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A Shot at Cancer

By Alice Park

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Back in 1999, two researchers at the National Cancer Institute (NCI) received a long-awaited green light to launch separate studies on cancer care. Six months apart, Dr. Douglas Schwartzentruber and Dr. Larry Kwak began enrolling subjects to test an entirely novel weapon in the war on cancer — one they hoped would bypass the toxic effects of chemotherapy and give patients a new edge in halting the spread of tumors.

Both had the blessings of Dr. Richard Klausner, then NCI director. But even Klausner, a well-respected researcher, had to be persuaded at first. "I came to the NCI being quite skeptical about it," he says of the new strategy.

And he wasn't the only one. What Schwartzentruber and Kwak were hoping to do was prove they could vaccinate a patient against cancer — educate a body to, in essence, recognize and round up tumor cells the same way it polices viruses and bacteria. It certainly made good biological sense: the immune system is the body's built-in defense mechanism, after all, so why not turn it against one of the most ornery diseases around?

The problem, of course, is that a tumor is not exactly a pathogen. What it is, at its core, is a collection of aggressively growing cells that can't stop dividing. It is not entirely foreign, as a virus is; it does not infect healthy cells, as bacteria and viruses do. Turning the immune system against cancer cells would involve turning the body's defense mechanisms against a part of itself. Designing a vaccine to do this entails creating the biological version of a stealth weapon encased in a smart bomb equipped with a guided missile.

And that was proving to be a bit too challenging. Nothing that hundreds of researchers in hundreds of trials had attempted had worked. While the vaccine idea made logical sense, the immune system, it seemed, just wasn't designed to battle cancer this way.

But in June, after nearly a decade of carefully inoculating patients suffering from either advanced melanoma or a type of lymphoma, both Schwartzentruber and Kwak announced positive outcomes of their trials, at the American Society of Clinical Oncology meeting in Orlando, Fla. Their results, along with those of a trial vaccine against prostate cancer and an early candidate against a type of brain cancer, suggest that we might finally be on the way to unleashing the immune system against the disease.

It's about time. Senator Edward Kennedy's death after a yearlong battle with brain cancer is only the most prominent reminder that while many current treatments are certainly effective, they can be made even better. Though malignancies are now being caught earlier than ever before and treatments that target and control the disease are more effective than ever before, cancer is still the second biggest killer in the U.S., claiming more than half a million lives each year. Surgery, chemotherapy and radiation can do only so much when tumor cells hide in plain sight and even a single overlooked cell can seed new disease.

That's where a vaccine-based strategy could make a difference. An immune system trained to recognize the first signs of new or recurrent growth can begin to attack malignancies far earlier than the best scans can detect them. And the latest vaccines incorporate clever new insights into how malignant cells can be tagged, exposed and destroyed. "Understanding how the immune system works is going to play a significant role in our treatment of cancer going forward," says Dr. Len Lichtenfeld of the American Cancer Society.

It's not just the biology that is getting better. Researchers are even fine-tuning when to give a cancer vaccine. The latest data from the lymphoma trial, for example, suggest that in some cases, the best time to train the immune system might be during a remission, when the body's defensive cells are at their strongest. "It's been a slow evolution, but we are seeing the first inklings that cancer vaccines can work," says Dr. Steven Rosenberg, chief of the surgery branch at NCI and a cancer-vaccine pioneer who trained Schwartzentruber, now at the Goshen Center for Cancer Care in Goshen, Ind.

When Is a Vaccine Not a Vaccine?

There may be no better example of what is meant by preventive medicine than the strategy of vaccination. A healthy person is given a tiny taste of a virus — flu or polio, say — that's too weak to cause illness but just enough to introduce the body to the pathogen. If the virus later shows up for real, the immune system is primed and waiting for it.

That's close to how a cancer vaccine works, but not precisely. Most experts see cancer vaccines as a hybrid of treatment and prevention. While it's true that the Food and Drug Administration has approved vaccines against cervical and liver cancer, both are actually designed to fight the viruses most responsible for causing the disease, as opposed to targeting cancer itself — human papillomavirus in the case of cervical cancer and hepatitis B in the case of liver tumors.

Using vaccines to prevent nonviral cancers in someone who is disease-free is a whole different matter. For one thing, it's much more difficult to determine a person's chance of developing a particular type of cancer

than it is to determine the likelihood of being exposed to, say, the influenza virus or chicken pox. What passes for "exposure" in the case of nonviral cancers is a combination of genes and environment and a range of other X factors that can vary from person to person. How do you vaccinate against your family legacy of breast cancer or your constant exposure to secondhand cigarette smoke?

But that doesn't mean the immune system can't be exploited in a different way. Cancer vaccines would ideally be used in patients whose disease has already been diagnosed and treated with surgery, chemotherapy or radiation. They would then be immunized as a way to prevent the cancer from coming back and spreading. Such metastases are actually the leading cause of death from cancer. "The charm of working with the immune system is that we can use the body's own defense mechanisms to possibly get to that last cancer cell or at least create a surveillance system that keeps that cancer under control," says Lichtenfeld.

Trial by Failure

Before they can seek out these smaller, hidden deposits of tumors, however, cancer vaccines must prove that they can actually target and shrink a cancer's more conspicuous growths. This, it turns out, is obvious in theory but devilishly challenging to show in reality.

Take melanoma. In 2002 scientists at the John Wayne Cancer Institute in Santa Monica, Calif., thought they had finally figured out a way to turn the immune system against the skin cancer. Instead of trying to activate immune cells with snippets of tumor proteins they had created in the lab, they decided to grind up melanoma tumors and use the malignant slurry to prod the right immune cells into action. The result was Canvaxin, a vaccine against aggressive melanoma that was loaded up with 20 different tumor-specific components of melanoma, teaching the body new ways to recognize the disease. More than 1,500 patients were given the vaccine after being treated with surgery and chemotherapy. In the first five years of follow-up, the shot proved safe and worthy of moving into the most advanced level of human testing. But in April 2005, the scientists and the biotech company they had enlisted to develop the vaccine were forced to stop their studies when it became obvious that the vaccinated patients were not living any longer than the unvaccinated ones. "That put a damper on things," says Schwartzentruber. "They had what they thought was a promising start, and it was an international, multi-institutional study with a large number of patients."

In retrospect, Schwartzentruber says, the problem may have been that the vaccine was forced to work alone. Even the most well-sensitized immune system may be fooled by the homegrown nature of cancer, recognizing malignant cells as just another part of the body — which they are — and thus giving them a pass. When the cancer finally grows big enough to represent a real threat, it's too late.

Schwartzentruber thinks he has a way around that problem. In some trials, after giving his vaccine to patients with advanced melanoma that has spread to other tissues, he adds an immune stimulator called interleukin-2 (IL2) for reinforcement. Alone, the vaccine would not cause any tumors to shrink. The IL2

treatment itself wasn't very effective either; it shrank tumors in only 10% of patients. But combining the vaccine and IL2 has caused tumors in 22% of patients to regress — a doubling of effectiveness. "This teaches us a lesson: that combinations of biologic treatments are more powerful than their individual components," says Schwartzentruber.

Kwak and his collaborators, led by Dr. Stephen Schuster at the University of Pennsylvania, see a similar power in pairing. Their vaccine, against a form of non-Hodgkin's lymphoma known as follicular lymphoma, takes a slightly different, more personalized approach. Rather than relying on a commonly found antigen or snippet of cancer protein to teach the body to recognize the malignancy, they designed each vaccine using individual patients' specific lymphoma profiles. They then partnered this customized concoction with another immune stimulator, GMCSF. Patients receiving the combination remained in remission on average 44 months after the vaccination, a 47% improvement in disease-free survival compared with those getting the uncustomized vaccine, who stayed in remission for just 30 months.

This study is also the one that yielded the most evidence that the best time to inoculate patients is when they're in remission from their disease. While Schwartzentruber elected to administer his melanoma vaccine when his subjects were in the most advanced stages of illness, Kwak and his colleagues decided to capture the immune system at its best. They waited until the patients had been in remission for six months after chemotherapy, which rid the body of the bulk of the tumor burden. Give the immune system a break from that life-or-death battle, and it might be better able to do the surveillance work of corralling stray cells that escape the initial treatment. "I envision that vaccine approaches like this could be useful as maintenance therapy," says Kwak, who is the chairman of the department of lymphoma and myeloma at MD Anderson Cancer Center in Houston. "We would use chemotherapy and surgery to debulk the tumor and then vaccinate to maintain remission."

The Riddle of Success

Another way to make a vaccine more effective might be to manipulate the very nature of the tumor, so that it is a more obvious target for the immune system — a little like tying a more colorful fly on a fishing hook. The idea, says Dr. Patrick Hwu, chair of melanoma oncology at the University of Texas' M.D. Anderson Cancer Center and a member of Schwartzentruber's team, is to "get the tumor itself to look like a virally infected site, to get the whole immune system going."

The untreated immune system is not helpless in all of this. Rosenberg has biopsied tumors and extracted immune cells called lymphocytes from patients with advanced cancer and has grown these cells in culture. In a test tube, the lymphocytes are perfectly capable of killing tumor cells. But in the body, for some reason, they can't seem to stop a lesion from growing. So for melanoma, some researchers are working with a cream that can increase a tumor's "foreignness" to the immune system, tagging it to look more like an unwelcome virus and less like a familiar self cell. Other groups are testing ways to shut off the immune suppressors that the tumor sends out to hinder the natural seek-and-destroy tendencies of the immune system. That makes sense. Supercharging the immune system while the immune suppressors are still at work is a little like

revving a car engine without releasing the emergency brake: in both cases, you're not going anywhere. And yet most early vaccine efforts have involved stepping on the gas alone.

One other way to get the immune system moving might be, in effect, to replace it with an entirely new one, says Rosenberg. If a vaccine can marshal the body's defenses to recognize and destroy a tumor, could you rebuild those defenses from the ground up and this time design them so they'll be especially good at fighting cancer cells?

Rosenberg's thinking is based on the now familiar strategy of the bone-marrow transplant for leukemia and lymphoma, which are blood- and immune-cell cancers. Radiation is used to obliterate a patient's cancer-tainted immune cells; those cells are then replaced by a population of new ones harvested from a healthy donor or grown from some of the patient's healthy cells. Rosenberg refines this method for melanoma by first exposing immune-system cells to tumor cells in a dish, thus "training" them to sprout proteins that target cancer cells, and only then infusing them into patients. Already he has shown that such a fortified mix can cause tumor regression in up to 70% of melanoma patients.

Even that, Rosenberg says, can be improved on. He is tipping the odds further in favor of the anticancer cells by genetically modifying the tumor-fighting T cells so that cancer cells aren't simply among the ones they recognize but are the only ones they recognize — eliminating the distraction of other infections and allowing the T cells to devote all their energy to the malignancy alone. In June he published results showing that such manipulation can cause regression of tumors in one-third of subjects. "I think the most important progress in using the immune system is not by a vaccine but by using cell-transfer approaches," says Rosenberg. "Those are looking to be far more effective."

Measuring that effectiveness will be another challenge. The melanoma- and lymphoma-vaccine studies both tracked only the extent to which tumors regressed and were not designed to document what most cancer experts — not to mention patients — see as the gold standard of any new therapy: survival. Do patients who are vaccinated live longer than those who are not? How do the vaccine's cancer-controlling powers compare with those of the expanding list of drugs designed to sneak in and halt growing lesions by shutting off their supply of nutrients and oxygen or hampering their growth spurts?

Solving those riddles might be the most formidable challenge yet for the vaccine field. Some experts are already questioning the need for the lymphoma vaccine when a drug, rituximab, exists to control the disease. Kwak points out, however, that in addition to being able to seek out small deposits of tumor cells that even the best-targeted drug therapies might miss, vaccines are generally less toxic. Rituximab, for instance, can lead to viral infections and heart problems and may be toxic to the kidneys. If, as some researchers hope, cancer is ever to become more of a chronic disease like diabetes, which can be managed for life, finding treatments that are safe and effective over many years becomes critical. "The risk-benefit ratio begins to swing more against chemotherapy or targeted agents for long-term maintenance," says Kwak. "Whereas a vaccine, with a favorable safety profile, is ideal for that kind of setting."

If that's true, then this first group of cancer vaccines is well on its way to seeding an entirely new field of immune-based treatments for cancer. "In some way, shape or form, our body repairs cancer cells and 'prevents' cancer," says Lichtenfeld. "If it didn't, we would have much more cancer than we actually see. How simple it would be for us to take some markers on a cancer cell's surface and create a vaccine to help the body do what it's supposed to do." It's not simple at all, as it turns out, but it's an idea whose power and potential certainly make it worth the effort.

The original version of this article misstated that Dr. Steven Rosenberg trained Dr. Larry Kwak at the National Cancer Institute (NCI); in fact, the doctors only worked at NCI at the same time. The original article also omitted the currently held positions of Dr. Douglas Schwartzenuber and Dr. Kwak, at the Goshen Center for Cancer Care and MD Anderson Cancer Center, respectively.

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