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MEDICINE

A New Ally against Cancer

The FDA recently okayed the first therapeutic cancer vaccine, and other drugs that enlist the immune system against tumors are under study

By Eric von Hofe

OR DECADES CANCER SPECIALISTS HAVE OFFERED PATIENTS THREE main therapies: surgery, chemotherapy and radiation. (Some cancer survivors pointedly refer to this harsh trinity as "slash, poison and burn.") Over the years continual refinements in these admittedly blunt instruments have made the more severe side effects increasingly manageable. At the same time, effectiveness has improved markedly. And new, very targeted drugs (Herceptin and Gleevec) have become available for a few specific cancers. All told, the average five-year survival rate for invasive cancers as a group has risen from 50 percent to 66 percent in the past 30-plus years. In spite of these gains, many cancer survivors will not have a normal life span.

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Photograph by Dan Saelinger



Researchers have long suspected that they could add a weapon that would dramatically increase cancer survival rates without producing serious side effects if they could just figure out how to prod the body's own immune system to do a better job of fighting malignancies. But decades of effort met with one failure after another. In the 1980s, for instance, overheated hopes that an immune system molecule called interferon would rouse the body's defenses to cure all or most cancers were dashed after a few more years of research. Today interferon has a place but is not the cure-all once envisioned. By the first decade of this century a great number of clinical trials were being conducted using lots of different types of vaccine-related approaches, but nothing seemed to be working. It was starting to look as though the long-hoped-for general weapon against a broad range of tumors would never materialize.

It still has not. But something happened in the summer of 2010 suggesting that the age of false starts and blind alleys in the effort to awaken the immune system may finally be drawing to a close: the U.S. Food and Drug Administration approved the first vaccine to treat a cancer. The drug, called Provenge, is not a cure, but it—along with standard chemotherapy—already has given hundreds of men with advanced prostate cancer a few extra months of life.

This positive turn of events occurred after scientists reexamined a few fundamental assumptions about how the immune system works against cancer cells as well as how tumors fight back against immunological attacks. Today cancer researchers are cautiously optimistic that we can develop additional, very specific immune-boosting therapies that can be used routinely alongside surgery, chemotherapy and radiation to subdue cancer while triggering side effects that are no worse than a bad cold.

A NEW ALLY

MANY OF US are focusing particularly on therapeutic cancer vaccines. Unlike most familiar vaccines, which prevent certain infections that can lead to brain damage (measles), paralysis (polio) or liver cancer (hepatitis B) from taking hold in the first place, therapeutic cancer vaccines train the body to recognize and destroy cancer cells that already exist within its tissues and to keep killing those malignant cells long after treatment has ended.

Developing such vaccines is easier said than done. Most preventive vaccines trigger a simple antibody response, which is usually pretty good for protecting against lots of different kinds of infections. The antibodies just stick to flu viruses, for example, and stop them from infecting cells. In general, however, antibody responses are not strong enough to kill cancer cells. For that kind of job, the immune system needs to stimulate a group of

IN BRIEF

Conventional treatments for cancer—surgery, chemotherapy and radiation—have increased survival rates since the 1970s, but many survivors still do not achieve a normal life span. **Researchers believe** the results would be better if they could recruit a new ally against malignancy: the body's own immune system. Over the past decade several attempts to boost the immune response artificially—through vaccination or other drug development—have failed. But the tide seems to be changing. A cancer vaccine for treating prostate cancer has been approved, and a new generation of therapeutic cancer vaccines is now being tested.

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cells called T cells. There are two main types of T cells in the body. Scientists often distinguish between different kinds by referring to various distinctive proteins, termed receptors—such as CD4 or CD8—that sit on their outer membranes. The kinds of T cells that are especially good at directly destroying malignant cells—assuming they can be induced to recognize the cancer cells as dangerous—display CD8 receptors. (These T cells are called CD8+ cells because the CD8 receptor is present.)

Despite these complexities, creating a cancer vaccine is not a new idea. In the waning years of the 19th century, long before anyone had ever heard of a CD8+ cell, William B. Coley started injecting cancer patients with a substance that came to be called Coley's toxin. An orthopedic surgeon at what is now Memorial Sloan-Kettering Cancer Center in New York City, Coley was intrigued by reports of cancer patients who apparently had been cured of their disease after a brief bout with a life-threatening infection. In an attempt to simulate the infection without risking its potentially deadly consequences, Coley prepared a solution that mixed two strains of deadly bacteria. He gently heated the preparation so that the bacteria were killed and rendered harmless. Enough of the bacterial proteins remained in the brew, however, that the patients' bodies responded by generating very high fevers.

Coley hypothesized that high fevers could jump-start his patients' moribund immune systems into recognizing and attacking the abnormal growths within their bodies. He extended the length of his patients' artificial fevers with daily injections of increasingly concentrated dead bacteria. Remarkably, long-term survival was greater among the cancer patients who received the toxin than among those who had not. Coley argued, with some justification, that his toxin had served as a kind of vaccine against cancer.

By the 1950s, however, physicians started getting more consistent results with chemotherapy. As Coley's bacterial toxins fell out of favor, the whole notion of creating vaccines to treat cancer ground to a halt.

But study of the immune system and its possible role in cancer did not stand still. Gradually researchers developed evidence to support the idea, first suggested by Paul Ehrlich in 1909, that the immune system continually surveys and destroys newly arisen cancer cells. This so-called immune surveillance theory gained further credibility in the 1980s, when investigators calculated that the high level of spontaneous mutation in human cells that they

The Long March

PERSEVERANCE -

Boosting the immune system's cancer-fighting ability has taken decades of research.

1890s

William B. Coley stimulates the immune systems of cancer patients by injecting them with mixtures of dead bacteria.

1975 Monoclonal antibodies are created, allowing development of highly specific immunological tools.



Paul Ehrlich suggests that the immune system may suppress tumor development.

AP PHOTO

were observing should have resulted in many more malignant growths than were indeed detected. Somehow the body was regularly finding and destroying numerous cancerous cells on its own.

Even after the occasional tumor managed to avoid eradication, the evidence suggested, the immune system kept fightingjust not as effectively. Pathologists had long noted that tumors were frequently infiltrated by immune cells, giving rise to the concept that tumors were "wounds that would not heal." In addition, further experiments showed that as a tumor grows, it releases more and more substances that actively suppress T cells. The question now became how to design cancer vaccines that would tip the balance in favor of T cells able to eradicate the tumor.

An answer began to emerge in 2002, when a team of scientists at the National Cancer Institute (NCI) showed that another immune T cell, known as a CD4+ cell, was a critical component of an effective anticancer response. CD4+ cells are sort of like the generals of the immune system: they give the orders about who and what to attack to the foot soldiers-which, in this scenario, are the CD8+ cells-that do the actual killing. The NCI team, led by Steven Rosenberg, took T cells out of 13 advanced melanoma patients whose tumors had metastasized, or spread, throughout their body. The researchers selectively activated the removed immune cells to target and attack the melanoma cells in a test tube. Then the scientists grew the activated cells in large amounts and infused them back into the patient. The NCI team's approach, referred to as adoptive immunotherapy, is, in effect, a kind of self-transplantation of immune cells (altered artificially outside the body) and, as such, differs from vaccination, which causes the immune system to generate its own targeted immune cells inside the body.

Previous adoptive immunotherapy treatments using just CD8+ cells had shown no benefit. But when the NCI team added CD4+ cells to the mix, the results were remarkable. Tumors shrank dramatically in six subjects, and blood tests from two of the six showed that they were still making powerful anticancer immune cells on their own more than nine months after the treatment had ended. For the most part, patients experienced temporary flu-like symptoms as a result of the treatment, although four of them also suffered a complex autoimmune reaction that led to the loss of pigment from parts of their skin.

The NCI results offered a convincing proof of concept: an im-

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combina ntron®A IM/SC mune response based on T cells could, in fact, be boosted precisely enough to destroy tumors. The number of cloned immune cells needed per patient in this experiment was staggering: more than 70 billion CD8+ cells and CD4+ cells-or several hundred milliliters in volume. But at least the scientific community now believed that immunotherapy against cancer could work. The next steps were to figure out how to obtain the same result in a simpler fashion-that is, without having to remove cells from the body, grow them in great numbers and reinfuse them later. In other words, it should be possible to make the body grow most of the additional cells it needed on its own-which is exactly what it does in response to an effective vaccine.

MULTIPLE STRATEGIES

MY COLLEAGUES AND I at Antigen Express were gratified when Rosenberg's group showed that a cancer vaccine would have to elicit both CD4+ and CD8+ cells to be effective. We had previously argued the same point based on animal studies and had essentially staked the future of our company on that belief.

Basically, there are three elements to making a cancer vaccine. The first is to decide precisely what molecular feature, or antigen, in a malignant tumor the immune system should recognize as foreign and target for killing. The second is to decide how to deliver a triggering agent (or vaccine) to the immune system that ramps it up to attack cancer cells. And the third is to decide which cancer patients to treat and when during the course of their disease to administer the vaccine.

Over the past several years researchers in the biotech industry have considered a wide range of proteins, as well as pieces of proteins (called peptides), as the potential starting points for driving an immune response robust enough to kill cancer cells. (Other possibilities for priming the pump include using bits of genetic material that encode cancer proteins or even whole cancer cells after they have been irradiated.) It turns out that the genetic alterations that allow cancer cells to grow uncontrollably also cause them to make some proteins in much higher amounts than are found anywhere else in the body. About 10 companies, including our own, have selected various examples of these peptides to fulfill the first two requirements for making a cancer vaccine: the starting point and the delivery mechanism.

Part of what makes peptide vaccines particularly attractive is



1986 The Food and Drug Administration okays interferon, the first proved immunotherapy against cancer, for the treatment of hairy cell leukemia.



1998

The FDA approves the monoclonal antibody Herceptin for the treatment of metastatic breast cancer.



2002

Researchers at the National Cancer Institute prove that a T cell-based treatment against cancer is possible and requires the contribution of two kinds of immune cell: CD8+T cells (gold, seen at left attacking cancer cell) and CD4+T cells.

2010 The FDA approves Provenge, the first vaccine meant to elicit an attack on an existing tumor, for advanced prostate cancer.

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right)

that these bits of protein are small in size, inexpensive to synthesize and very easy to manipulate, which means that they can be readily formulated into a vaccine that is simple to manufacture in large amounts. Furthermore, since the peptides that have been identified show up in many people with different types of cancer, they can be used in formulations that would help many people without doctors having to compose individual vaccines for each person, which they have to do with cell-based immunotherapies. Finally, all the peptide vaccines tested so far produce relatively mild side effects, such as temporary irritation at the injection site and perhaps a fever or other flulike symptom.

Ten years ago scientists at Antigen Express made a few key modifications to a peptide that had been used in an experimental vaccine against breast cancer. Known as HER2, this particular protein is also the target of Herceptin, a monoclonal antibody treatment against certain types of breast cancer. Our researchers found that adding just four more amino acids to the peptide dramatically increased its ability to stimulate CD4+ cells, as well as CD8+ cells, against breast cancer cells that make the HER2 protein. This finding was the innovation on which we bet the company's future. Preliminary data published earlier this year from an independent study that compared our HER2-enhanced vaccine against two other peptide vaccines designed to stimulate only CD8+ cells suggests that we are on the right track.

Some companies, such as Dendreon, makers of the newly FDA-approved Provenge, placed their bets differently. Dendreon and some other companies are providing targets specific for cancer cells directly to an immune cell known as a dendritic cell. Scattered throughout the body, particularly in tissues that come into contact with the outside world (such as the skin or the lining of the digestive tract), dendritic cells act like the immune system's sentinels and are among the first defenders to alert the T cells that something is wrong. Because immune cells take orders only from other immune cells that are genetically identical to them, however, the necessary dendritic cells must be harvested from each individual patient, loaded with the cancer-specific protein and then reinfused back into the patient-all at a cost of about \$93,000 for a full course of treatment. Side effects include chills, fever, headache and, less commonly, stroke. But a shortterm clinical study proved that people with advanced prostate cancer who were treated with Provenge lived, on average, at least four months longer than their untreated counterparts.

NEXT STEPS

THE FDA'S APPROVAL of Dendreon's Provenge plus promising preliminary data from clinical trials conducted by various companies, including our own, suggests that we are entering a new era in the development of cancer vaccines. As scientists venture further in this promising new endeavor, however, we are discovering that we cannot use the same yardsticks for measuring progress against cancer with immunotherapy as we do for chemotherapy or radiation. The latter two show their benefits rather quickly—within a few weeks the tumors either shrink in size, which is good, or they do not, which is bad. But data from several clinical trials suggest that it may take up to a year after treatment with a cancer vaccine for the immune system to really start making substantial progress against tumor growth.

This lag time is not entirely surprising, because the immune system needs a good deal of coaxing to attack cells that look awfully similar to normal cells in the body, as opposed to a bacterium or virus. Breaking tolerance—or the immune system's reluctance to attack cells that have arisen from the host—is perhaps the biggest obstacle in generating effective therapeutic vaccines to fight cancer. Another surprise is that tumors may actually appear to grow in size after treatment with cancer vaccines. Analysis of tumor tissue, however, shows that this increase can be the result of invading immune cells, not of tumor cell replication.

The deliberate pace with which the immune system so far seems to respond to the therapeutic cancer vaccines being developed, however, suggests two important intermediate conclusions. One, individual cancer vaccines will probably be most effective in the near term in people at earlier stages of their disease, when their tumors are not big enough to depress their immune system and they have enough time to wait for a more powerful immune response to kick in. Two, people with advanced disease probably will usually need to have their tumors shrunk through conventional treatment before they can benefit from receiving a cancer vaccine. Starting with a small tumor or shrinking existing ones are important because large, long-lived tumors are just that much better than smaller, younger ones at suppressing or evading the immune system. They have more cells that can release greater amounts and types of immune-suppressing chemicals. Late-stage cancer patients may simply have too much cancer present for even a healthy immune system to dispatch.

In spite of these obstacles and complexities, the signs are clear: a patient's own immune system can be effectively enlisted to help combat cancer. This realization has given tremendous encouragement to investigators in academia and industry who have persevered in the face of so many failures. Previous clinical trials that had been written off as failures are being reexamined to see if perhaps evidence of immune-related responses may have been overlooked. Indeed, one such trial of a potential prostate cancer vaccine (Prostvac) showed that while the compound failed to meet its original predetermined end point—lack of tumor growth—it boosted overall survival. Of course, this discovery came after the small biotech company that developed Prostvac had already gone out of business for having failed to meet the primary end point of the trial. Fortunately, another company secured the rights to develop the drug.

As for the survivors in the industry, we have been conditioned by years of frustrating results to look beyond setbacks and not to make too many promises. But the evidence from the research and clinical trials over the past couple of years leads a growing number of investigators to believe that therapeutic cancer vaccines will take a prominent role alongside surgery, chemotherapy and radiation over the next decade as an effective treatment for some of the most common cancers that plague humanity.

MORE TO EXPLORE

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PLACE YOUR BETS

Three Therapeutic Vaccine Strategies

The immune system does not easily recognize cancer cells as dangerous or foreign, as it generally does with microbes. Scientists have shown that they can boost the response by flooding the body with immune cells known as T cells that are artificially grown outside of it.

Basic Cellular Immune Response to Cancer An immune cell called a dendritic cell ingests a tumor cell and then presents substances called antigens (red) from the tumor to two other immune cells, the CD8+ and CD4+ T cells. The CD4+ cell releases cytokine molecules that help to activate the CD8+ cell, prompting it to attack other cells with the same antigen. Alas, the response is not always strong enough to destroy an entire tumor.

