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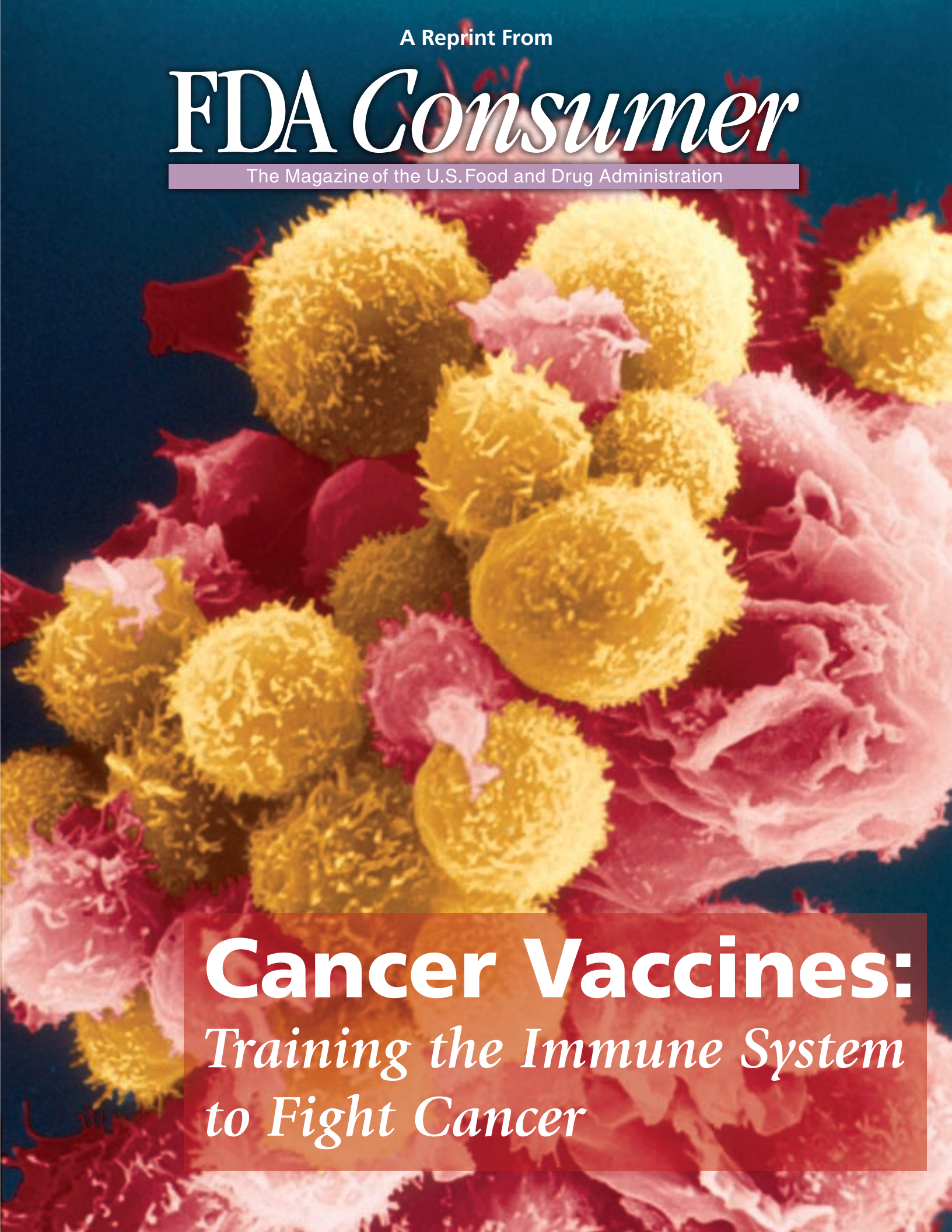

Cancer Vaccines:

Training the Immune System to Fight Cancer

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Training the Immune System to Fight Cancer

By Michelle Meadows

Vaccines traditionally have been used to prevent infectious diseases such as measles and the flu. But with cancer vaccines, the emphasis is on treatment, at least for now. The idea is to inject a preparation of inactivated cancer cells or proteins that are unique to cancer cells into a person who has cancer. The goal: to train the person's immune system to recognize the living cancer cells and attack them.

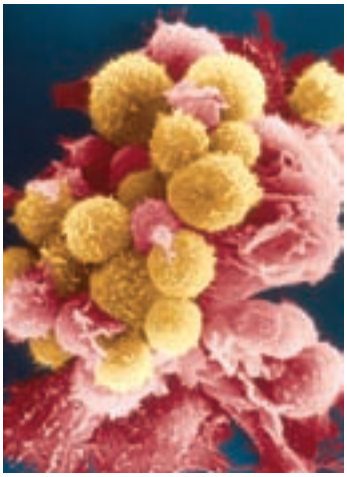
"The best settings are for treating people who have minimal disease or a high risk of recurrence," says Jeffrey Schlom, Ph.D., chief of the Laboratory of Tumor Immunology and Biology at the National Cancer Institute (NCI). "But at this time, most therapeutic cancer vaccines are being studied in people who have failed other therapies."

Cancer vaccines are experimental; none have been licensed by the Food and Drug Administration. But there are about a dozen cancer vaccines in advanced clinical trials, says Steven Hirschfeld, M.D., a medical officer in the FDA's Center for Biologics Evaluation and Research. "Research has shown us that the fundamental approach to cancer vaccines is right; we are moving in the right direction," he says.

The three standard cancer therapies are surgery to remove tumors; chemotherapy, which modifies or destroys cancer cells with drugs; and radiation, which destroys cancer cells with high-energy X-rays. Immunotherapy, which includes cancer vaccines, is considered a fourth, and still investigational, type of therapy. Cancer vaccines are sometimes used alone, but are often combined with a standard therapy.

While standard treatments alone have proven effective, they also have limitations. Radiation and chemotherapy can wipe out a person's cancer cells, but they also damage normal cells. "We want to find treatment that is more targeted and less toxic," says Hirschfeld. "Cancer vaccines are designed to be specific, targeting only the cancer cells without harming the healthy ones."

The approach has made cancer vaccines generally well tolerated, allowing them to be used in outpatient settings. And they can be added to standard therapy with a low likelihood of causing further serious side effects.



Phototake

A photograph taken through a microscope shows a cancer cell (red) being attacked by T lymphocytes (yellow).

How Cancer Vaccines Work

Cancer is a term for more than 100 diseases characterized by the uncontrolled, abnormal growth of cells. To the immune system—the body's natural defense system against disease—cancer cells and normal cells look the same. The immune system tends to tolerate the cancer cells, just as it tolerates the normal cells. That's because the immune system doesn't recognize cancer cells as something foreign, Hirschfeld says. Rather, cancer cells are once-normal cells that have gone awry. Cancer vaccines try to get the immune system to overcome its tolerance of cancer cells so that it can recognize them and attack them.

All cells have unique proteins or

Gary Montgomery, a retired engineer from Redmond, Wash., found a clinical trial at Georgetown University's Lombardi Cancer Center in Washington, D.C., that offered a cancer vaccine to treat his rare form of abdominal cancer.

Black Star/Doug Wilson

bits of proteins on their surface called antigens. Many cancer cells make cancer-specific antigens. The goal of using cancer antigens as a vaccine is to teach the immune system to recognize the cancer-specific antigens and to reject any cells with those antigens. The antigens activate white blood cells called B lymphocytes (B cells) and T lymphocytes (T cells). B cells produce antibodies that recognize a particular antigen and bind to it to help destroy the cancer cells. T cells that recognize a particular antigen can attack and kill cancer cells. In 1991, the first human cancer antigen was found in cells of a person with melanoma, a discovery that encouraged researchers to search for antigens on other types of cancer, according to the NCI.

The two main approaches for cancer vaccines are whole-cell vaccines and antigen vaccines. Whole-cell vaccines may take whole cancer cells from a patient or sometimes several patients, or use human tumor cell lines derived in a laboratory. "Some cell-based vaccines use tumor cells from the patient, some contain something that looks like a tumor cell but was created in a lab, and others are personalized vaccines that use some cells from the patient and some from the lab," Hirschfeld says. Cells that are taken from people with cancer are altered in a lab to inactivate them so that they are safe to re-inject.

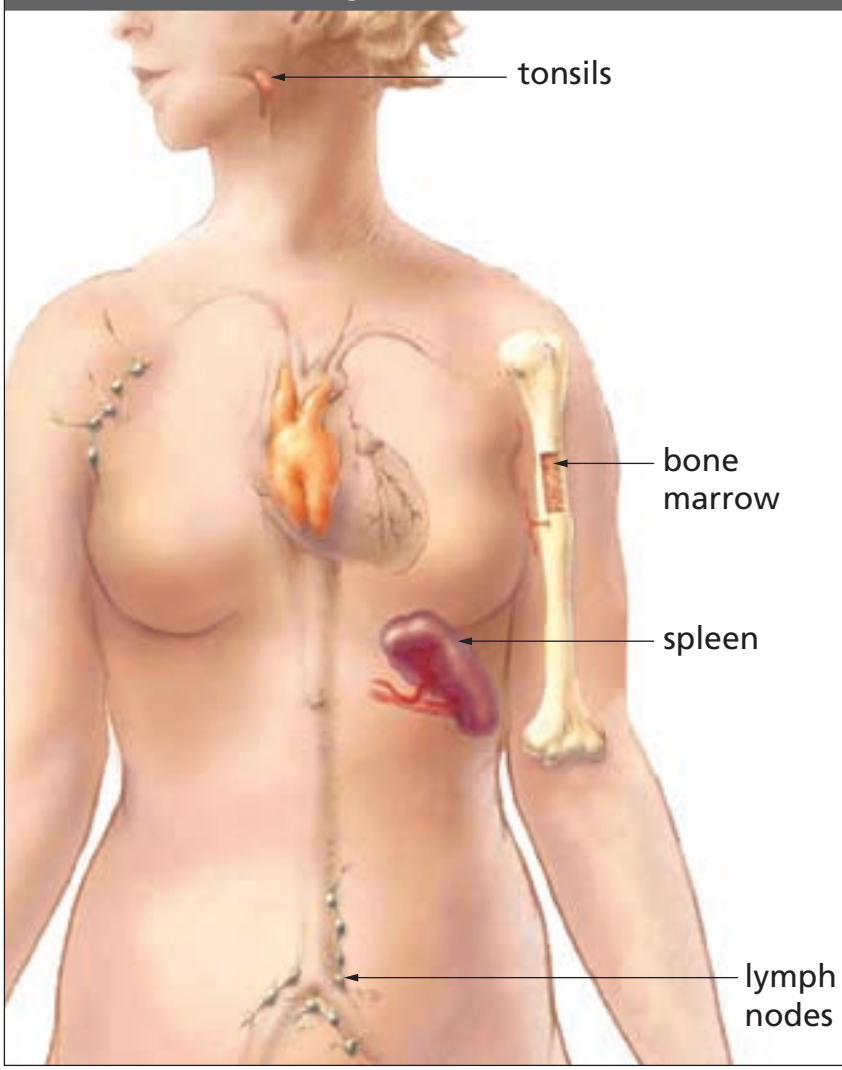
Regardless of the exact source of the cells, whole cell vaccines potentially use all the antigens found on the tumor cells. Antigen vaccines try to trigger an immune response by using only certain antigens from cancer cells. Hirschfeld says antigens may be particular to an individual, to a certain type of cancer, or to several types of cancers.

Boosting the Immune Response

In the early 1990s, Steven Rosenberg, M.D., one of the pioneers of immunotherapy and chief of surgery at the NCI, wrote that trying to use the immune system to fight cancer is so difficult that it made him feel "like a dog trying to bite a basketball." Among Rosenberg's contributions was identifying the antigens that trigger an immune response, and cloning genes that look for, or "code for," those antigens.

Researchers have been working to develop cancer vaccines for more than 100 years in one form or another, and the main mission has always been to

The Immune System and How It Works



Your immune system includes your spleen, lymph nodes, tonsils, bone marrow, and white blood cells. These all help protect you from getting infections and diseases. When your immune system works the way it should, it can tell the difference between "good" cells that keep you healthy and "bad" cells that make you sick. But sometimes this doesn't happen. Doctors are doing research to learn why some immune systems don't fight off diseases like cancer.

White blood cells are an important part of your immune system. When your doctor or nurse talks about your white blood cells, he or she may use words like:

- **Monocytes** (MON-o-cites) are types of white blood cells.
- **Lymphocytes** (LYM-fo-cites) are types of white blood cells.
- **B cells, T cells**, and **"natural killer cells"** are kinds of lymphocytes.

National Cancer Institute

make the immune system's response to the cancer antigens as strong as possible.

One major strategy involves combining vaccines with additional substances called adjuvants, which act as chemical messengers that help T cells work better. An example of one type of adjuvant, called a cytokine, is interleukin-2. This protein is made by the body's immune system and can also be made in a lab.

There have also been improvements in vaccine delivery. For example, Schlom developed a vaccine in which genes for tumor antigens are put into a weakened virus called a "vector" that delivers genetic materials to cells. This makes the tumor antigen more visible to the immune system. The CEA-TRICOM vaccine was developed at the NCI through a cooperative research and development agreement with Therion Biologics in Cambridge, Mass. Researchers use the vaccinia virus, the same virus in the smallpox vaccine, as the vector. The carcinoembryonic antigen (CEA), which is found on most breast, lung, colon, and pancreatic tumors, is added to the virus. Researchers also add three molecules, called "costimulatory molecules," which serve as signals that make the vaccine more potent than it would be if the antigen were used alone. A similar vaccine developed under the NCI agreement with Therion is the PANVAC vaccine, which has now entered advanced study as a treatment for pancreatic cancer.

In addition to studying this type of virus-based technique, researchers at Duke University's Cancer Center in Durham, N.C., have been studying vaccines that mix white blood cells called dendritic cells with genetic material from a person's tumor.

Dendritic cells, which can activate T cells, work by looking around, finding antigens, and showing them to the fighter T cells. Researchers have found ways to increase the number of dendritic cells in a vaccine. "Employing millions of 'pumped up' dendritic cells can help elicit a strong immune response," says H. Kim Lyerly, M.D., director of the Duke cancer center.

Recent work by Lyerly and Duke investigators Michael Morse, M.D., and Timothy Clay, Ph.D., has focused on modifying dendritic cells with viruses so that they activate even stronger T cell responses against cancer antigens.

"This is an evolving area, and it's exciting to be able to make progress," says Lyerly. "For decades, people thought it wasn't even fundamentally possible to develop cancer vaccines, and here we are. The science behind cancer vaccines is leading us to believe that we will find the answers."

Promising, But Still Early

As with any new treatment, cancer vaccines must be first studied in lab animals and then tested for safety and effectiveness in three phases of human studies, called "clinical trials," before they can be approved by the FDA. In Phase 1 clinical trials, cancer vaccines are used alone and studied for safety and to determine the proper dose. In Phase 2 trials, they are tested for effectiveness and may be used alone or in combination with another therapy. Phase 3 trials are large-scale studies testing effectiveness and usually comparing a vaccine with some standard therapy. Researchers are testing vaccines using various adjuvants, delivery methods, and types of antigens.

Cancer vaccines have shown promise in clinical trials with many types of cancer. According to Howard Streicher, M.D., a senior investigator with the NCI's Cancer Therapy Evaluation Program, it's too soon to say which cancers will be treated with vaccine therapy. The types of tumors that have proven most susceptible to vaccines so far, he says, are: skin cancer (melanoma); kidney cancer (renal cell); a group of cancers that affect the lymphatic system (lymphoma); a malignant tumor of the bone marrow (myeloma); and solid tumors, such as lung cancer. The most work has been done in the area of melanoma, a type of skin cancer in which treatment options are limited when the disease is in advanced stages.

"After having a tumor removed, about half of patients with stage III melanoma may have a recurrence, and we want to prevent that," Streicher says. "Chemotherapy doesn't work in this area, so our hope is that this could be just the right place for a vaccine."

James Mulé, M.D., Ph.D., associate director of the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Fla., says, though some early studies have shown that some people's tumors shrank or even disappeared in response to a cancer vaccine, it's still early. Mulé was an investigator on the first study that tested dendritic cells in children. In the Phase 1 study, one 16-year-old with cancer that had spread to her lungs and spine showed significant shrinkage of tumors.

"There is promise in the sense that

Cancer Vaccine Facts

- Cancer vaccines are intended either to treat existing cancers (therapeutic vaccines) or to prevent the development of cancer (prophylactic vaccines).
- Therapeutic vaccines, which are administered to cancer patients, are designed to treat cancer by stimulating the immune system to recognize and attack human cancer cells without harming normal cells. Prophylactic vaccines, on the other hand, are given to healthy individuals to stimulate the immune system to attack cancer-causing viruses and prevent viral infection.
- To date, the only cancer vaccine licensed by the Food and Drug Administration is a prophylactic vaccine against hepatitis B virus, an infectious agent associated with liver cancer.
- Scientists are currently evaluating several different vaccines in large human trials to determine which approaches are most effective for particular kinds of cancers.

Source: National Cancer Institute

With a cancer vaccine, there may be fewer signs of tumor shrinkage, but a person might live longer.

some of these vaccines can illicit a powerful immune response in some patients, but I think we have to be careful about getting too excited over early studies that can't be reproduced," Mulé says.

Jeffrey Weber, M.D., Ph.D., director of the Norris Melanoma Center at the University of Southern California, says there is also still a lot of work to be done in discovering new antigens and adjuvants and more sophisticated strategies to overcome the immune system's tolerance of cancer cells. "We are still discovering molecules that regulate the immune system such as CTLA-4, so we're still in the dark in some areas," Weber says. Recent research has found that inhibiting CTLA-4 can help the immune system attack some tumors.

Experts say that no therapeutic cancer vaccine has been licensed yet because few Phase 3 studies have been completed, and those that have been completed did not meet their goals of demonstrating safety and effectiveness of the vaccine. "We are still working with industry to define the characteristics, including potency," says the FDA's Hirschfeld. "So a trial may look promising early on, but our job is to make sure it can be reproduced. We have to ask: 'Will this treatment work in the larger population?'"

One of the challenges is that cancer vaccines may produce different effects than those caused by cancer drugs. With cancer drugs, experts ask whether there is an objective, measurable response, such as tumor shrinkage. A cancer drug may cause tumors to shrink, but a person still may not live longer. With a cancer vaccine, there may be fewer signs of tumor shrinkage, but a person might live longer.

There aren't the same landmarks that you would see with traditional therapies, says Natalie Sacks, M.D., medical director in the clinical research division at San Francisco-based Cell Genesys, which is studying its vaccines, called GVAX, in people with prostate cancer, pancreatic cancer, leukemia, and myeloma. These whole-cell vaccines all use a hormone that stimulates immune response, called granulocyte macrophage colony stimulating factor (GM-CSF).

"As sponsors, we want to develop treatments and get them out to the market and help patients," Sacks says. "In the case of cytotoxic chemotherapies, the traditional endpoints used in drug development are shorter-term outcomes, such as tumor response and progression-free survival. Where I expect immunotherapy to be successful is in longer-term outcomes and increased survival. Because of the mechanism of action, the patient may not show an immediate response as is generally observed with standard chemotherapies, and the trial may take longer."

Finding a Clinical Trial

Cancer researchers say their work won't mean much if more people don't enroll in clinical trials. According to the NCI, less than 3 percent of U.S. adults with cancer participate in clinical trials.

If there is a standard treatment available for a type of cancer, the NCI recommends choosing it over an experimental therapy. Cancer vaccines show the most promise at preventing a recurrence of cancer after surgery, radiation, or chemotherapy because the immune system will need to recognize and attack a smaller number of cancer cells. Cancer vaccines are also being tested as a treatment for advanced cancer.

Gary Montgomery, 66, of Redmond, Wash., enrolled in a cancer vaccine trial in 2002 to treat a rare form of abdominal cancer called pseudomyxoma peritonei. According to the National Organization for Rare Disorders, the disease is characterized by the accumulation of mucus-secreting tumor cells in the abdomen and pelvis. As the mass of tumor cells grows, the abdomen swells and digestive function becomes impaired.

Montgomery first had the standard therapy of surgery to remove the tumors in 2000. "They opened me up like a sardine can—from the sternum to the abdomen—and took out as

The Role of FDA and NCI

After conducting preclinical research in lab animals, drug companies or clinical investigators submit an investigational new drug application to the Food and Drug Administration, requesting permission to move forward with testing in humans called clinical trials. The agency and the sponsors continue to communicate throughout the three phases of clinical trials, and the FDA ensures that treatments are safe and effective before they can be marketed.

The National Cancer Institute (NCI) is the main federal agency that supports and conducts cancer research. The NCI funds studies conducted by hospitals, universities, and businesses. The institute also supports a network of cancer centers across the country.

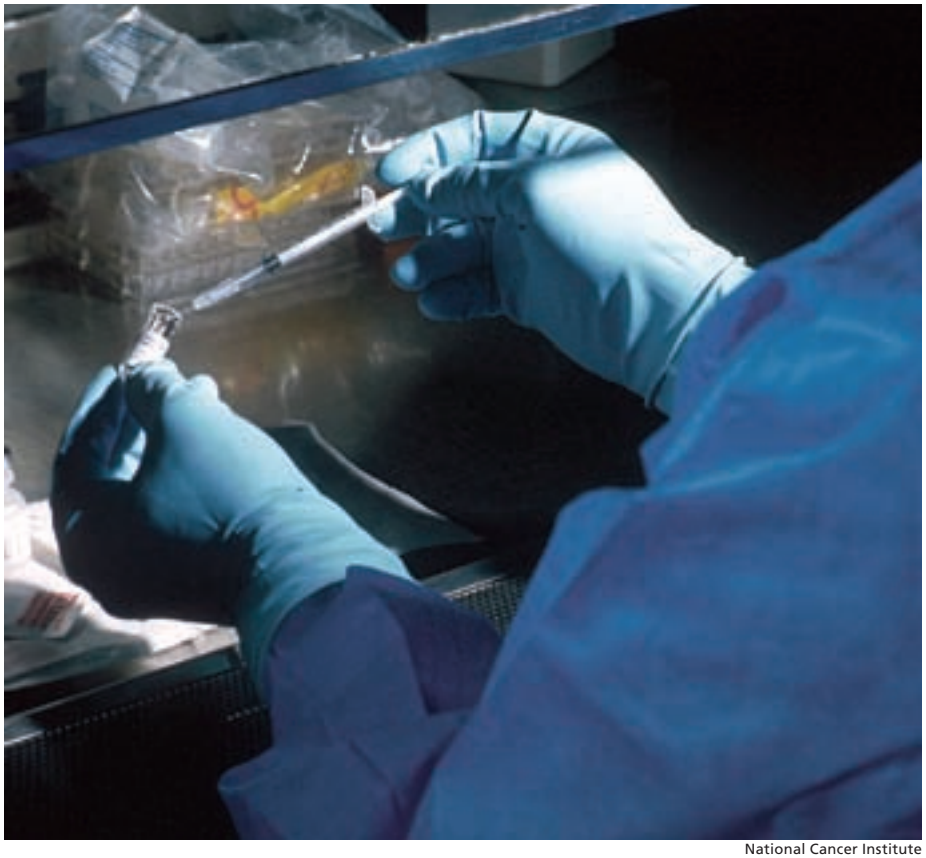
Both agencies are part of the U.S. Department of Health and Human Services, and they share responsibility and oversight for clinical trials. In 2003, the FDA and the NCI entered an agreement to enhance the efficiency of clinical research and the evaluation of new cancer medications. An NCI–FDA Oncology Task Force involves senior staff from both agencies and oversees the agreement. The agencies collaborate on developing the markers that show whether a treatment is effective, such as survival time, tumor shrinkage, and time to relapse. ■

many tumors as possible," Montgomery says. Then they inserted a tube into the abdomen, which delivered chemotherapy for six months. He experienced no tumor growth for about a year, but then the tumors came back. "It's known as a relentless form of cancer that wears you down," he says. "The doctor said that with the exception of another surgery, there was really nothing else they could do."

So Montgomery started with the Internet and found one NCI study that involved surgery and chemotherapy with an agent different from the one he had before. But the trial was closed. Taking advice from a friend, he checked at the Lombardi Cancer Center at Georgetown University in Washington, D.C. "I was feeling pretty low at this point," he says. He found out the one vaccine study he was interested in had just ended. But a nurse told him that another trial with newer versions of cancer vaccines developed at the NCI was about to start. "There were two slots left," he says. "Luckily, I met the criteria."

Montgomery received a "prime-boost regimen" of Therion Biologics' TRICOM vaccine. He first received an injection in the upper leg of a modified version of the smallpox vaccine to prime the immune system. Then he received monthly boosters of a vaccine called fowlpox CEA (carcinoembryonic antigen), an antigen found on most colorectal and pancreatic cancers. He also received a shot of the hormone GM-CSF, which helps stimulate the cells of the immune system. He had to give some of the injections to himself when he arrived back home in Washington state.

He says he experienced minimal side effects, such as soreness at the site of injection and mild flu-like symptoms. Though most cancer vaccines have been well-tolerated, in other trials some people have experienced autoimmune problems such as inflammation of the thyroid gland, skin disorders, and colitis. Autoimmune conditions are those in which the immune system mistakenly attacks the body's tissues and organs. Before he began the trial, Montgomery signed an informed consent form acknowledging that he was aware of all the risks.



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A researcher prepares the carcinoembryonic antigen (CEA) vaccinia vaccine.

Montgomery continues to participate in the trial and flies to the nation's capital every month to receive treatment because it's been working. "It hasn't cured the cancer," Montgomery says, "but it seems to be keeping it in check. And that's good enough for me."

Those interested in finding out about clinical trials to treat cancer should talk with their doctors and contact the NCI at (800) 4-CANCER (422-6237) or on the Web at *www.clinicaltrials.gov.* ■

New Cancer Office and Program

In July 2004 the FDA announced plans to create the Office of Oncology Drug Products, which will be housed in the agency's Center for Drug Evaluation and Research (CDER). The new office will consolidate three existing areas within CDER that are responsible for reviewing drugs and biologics used to prevent, diagnose, and treat cancer. The creation of this office will improve the consistency of review and policy toward oncology drugs and bring together oncologists who will help develop new therapies.

"Biomedical research in the United States is second to none, and it is our responsibility to see that patients reap the fruits of that research," says Health and Human Services Secretary Tommy G. Thompson. "We are committed to creating the most effective and efficient review process possible to ensure life-saving treatments are made available to cancer patients."

The FDA also is creating a new oncology program within the office, which will coordinate cancer-related work performed throughout the FDA. The program will promote cross-agency consultation and discussion and the development of regulatory policy and standards, and will serve as a focal point for agency interactions with the National Cancer Institute and other stakeholders. ■

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