Geskin and Falo have developed an experimental vaccine for cutaneous T-cell lymphoma that seems to work. Here, dendritic immune cells (green) interact with a tumor.
NOT ALL TUMORS ARE CREATED EQUAL

MADE-TO-ORDER CANCER VACCINES

BY ROBIN MEJIA

When Richard Nixon launched the “War on Cancer” in 1971, he couldn’t have known the battles ahead. At the time, doctors seemed to be beating back disease everywhere you looked. Vaccines had relegated the most horrible of the childhood diseases to the realm of memory (in the Western world, at least). Antibiotics were still at their peak of effectiveness, leading many to predict the same fate would befall infectious disease. Why not cancer?

Of course, history has shown that not all diseases are as amenable to controlling as measles and polio. (World Health Organization officials are still struggling to completely wipe these diseases out.) Bacteria and viruses have fought back with remarkable ferocity. And, though our understanding of cancer has developed at a terrific pace, much of what we have learned has simply taught us that we are dealing with a remarkably crafty enemy.

That’s not to say that treatments for cancers haven’t improved tremendously; they have. Yet for the most part, the weapons at a doctor’s disposal have been blunt instruments: surgical removal, radiation therapy, difficult chemotherapy regimens. More recently, a new level of understanding of cancer has developed at a terrific pace, much of what we have learned has simply taught us that we are dealing with a remarkably crafty enemy.

But a small number of researchers have pursued another approach in the development of targeted therapy, taking a page from the playbook of Jonas Salk.

“This may be the ultimate targeting,” says Louis Falo, an MD/PhD and chair of the School of Medicine’s Department of Dermatology, who works with a number of Pitt researchers on cancer vaccines. The term “vaccine” is a misnomer; Falo and colleagues are not pursuing preventative inoculations, like Salk’s polio vaccine, but rather treatments for patients who already have cancer. Still, if you think in terms of analogy, the name makes sense. Just as a polio vaccine uses some of the virus itself to arm the body’s immune system against the disease, a cancer vaccine uses a tumor’s own antigens for the same purpose.

Larisa Geskin (MD ’98, Res ’01, Fel ’03), an assistant professor of dermatology, is leading a clinical trial of a cancer vaccine that she developed with Falo. Geskin’s patients have cutaneous T-cell lymphoma, a rare form of cancer that targets the immune system. In advanced stages of the disease, most of a patient’s key immune cells have been replaced by cancer cells. Patients who enroll in Geskin’s trial are generally no longer able to respond to traditional therapies.

“There really is not great chemotherapy for end-stage cutaneous lymphoma,” Geskin explains. “There is not a single therapeutic agent that prolongs life.”

She’s hoping to change that. The trial is still in its early stages; she’s only given her cancer vaccine to four patients. But they have responded astonishingly well. The first patient to enroll was a man in his 50s with leukemia and a skin lymphoma that left him nearly bedridden, all of his skin red and cracked. Within two months, he was walking again and even pouring cement in his garage. Because the vaccine is an experimental therapy, Geskin only was able to give him eight injections, and he eventually relapsed, but she says he is in better health than he was before the trial. She intends to enroll another 15 patients in the trial. Yet, the initial results have been so startling that Geskin and Falo plan to publish their immediate findings in the next few months.

Pitt researchers believe the process they use to make the vaccine is unique. They start with precursors to dendritic cells. Dendritic cells are immune cells that recognize antigens and prime the body’s T-cells to attack. They go after whatever has that antigen on it, typically a virus or bacterium. Geskin harvests precursors to dendritic cells, along with cancer cells, from each patient. By growing the dendritic cells in the presence of tumor cells, the dendritic cells learn the tumor’s antigens. Geskin then matures dendritic cells with a chemical cocktail that makes them capable of presenting tumor antigens to the immune system as foreign invaders. Once she injects those dendritic cells into the patient’s lymph nodes, the body starts attacking the cancer cells. John Kirkwood, an MD professor and vice chair for clinical research in the Department of Medicine, is collaborating with Falo on a similar vaccine targeted at melanoma.

Geskin thinks that the personalized approach is the reason she’s seeing results.

“This is a key concept. Many vaccines for cancer failed because people used someone else’s tumor to treat another person’s cancer,” she explains.

Another innovation in the Pitt process is the way researchers capture antigens from entire tumor cells.

“Other vaccines use short peptides,” explains Falo. “We use whole cancer cells. The advantage of that is that you capture a broad range of antigens.”
10,000 to 25,000 genes are active in most cells at any given time. Some turn on and off at different points in the body’s development. Others respond to stimuli such as diseases. Yet it can be tough to measure whether or not a gene is actively producing protein at any given moment. Assays do exist that are designed to measure gene activity—but they have limited application and it doesn’t appear that they’ll ever be suitable for use in humans. Some assays require killing the animal that received the compound and staining its tissue. Others are themselves toxic. Still others involve using compounds that are visible only near the surface of the skin.

Eric Ahrens, an assistant professor of biological sciences at Carnegie Mellon University and an adjunct assistant professor of neurobiology at Pitt, and William Goins, a Pitt assistant professor of molecular genetics and biochemistry, have developed a technique that uses MRI to measure gene activity in live animals, without—as far as they can tell—harming them.

Because MRI machines use magnets to polarize the nuclei of atoms, it makes sense that magnetic molecules in the body would affect the image an MRI produces. Goins and Ahrens inserted a ferritin-producing gene into cultured human cells and also live mice. When the gene is active in the cell, the ferritin sequesters a small amount of a harmless form of iron.

“You can detect a signal from this iron when you put it in a magnetic field,” explains Goins. The iron doesn’t appear to influence the functioning of the cell, but it does change the way the cell looks to an MRI machine. MRI scanning isn’t toxic, so this process could help scientists perform long-term animal studies. They would be able to MRI the animals far more frequently than they could, say, x-ray them.

To get the ferritin gene into cells, Goins and Ahrens used a viral vector. (To create the vector, the virus was modified, so that instead of delivering illness-inducing DNA, it delivers DNA chosen by a scientist.) Viral vectors are commonly used in gene therapy trials. One challenge for those researchers has been confirming that the intended cells have accepted the therapeutic gene. Goins sees a potential future for genes like ferritin in providing a nontoxic marker.

By inserting both the therapeutic gene and ferritin-like gene in the vector, explains Goins, you could see where the genes are expressed. He notes that many current targets for gene therapy, such as Parkinson’s disease, are in the brain, a particularly tough place for scientists to assess activity using current techniques. He and Ahrens, however, have watched gene expression in mouse brains. But applying their technique in humans is a long way off, cautions Ahrens: “We’re not in any rush to get into people. I think our focus is going to be preclinical work or animal studies.”

Ahrens explains that though he and Goins used viral vectors, the ferritin gene could be inserted using just about any of the technologies scientists apply to develop transgenic animals. This would help researchers confirm information about gene activity in animal models of arthritis or cancer, for example.

In theory, the ferritin gene also could be inserted next to native genes to report on their activity.

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unning a hospital today without access to an MRI scanner would seem ludicrous. How else would doctors see detailed images of the body’s organs and other soft tissues?

Speeding and confirming diagnosis of everything from herniated disks to cancer, the technology has become part of the common healthcare vernacular.

But, in the 1950s, when the technology that drives MRI was first developed, it was heralded as a breakthrough in a different field. MRI was invented by researchers interested in studying chemical compounds. It took a couple of decades before scientists applied the principle of nuclear magnetic resonance—basically, using a large magnet to polarize the nucleus of an atom—to the human body. By the time the 2003 Nobel Prize in Physiology or Medicine recognized the pioneers of this work, including chemist Paul Lauterbur, who earned a Pitt PhD in 1962, the MRI’s place in medical history was quite secure.

Today, Pittsburgh researchers are once again using MRI technology to see new things. They’ve developed a technique to visualize the activity of genes in a living animal.

Only a fraction of the body’s estimated
One day, a 60-year-old man was diagnosed with terminal cancer; the melanoma started on his foot and spread throughout his body. He squeezed into the last spot in a clinical trial in another town and lived with his wife in their motor home there so he could receive an experimental treatment. He felt it was his only hope, and his gamble paid off. He’s enjoying time with his wife that some doctors never thought he would have.

We hear about such stories from time to time that remind us about the promise of medical research. Yet very few people volunteer for clinical trials. Overall figures are hard to come by, but as an example, among adults with cancer eligible for drug trials in this country, only about 3 to 5 percent volunteer to participate.

And these kinds of stories can also create the wrong impression. Many people, like the man in this story, consider enrolling in clinical trials only when their other options look dire. “Too many patients incorrectly assume that if you’re in a trial, it’s a last resort. Trials are essential in testing treatments at all stages of cancer as well as new methods of cancer prevention and screening,” says Ted Gansler (MD ’81), director of medical content at the American Cancer Society.

The shortage of volunteers slows the availability of new treatments and drugs, notes Samuel Jacobs (Res ’73), clinical professor of medicine at the University of Pittsburgh. With the help of a $1.2 million grant from the National Cancer Institute, he intends to both figure out why so few people volunteer and develop new ways to recruit participants. Although Jacobs is an oncologist, the tools he’s developing can be applied by other specialists looking to recruit.

Jacobs says there are many reasons for the lack of patient participation in trials. Among them: confusion about the risks of taking part and a dearth of awareness among both doctors and patients. “Some patients are very fearful of whether they’ll get a placebo or a real drug,” he says. “Some are mistrustful of the medical system. Others worry about drug toxicity and hidden costs involved.”

To help dispel fears and build trust, Jacobs is developing an interactive Web site for potential volunteers. His years of experience have helped him anticipate questions trial candidates are likely to ask. To make sure they cover all the bases, his team has asked patients and their families and friends to suggest information they’d like to see on the site.

The site lets users ask questions of a nurse whose prerecorded video responses simulate a one-on-one conversation. “We’ve got smart features built into the system that can respond to the different ways people may express themselves,” says Jacobs.

There’s been some buzz about how HIPAA privacy regulations have thrown up what seem like insurmountable hurdles to trial organizers, especially those who require healthy volunteers or are pursuing large epidemiological studies. Most other clinical researchers we spoke to have found the regulations to be a hassle they can live with. Their solution is mundane: more forms (in concert with patient orientations).

For Jacobs and others, a more significant part of their struggles in recruiting patients has been getting other doctors on board. Many physicians don’t tell patients about trials for which they’re eligible. For an oncologist, who’s likely to have a patient load of 2,000 a year, figuring out how to make the additional time for individual patient meetings on clinical trials isn’t always straightforward. And many docs aren’t informed about ongoing trial research.

“We’d like to develop a culture where we get all 70 UPMC oncologists involved,” Jacobs says. As part of his grant, he established videoconferencing for oncology grand rounds that allows doctors outside of Pittsburgh to learn about new trials at the University. Using AvantGo, an online PDA application, Jacobs has also developed a quick way for his colleagues to look up disease-specific trials for which their patients may be eligible.

He sees his work as urgent: “With rapid advances in molecular biology and the enormous number of new drugs being developed, we need more volunteers to determine [treatment] efficacy.” His goal is to increase participation in Pitt trials to 10 to 15 percent of eligible patients.