneity could still turn out to be immunotherapy's Achilles' heel.

The animal work also showed that nonspecific immune stimulants, such as the BCG used by the Hanna group, when given with the tumor cells in the vaccines, help boost the resulting immune responses. And here again, the various researchers have adopted different strategies. Mitchell uses a bacterial derivative called Detox, for example, and McCune employs another microorganism, *Corynebacterium parvum*, as his nonspecific immune stimulator.

Berd uses BCG. In addition, he has found that the drug cyclophosphamide, when given 3 days before the vaccine injections, can



Complete regression. *Therapy with a melanoma cell vaccine produced this result.* [*Reprinted with permission from D. Berd, H. C. Maguire, Jr., M. J. Mastrangelo*, Cancer Res. ***46,*** *2572 (1986)*]

further potentiate the patients' immune responses. Cyclophosphamide is generally considered to be immunosuppressive, but in this case it may repress the activity of the suppressor cells that normally serve to keep immune responses in check.

Other researchers, including Marc Wallack of Mount Sinai Medical Center in Miami, Florida, and Volker Schirrmacher of the German Cancer Research Center in Heidelberg are exploring still another approach to boosting the activity of tumor cell vaccines. They make the tumor cells more immunogenic by infecting them with viruses.

In a preliminary trial in human cancer patients, Schirrmacher has found that nearly 80% of the patients treated with his vaccine subsequently develop an immune response to their tumor cells. "But whether this response is sufficient to have the desired effect against the tumor we do not yet know," Schirrmacher says. The result is nonetheless encouraging in view of the other reports of a correlation between vaccine-stimulated immune response and tumor suppression.

The generally promising results being obtained with tumor cell vaccines do not mean that all the problems have been solved. Mitchell, for example, has noted a troubling development in his melanoma patients. Melanomas often spread to the brain, although the patients' other metastases usually kill them before the more slowly growing brain tumors become apparent.

Mitchell is now finding that patients who have had remissions are relapsing because they are developing brain metastases. This has happened to the woman who had the complete remission, although she had only a single, operable brain tumor, and is still living more or less normally. Apparently, the tumor cell–killing immune cells cannot get into the brain to control metastases there. "No matter how successful we are with this immune therapy, we are still going to be backed up against the blood-brain barrier," Mitchell says. Learning how to crack that barrier will be one of the future directions for his work.

In addition, the cloning of the interferon and interleukin genes has made these natural immune stimulators available in large quantities. So the researchers are also beginning to investigate whether these agents can improve the efficacy of their vaccines.

Although everyone is optimistic about the vaccine results, no one would want to claim a cure for cancer at this stage of the work. "Let's be realistic," Bystryn says. "People have been trying to develop cancer immunotherapy for 20 or 30 years without success. The odds are fairly long, but I think that this approach has as good a chance of working out as any other." ■ **JEAN L. MARX**

Math Team Vaults Over Prime Record

No, this isn't yet another story about how high-speed computers have allowed number theorists to set a new record for the largest known prime number. This is about a prime that is not only larger but of a different kind from all those that have reigned in recent years. And the techniques used to verify it actually have real-world applications.

The new king of the mountain is $391581 \times 2^{216193} - 1$. The mathematical pole vaulters who achieved it were six computer scientists at the Amdahl Corporation in Sunnyvale, California.* The Amdahl team sifted through hundreds of thousands of possible primes before settling on several thousand mega-numbers for final testing. The computations ran quietly in the background for a year and a half. On 6 August, the Amdahl team had achieved new heights— a number they officially announced only after an independent check, run by Jeff Young at Cray Research Inc. in Mendota Heights, Minnesota, had verified (see box) the number as prime.

Until the Amdahl group's claim, recent record large primes have belonged to a class known as Mersenne primes: numbers that are one less than a power of 2. The largest known Mersenne prime is $2^{216091} - 1$, which was proved to be prime by David Slowinski at Cray Research Inc. in 1985. Written out in full, Slowinski's Mersenne prime has 65,050 digits. (Decimal digits, however, are not the best way to write out Mersenne primes; binary, base 2 digits, which the computer prefers anyway, are better: Slowinski's prime appears in base 2 as a string of 216,091 1's.)

The Amdahl prime tops Slowinski's number by 37 decimal digits—the mathematical equivalent of adding an eighth of an inch to the current world mark in the pole vault.

Of course, some will say that finding a new largest known prime has about the same intrinsic value as setting a new pole vault record. Indeed, any such record is made to be broken, for mathematicians proved a long time ago that the list of prime numbers is infinite. But finding a new prime represents more than an entry in the record books. Bodo Parady of the Amdahl group calls it "a clear level of accomplishment," comparable to going to the moon. Even if he's exaggerating, the fact is that the underlying number theory has implications for computer science. "In the future you're going to see number theory playing an increasing role in the development of new computer architectures," Parady predicts.

Actually, there have already been useful spin-offs. In the course of their prime number search, the Amdahl group developed a new algorithm for high-speed convolution (a key ingredient for multiprecision multiplication) tailored to the Amdahl computer architecture. That algorithm has possible applications in seismic research, weather prediction, and aeronautical simulation, Parady notes. And it has already been sent to the University of Manchester for use in a pulsar search system; the search for astronomical prime numbers may have applications in astronomy itself.

■ **BARRY A. CIPRA**

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Is It Prime?

How is primality verified for such large numbers? The obvious method of trial division is out of the question: even a modest hundred-digit prime can't be verified that way.

The test for Mersenne numbers works as follows: Starting with the number 4, square it and subtract 2. Do this again (square and subtract 2) on the resulting number, repeating the procedure a total of $m - 2$ times. If the Mersenne number $2^m - 1$ divides the final result, then $2^m - 1$ is a prime (and if it doesn't, then it isn't). For example, the first three numbers that are produced are 14, 194, and 37,634, and these are enough to prove that $2^5 - 1 = 31$ is prime, since 31 divides 37634. A modified version of this test works on numbers of the form $k \times 2^m - 1$, in which the starting number 4 is replaced by a number related to the square root of k.

For numbers with tens of thousands of digits the amount of computation becomes daunting, especially since most of the time the test succeeds only in verifying that the large number is *not* prime. Indeed, one reason the Amdahl group decided not to look for a Mersenne prime is that the next Mersenne prime is expected to occur at around the 500,000th power of 2, and the computational loads start to get fearsome by then. ■ **B.A.C.**

*John Brown, Landon Curt Noll, Bodo Parady, Gene Smith, Joel Smith, and Sergio Zarantonello.