

**Story
Summary**

➤ **"Occult tumors,"** too small to find in lymph node biopsies, boost the risk of recurrence in sites beyond the colon for many people with early-stage colon cancer.

➤ Developed over 15 years of research at Jefferson, **an experimental cancer vaccine teaches the immune system** to spot a unique target on cancer cells and then to destroy them.

A photograph of two men in a laboratory or office setting. The man on the left is younger, with dark hair and a beard, wearing a white lab coat over a blue and white checkered shirt. The man on the right is older, with grey hair, wearing a white lab coat over a white shirt and a patterned tie. They are both looking towards the right, and the younger man is pointing at a document held by the older man.

a colon cancer vaccine

➤ **The vaccine entered its first human trial** recently and was found to be safe and to elicit an immune response from some participants. More human studies are planned.

In 20 percent of people with early-stage colon cancer, hidden tumor cells have already spread. An experimental vaccine trains the immune system to seek and destroy them.

BY SARI HARRAR

PHOTOGRAPHY BY KEVIN MONKO

reaches clinical trials



Colorectal cancer is the second-leading cause of cancer deaths in the United States, the killer of more than 49,000 Americans each year. The mantra for survival: Catch it early. Yet even with a great prognosis—early-stage disease and no sign the cancer has spread—it can be a deadly time bomb.

For one in five people with “lymph node-negative” colon cancer—and up to 40 percent of African-Americans—rogue tumor cells *have* escaped the colon. They’re too tiny and far-flung to be spotted when a pathologist checks lymph node biopsies. “But when occult disease is present, at least 50 percent of colon cancer returns within two to five years. And when it does, it’s not confined to the colon any longer,” says Scott A. Waldman, MD, PhD ’80, professor and chair of SKMC’s Department of Pharmacology & Experimental Therapeutics. “It can metastasize to the liver, the lungs, the abdomen. Patients need chemotherapy. And if they have metastatic disease, their risk for dying can be higher than 90 percent.”

Now, an innovative colon cancer vaccine developed by research instructor Adam Snook, PhD ’08, in collaboration with Waldman and a large, interdisciplinary team from the departments of Microbiology and Immunology, Medical Oncology, Dermatology and Surgery shows promise for disarming colon cancer’s time bomb.

After 15 years of research and dozens of lab studies, the vaccine was recently tested for the first time in humans when 10 women and men rolled up their sleeves for a phase 1 clinical safety trial. A second human trial looking more closely at the vaccine’s ability to trigger an immune

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From left: Scott Waldman, MD, PhD '80; Scott Goldstein, MD; and Adam Snook, PhD '08.

response is being planned. If it works as expected, one shot in the arm could protect against cancer cells that linger long after surgery.

“It has been incredible to see this vaccine move from the lab to a human trial,” says Snook, who joined Waldman’s lab as a doctoral student in 2002 to work on concepts that led to the vaccine. “Cancer immunotherapy has exploded in the past two to three years, with exciting new treatments emerging nationally and here at Jefferson. Now there’s a possibility for colon cancer. Rather than being forced to wait and hope the disease does not come back, the vaccine could give patients and their doctors an opportunity to actively fight and prevent recurrence.”

TARGETS AND WALLS

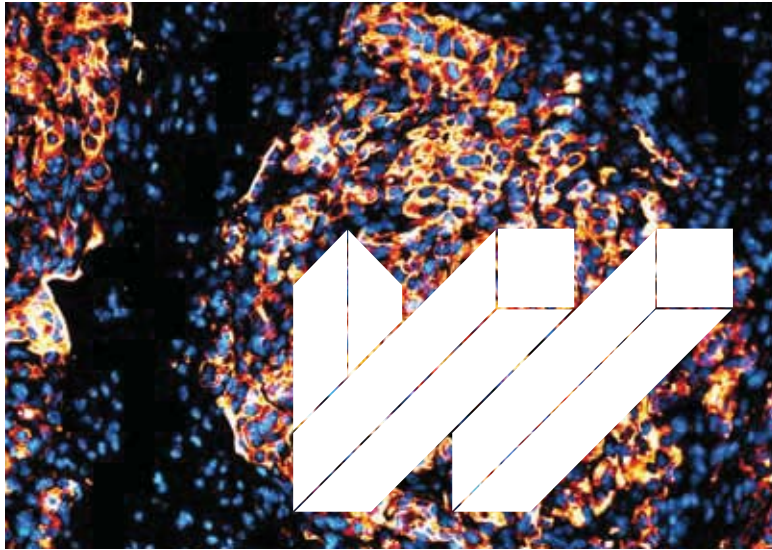
The vaccine is called Ad5-GUCY2C-PADRE. Like a bacon-lettuce-and-tomato sandwich or a soy latte with a caramel shot, the lengthy name is just a list of ingredients. Together, they teach the immune system to recognize and destroy cancer cells that display a specific chemical marker. In mouse studies, the vaccine reduced the formation of colon cancer tumors in the liver by more than 88 percent and in the lungs by 78 percent.

The vaccine’s formula evolved through a series of discoveries and roadblocks. At its center: the protein guanylyl cyclase C (GUCY2C or GCC for short). “GCC is a hormone receptor normally expressed only by normal cells in the lining of the intestines,” Snook explains. “Scott Waldman was the first to identify the relationship between GCC and colon cancer in 1994, finding that tumor cells also express it.”

If you’ve ever had traveler’s diarrhea, you’ve experienced GCC’s dark side: It lets bacterial toxins latch on to intestinal cells and wreck your vacation. But GCC’s got plenty of real jobs, too, including regulating fluid and ion levels in cells and suppressing DNA mutations. No other healthy cells in the body make GCC, but the discovery that colon cancer cells churn it out made it an ideal vaccine target. And a 2011 study in the journal *Clinical Cancer Research* suggests how important it could be. When Waldman’s team measured GCC in the lymph nodes of 299 lymph node-negative colon cancer survivors, they found that 40 percent had intermediate to high levels; cancer recurred within two years for 31 to 68 percent of them.

But would aiming the immune system at GCC-producing cancer cells damage healthy ones, too? Borrowing a lesson from HIV vaccine research, Snook suspected the answer was no. “Mucosal cells lining the intestines are in a completely separate compartment of the immune system from the systemic immunity in the rest of the body,” he explains. HIV vaccine researchers come up against this barrier in trying to deliver vaccines to the right places. “The colon cancer vaccine is delivered systemically, by a shot in the arm muscle,” he says. “This keeps it away from healthy intestinal cells.”





A close look at cells in the lungs of mice. The researchers created metastatic colorectal cancer in mice and stained the metastases in their lungs. Here, the blue stain shows cell nuclei; the “fire” shows GUCY2C in the metastases (red to yellow to white indicates increasing levels of GUCY2C expression). The team’s vaccine is designed to create immune responses to GUCY2C that seek out and destroy those GUCY2C-expressing metastases. In this image, there is a central mass of GUCY2C-expressing cells representing a colorectal cancer metastasis, as well as part of a second mass on the left.

“WE WERE ECSTATIC”

Snook had another puzzle to solve: Mouse studies showed that the experimental vaccine didn’t activate helper CD4 cells that command killer CD8 cells and B cells to go on the offensive.

“Killers need helpers to replicate and get strong. Without them, there’s no immune attack,” he says. “We found a hole in the immune system. CD4 cells would not recognize GCC.” Snook suspects it’s one way the body protects against an auto-immune attack. The work-around: adding a snippet of protein called PADRE, which lets the vaccine trick other CD4 cells into mustering the killers. “We didn’t invent PADRE, but nobody’s used it this way before,” Snook notes. In a mouse study, a similar trick increased CD4 activity and as a result boosted killer CD8 activity tenfold. It also activated CD8 killer cells with a long-term memory for GCC, which may be able to protect the body for many years.

The last ingredient—Ad5—is a common-cold virus added to the vaccine to activate the immune system. It’s engineered so it won’t cause cold symptoms. But in their human study, the researchers found that volunteers who already had lots of antibodies to the virus didn’t respond to the vaccine. In contrast, those with low levels did. “This isn’t a setback. The first study was a proof of concept,” Waldman says. “We were ecstatic. The vaccine was safe—two participants had soreness at the injection site and three others had aches, chills, sweating and in one case a fever. And we saw an immune-system reaction. We can move ahead.”

“IF IT HELPS SOMEBODY, IT’S WORTH IT”

As a graduate student, Snook sometimes rode SEPTA’s R3 train home late at night with Takami Sato, MD, PhD, the K. Hasumi Professor of Medical Oncology at SKMC and director of the Metastatic Uveal Melanoma Program in the Department of Medical Oncology. “We definitely talked about the concept and translating this to humans,” Snook says. “Dr. Sato has been involved from the beginning because of his expertise in experimental cancer immunotherapy.”

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As co-principal investigator with Snook for the phase 1 trial, Sato planned the details of the vaccine's first human study and helped secure funding. "We were all there when the first patient received the vaccine," Sato says. "It was an important moment." The results, he says, are promising—and may have applications for occult tumor cells from cancers of the stomach, esophagus and pancreas, which, it turns out, also produce GCC. "We've seen a signal," Sato says. "Now we need more studies."

The project was financed with a \$4.5 million grant from Pennsylvania's Commonwealth Universal Research Enhancement Program, which is funded by the landmark 1998 tobacco settlement between major tobacco makers and state governments. The grant also involved collaborations with Cheyney University, Fox Chase Cancer Center, Lincoln University, St. Joseph's University and the University of Pittsburgh on studies to identify and remove factors that prevent colon cancer patients from signing up for cancer vaccine trials. That research was led by Ronald E. Meyers, PhD, director of the Division of Population Science in Jefferson's Department of Medical Oncology.

Colorectal surgeon Scott D. Goldstein, MD, professor and director of the Division of Colon & Rectal Surgery, recruited Jefferson patients with early-stage, node-negative colon cancer for the human study. "They know what it's like to go through this and want to make it better for others down the road," he says. "It's great to know that the vaccine's safe and elicits an immune response. As a surgeon, I'm really waiting for later-stage studies with benefits for patients. That will be really exciting."

Ed Bailey, 77, a U.S. Navy veteran and retired electric utility supervisor and procedure writer from West Deptford, N.J., needed no encouragement when asked to join the study. He found out he had early-stage colon cancer in spring 2012 after a routine colonoscopy. A Jefferson surgeon removed the tumor, and Bailey returned every two to three months for a sigmoidoscopy to check his colon and for blood tests aimed at finding recurrences as soon as possible. So far, so good. "I have five children—including two sets of twins—and several grandchildren," he says. "I want to be around for them."

Bailey had few fears and plenty of hopes. "I wasn't worried that the vaccine was experimental," he says. "And the shot didn't even hurt—though I joked with the nurses and yelled a little. I've been through colon cancer. Anything I can do to help someone else avoid going through this, I'll do." 🙏

To learn more about Drs. Waldman and Snook's research or support their work, contact Michael Burton, Associate Vice President, Sidney Kimmel Cancer Center, at 215-955-7943 or michael.burton@jefferson.edu.

COLON CANCER'S DEADLY RACIAL DISPARITY

Among African-Americans, colorectal cancer death rates are 52 percent higher in men and 41 percent higher in women compared to whites, according to the American Cancer Society. Lower screening rates account for just 19 percent of the difference. Black patients are less likely to receive recommended surgical treatments and chemotherapy. And black individuals may also be at higher risk for occult disease—the undetected spread of tumor cells to lymph nodes in early-stage cancer.

A 2012 Jefferson study of 282 people with early-stage colon cancer found four times more hidden disease in lymph nodes from black than from white volunteers. Over two years, black volunteers were five times more likely to see cancer recur. "African-Americans may have more occult disease for genetic reasons," Waldman says. "Delays in screening may also explain some of the difference. Colon cancer grows slowly. A stage 1 or 2 tumor can take years to develop. The later it's caught, the greater the chance that there's disease somewhere else as well."

Jefferson researchers hope their experimental colon cancer vaccine can help by destroying small groups of tumor cells before they can grow. "We want to close this gap," Waldman says.

