FEATURE STORY

Getting Personal

BY KATY HUMAN

Using personalized vaccines, researchers enlist the immune system to oust tumors.

In 2003, Stephen Creel, a manager at a software company in Austin, Texas, suddenly started passing blood in his urine. He had just celebrated his 40th birthday with friends and his wife, who was pregnant with their daughter, and he was as fit as he'd been in years.

The diagnosis of kidney cancer—renal cell carcinoma—was "shocking," Creel says.

His father-in-law, a cancer researcher, directed Creel to M.D. Anderson Cancer Center in Houston, almost 170 miles away, where oncologists were testing an experimental vaccine to treat kidney cancer.

They surgically removed patients' tumors, sent samples away for processing, and then re-injected cancer-specific proteins back into the patient. They were trying to activate the patients' own immune system cells, train them to recognize cancer as an invader, and fight it off.

"I really liked the idea of that, getting your body to do the work, not just chemicals," Creel says.

Preventive vaccination, also referred to as immunization, has become a critical part of global public health. Since the body has a much easier time developing immunity against foreign proteins that come from viruses or bacteria, vaccines to prevent cervical and liver cancers (associated with viral infection) are already available. But tricking the body into fighting existing cancer has proved more complicated because most cancer cell proteins are similar to normal proteins, and the body is "educated" not to develop immunity against its own proteins. Nonetheless, treatment vaccines for prostate cancer, lymphoma, melanoma, and other cancer types are undergoing late-phase tests in people, and the results are inspiring restrained optimism.

Stephen Creel often played tennis the night before receiving a vaccine to treat his kidney cancer. Photo by Glenn Zamora.

"We're training the body to reject the tumor," says Leisha Emens, MD, PhD, a breast cancer researcher and vaccine developer at Johns Hopkins University in Baltimore. The immune approach is unlike new types of chemotherapy, radiation, or hormonal therapy, Emens says. Treatment vaccines target cancer cells more precisely, have far fewer side effects, and may be less likely to foster drug resistance. “This works completely differently,” Emens says. “With immune-based therapy, you’re actually changing how the body responds to cancer.”

Emens and other cancer vaccine researchers caution that it could be years before clinicians routinely use this immunological approach to treat cancer. Scientists have been experimenting with the technique for decades, and have tripped over many obstacles. One of the most fundamental: The immune system discriminates “self” from “nonself” at a basic level. Viral or bacterial infections are “nonself” and perceived as a threat, but cancers come from the body’s own tissue, so the immune system generally develops “tolerance” and recognizes cancer cells as “self,” and does not respond.

But as scientific understanding of the complex immune system has grown, many of those obstacles are falling away. Today, the Food and Drug Administration is considering data from a phase 3 clinical trial of a vaccine against metastatic prostate cancer called Provenge (sipuleucel-T). The FDA will decide whether to approve the vaccine by May 1.

“This is such an exciting time to be in the field of cancer vaccine research,” says James Gulley, MD, PhD, director of the clinical trials group within the Laboratory of Tumor Immunology and Biology at the National Cancer Institute. “We’re on the verge of having approved an entirely new approach to cancer treatment.”

View Chart: Vaccines to Treat Cancer

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Bringing the Body into the Fight

In 1891, New York doctor William Coley was frustrated by the deaths of patients with metastatic bone sarcomas. He pored over the literature of the time, and found reports that sarcomas sometimes disappeared in patients who suffered unrelated bacterial infections.

“Coley began injecting different types of bacteria, anything into tumors, to trigger an immune response,” Gulley says. Anecdotally, the technique worked on occasion: “Coley’s toxins” appeared to activate patients’ immune systems against cancer as well as bacterial invaders (the immune system sometimes “cross-reacts” with a broader set of proteins than the triggering infection).

But when researchers began conducting carefully controlled clinical trials with cancer vaccines, many simply didn’t work. Part of the reason may have had to do with patient selection, Gulley says. “We started testing these therapies in patients who failed everything else and have no other options. They’ve had every other poison around. They have very advanced disease. So when vaccines were tried, lo and behold, there wasn’t a lot of activity.”

Even in the past few years, a few high-profile “failures” diminished some hope for the technique. A much-discussed vaccine against melanoma known as Canvaxin showed no benefit, and a phase 3 trial for the vaccine Oncophage (vitespen) delivered mixed results in kidney cancer: One specific group of patients with stage 1 or 2 disease saw significant improvement in recurrence-free survival, but there was no positive effect when all study participants, including later-stage patients, were evaluated as a group.

Creel, in Austin, was one of the lucky ones. After surgery to remove the kidney that harbored his cancer, researchers sent a piece of tumor to vaccine maker Antigenics. There, heat shock proteins—proteins that carry around various tumor-specific peptides—were extracted from the tumor and formed the basis of Creel's personalized vaccine. The theory was that Creel's immune cells would "meet" the injected heat shock protein complexes and learn to recognize and target them—and activated killer T cells, a soldier-like type of white blood cell, would also then identify and target any metastatic cancer cells still floating around in Creel's body.

Every two weeks for a year, Creel drove to Houston for vaccinations. He often played tennis with old friends the night before treatment. And he drove himself home.

"I was fortunate," Creel says. "I saw the treatments that other people there were going through. They were going through heavy chemo, walking around with oxygen masks and wearing bandanas ... and I had none of that. I got a red spot on my skin. I'd go in, get my injection and run back down 10 flights of stairs, and get in my car." Creel is now cancer-free.

All Eyes on the FDA

Many researchers believe Provenge for prostate cancer will likely be the first cancer treatment vaccine approved by the FDA.

Dendreon, the maker of Provenge, based its technology on powerful dendritic cells. These immune cells normally help process molecules called antigens found uniquely on invaders, such as bacteria or viruses. Dendritic cells present those antigens on their own surfaces and interact with T cells, priming the T cells to attack anything bearing those antigens.

For Provenge, the company takes a patient's blood, finds dendritic cells, and loads those cells with a recombinant fusion protein composed of an antigen called PAP (prostatic acid phosphatase, found primarily on normal prostate cells) that is fused to an immune stimulant called GM-CSF (granulocyte--macrophage colony-stimulating factor). The antigen-loaded cells are then reinjected into a patient, a process that is repeated three times in one month.

The immunization appears to stimulate a powerful immune response involving T cells. Men receiving the vaccine survived, on average, nearly 26 months, compared with 21.7 months for the placebo group, according to updated phase 3 data reported in early March. Typical side effects of the vaccine included transient chills, fever, and sometimes headaches during administration.

View Illustration: Taking a Shot Against Cancer

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Larry Kwak, MD, PhD, of M.D. Anderson Cancer Center, presented similarly promising results for a patient-specific vaccine against follicular lymphoma called BiovaxID at last year's annual meeting of the American Society of Clinical Oncology. Like Provenge, the lymphoma vaccine also included the immune stimulant GM-CSF, but Kwak and his colleagues used tumor-specific molecules called "idiotypes" to trigger an immune response.

The scientists treated patients whose follicular lymphoma had gone into remission following chemotherapy, and those treated with the vaccine remained in remission almost 14 months longer than patients on a placebo (44.2 months versus 30.6 months).

Devil in the Details

Patrick Hwu, MD, also at M.D. Anderson Cancer Center, is taking a different vaccine approach to treating cancer, his against metastatic melanoma. The non-customized protein-based vaccine called gp100 had shown a relatively weak immune response in many patients, so Hwu and his colleagues added the powerful immune booster interleukin-2. Progression-free survival increased from about 1.6 months in control patients to 2.9 months in those receiving the vaccine.

One of his patients was Audhild Stapleton, 53, of south Texas, who had received a prior experimental vaccine at the University of Virginia in 1999. "It did work for seven years, I believe," Stapleton says. When her melanoma recurred in 2006, she participated in a second trial, this one under Hwu's care, and with the updated vaccine/interleukin-2 combination.

"The vaccine injection itself was not a problem, but the interleukin, it was very, very hard," she says. "I was in intensive care for three to four days each time, my skin dried out, I gained 40 pounds of water weight. … But I believe you need to take a stand and fight this disease every way possible."

Armed with a better understanding of the immune system, researchers are now doing just that. One of the most important next steps, Hwu and Emens say, is to understand how to best combine vaccine treatments with other therapies. Emens and others have shown that vaccines can work in synergy with drug therapy or radiation.

The researchers are also working closely with regulators to figure out how best to measure outcomes of cancer vaccine trials. In theory, it should take longer to see an effect of immune therapy, says NCI's Gulley. "The immune system keeps knocking off a few cells, so it's like compounding interest. … Early on, you see only modest improvement, but many months or years down the road, significant benefits accrue. And in theory, this can be going on long after the vaccine treatment." Considering it may take longer to develop an immune response, therapeutic vaccines may be particularly impactful against early-stage cancers, which can sometimes recur years later.

The value of vaccine therapy continues to grow with promising data from late-phase trials in prostate cancer, metastatic melanoma, and lymphoma. "I wouldn't call any of these three results home runs, but they are all base hits," Hwu says. “We just need to continue swinging away at the plate.”