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CAN OUR OWN IMMUNE RESPONSES  
TAKE ON CANCER? | BY ELAINE VITONE

# RIGHT UNDER OUR NODES

**H**e could not eat. Two months earlier they'd pruned an orange-size tumor from his neck, but again the cancer was thriving, all but choking him as it spread, taking root in his tonsils and hanging grape-shaped growths below his left ear. In his tenement bed on the Lower East Side, Mr. Zola lay waiting to make medical history, though history would not remember this poor Italian immigrant's full name.

It was October 1891, "The Golden Age of Quackeries," when cancer therapy employed such barbarisms as mercury, quicklime, and electrocution. As Zola lay dying, a young doctor named William Coley visited his home to conduct an experiment so dangerous that New York Hospital would not allow it on its campus—injection of a killer bacterium known today as *Streptococcus pyogenes* directly into the tumors in Zola's neck. He'd been trying to infect Zola for months to no avail, but this time, within hours, chills, vomiting, and fever roared through Zola, and his skin turned bright red. For a man in Zola's condition—or anyone in this prepenicillin era—this could have been a life-ending act.

Olivera Finn is convinced the immune system is our best cancer watchdog. Case in point: The bottoms of the wells on this plate are coated with tumor antigen and filled with serum from cancer patients. The brighter the yellow, the higher the concentration of antitumor antibody in the serum. This tells Finn that the immune system is trying to control tumor growth.

PHOTO COURTESY FINN LAB



But Olivera Finn, chair of the University of Pittsburgh Department of Immunology, thinks of Coley as a hero.

Coley was attempting to duplicate the success of a single, fluke case he'd read of in the hospital's medical records. A cancer patient had suffered a violent *Streptococcus pyogenes* infection—St. Anthony's fire, as it was commonly called—and once it subsided, he went into remission.

It was a shot in the dark, but it worked. Zola survived, barely. His tumors shrank, his airway cleared, and as long as he continued taking Coley's treatments, his cancer ceased to spread. Zola lived another eight and a half years before cancer finally won. Coley had abetted an elusive phenomenon of the body known as immunosurveillance.

To grasp the concept, you must first entertain a thought even scarier than 19th-century medicine: Cancer's predecessors may be far more prevalent than you imagine. As you read this, the smallest seeds of cancer may be hiding in people all around you, or even struggling to make a vineyard out of your throat. But Finn says that if you're healthy—especially if your immune system is in top shape—you're likely to render your tumors harmless, or even kill them before they have the chance to form. Immunosurveillance is an unheralded success of the body that probably happens more often than you'd ever want to know.

Finn is the immune system's biggest fan, and when she's excited about something, it shows. While a student at Stanford University, she shared a lab bench with the late Shraga Segal, who was a postdoctoral fellow at the time and later became a leading cancer immunobiologist. Finn would rush home to nurse her son while waiting for results of experiments. Before she left the lab, she would make Segal promise not to check the results until she returned.

"I wanted to see it together," says Finn. "I didn't want to be the second. It's like when a child starts walking."

Finn recalls that when she and Segal worked together in the '70s, and immunology was a newly developing field, he believed that every experiment held the promise of teaching them something important. Segal couldn't imagine doing anything other than immunology, and Finn feels the same way now.

"Whatever I love, I advocate," she says, and advocate she does, as a member of the Immunology Task Force for the American

Association of Cancer Research; council member of the International Union of Immunology Societies; president-elect of the American Association of Immunologists; and senior editor for immunology for the world's premier cancer-research journal, *Cancer Research*.

Finn hopes that once the rest of the world catches on, maybe it will become commonplace to see immune response as she does—not only as a system that engages in the well-known role of warding off invaders, but also as a promising means of both detecting and defeating cancer.

Even the immune system's biggest fan knows that the system isn't perfect. Finn says that all too often, cancer can win for a number of reasons. For one, the immune system may be hindered by genetic predisposition, environment, immunosuppressive drugs, or age. For another, genetic mutation in either the patient or the cancer can cause the immune system to respond in ways that may only control the cancer temporarily. And sometimes, the immune system mounts a less-than-ideal response that ultimately gives cancer the upper hand.

Robert Schreiber, a professor of pathology and immunology at Washington University in St. Louis, explains that in its fight to eliminate tumors, the immune system alters the type and amount of antigens cancer uses to attack the body. Schreiber has coined immunosurveillance "immunoediting," finding the moniker better suited for the "seesaw" relationship between the immune system and tumors.

Although it's true that immune response is a mixed bag, laboratory evidence (including Schreiber's) shows that healthy mice grow tumors, but immunocompromised mice grow übertumors. We're better off with a flawed champion than no champion at all, Finn would say.

Finn points out that to date, only one laboratory test has been recommended by the American Cancer Society—PSA, which measures increased levels of prostate-specific antigen.

Unfortunately, benign functions of the prostate can cause spikes in PSA levels as well. The result: overdiagnosis and unnecessary biopsies. Finn calls PSA "antique."

Yet, although we still use poisons and knives to try to defeat cancer, we've come a long way since the Golden Age of Quackery. Today researchers are developing early detection methods using advanced molecular technologies. Bill Bigbee directs the University of Pittsburgh Cancer Institute's (UPCI) Clinical

Proteomics Facility. He says we're in the midst of an "omics revolution" in cancer research initiated by the Human Genome Project. Researchers continue to develop new "omics" approaches; they started with genomics, which gives an analysis of cancer-cell genes and their expressions. Then came proteomics, peptidomics, metabolomics—"and the omics keep coming," he says, including—you guessed it—immunomics.

However, Finn wrote in a *New England Journal of Medicine (NEJM)* editorial last September, these applications "are not being developed fast enough."

Investigators are using proteomics to try to find useful cancer biomarkers. But generally, by the time the tumors are substantial enough to produce cancer-specific proteins that these tests can detect, doctors can tell the patients are sick just by looking at them, Finn says. The challenge is detecting cancer early enough to be able to do something about it.

Bigbee notes that a number of candidate biomarkers—products of genomics and proteomics studies now in the evaluation and validation pipeline—appear to be sensitive in early stage patients.

He says that a couple of years ago, he would've agreed with Finn's skepticism of things "omic," but considering the rapid pace at which the technologies are emerging, he's now thinking we should cast as wide a net as possible. Yes, it's costly; and yes, it's technically and intellectually challenging.

"But that's what we're about," he says. "That's modern science."

But perhaps it doesn't have to be that way, Finn suggests. She believes we've lost sight of the fact that cancer doesn't happen in a vacuum, but within the complexities of a living host. We have everything to gain from studying the battle between tumor cells and our own bodies, Finn says. As the immune system encounters the earliest inklings of cancer, it releases antibodies—air raid warnings. Perhaps the world's most effective cancer detection method has always been right under our noses.

Last year, Finn and John McKolanis, a research associate in the Department of Immunology, collaborated with Harvard University researchers. The group compared ovarian-cancer patients to a control group. They looked for evidence of immune response to MUC1, an antigen associated with ovarian tumors as well as lactation, pregnancy, oral contraceptive use, and pelvic surgery, among other events. The researchers found that the



William Coley (top) used a deadly bacterium to kill an advanced cancer in Mr. Zola (bottom).

more MUC1-antibody-producing events these women experienced early in life, the lower their risk for ovarian cancer. The immune system responds to new threats more effectively in youth. If a woman generates anti-MUC1 antibodies for the first time at a later stage in life, it could mean cancer is on the way.

A team at the Scripps Research Institute in La Jolla, Calif., pursued a study examining seven tumor-associated antigens. The antibodies worked as biomarkers in 92 percent of the patients and even specified the types of cancer in 91 percent. The study supports Finn's credo, which she wrote in her *NEJM* editorial: "There is no detection instrument that rivals the sensitivity and specificity of the immune system." She's eager to see the Scripps researchers draw more attention to their study—typical Finn zeal. Schreiber credits her as "one of the true public voices" of the field.

"[A] public voice or a loudmouth?" Finn jokes. She admits she can't help goading people. "I get them all busy."

More than an ideal biomarker, immune response is a bio make-or-breaker—a key player in the battle for your life. Finn says, "You can either let it do what it does, or you can make it do it better"—meaning you can take a lesson from Coley's experiment.

This may sound foolhardy. After all, Coley nearly killed Zola and, in fact, did kill two of his first 12 test patients with his live-bacteria injections. However, Coley subsequently tempered his methods, opting for a mixture of innocuous bacteria instead, and in at least one

case, it worked.

As a deathly ill German immigrant with an eggplant-sized tumor on his abdomen fought off a Coley-induced infection, he shrunk his tumor by 80 percent in less than three months. He lived another 26 years before dying of a heart attack.

Unfortunately, no one could duplicate the results of that singular case. Coley was dismissed as just another quack.

Finn and Chandra Belani, professor of medicine and codirector of the Lung and Thoracic Malignancies Program at UPCI, hope to harness the mechanisms behind Coley's infrequent successes, boosting and/or initiating immunosurveillance.

They've secured funding for clinical trials of a lung-cancer prevention vaccine as part of the Specialized Program of Research Excellence in Lung Cancer. The vaccine is designed to prevent recurrence by boosting immune response to cyclin B1, a lung-cancer antigen Finn has been investigating for years.

Preliminary data from the study indicate early-stage lung-cancer patients with anti-cyclin-B1 antibodies are able to fight off recurrence longer than other patients. Out of seven antibody-producing patients studied, only one developed cancer again in the first 22 months after surgery; of the nine antibody-negative counterparts studied, six experienced a recurrence.

Finn also would like to pursue clinical trials of a vaccine designed to boost immune responses to chronic pancreatitis (linked epidemiologically to pancreatic cancer) and advanced autonomous polyps (precursors to colon cancer). Such trials would be the first to test a cancer vaccine on nonvirally caused cancers.

If this amazing, diagnosing, remission-prolonging, and even curative device—the immune system—is as close as our own lymph nodes, why does it get so little attention?

"I think that a lot of people like gadgets," Finn says with a laugh. "I think gadgets win over ideas every time." She adds that bias has a lot to do with it as well.

Critics used to say that because cancer is born within the body, the immune system cannot react to it. It's clear that the immune system reacts to cancer, says Finn. Now critics contend that the immune system is no match for it.

Not enough was known about the immune system to test the immunosurveillance hypothesis effectively when it was first

proposed in 1957. In the next several years, researchers tested control mice against immunocompromised mice, but unbeknownst to them, the latter turned out to be immunocompetent after all, so both groups developed cancer at the same rate. Animal studies have since made a strong case for immunosurveillance, but skepticism remains.

A group at Rockefeller University is studying the first documented cases of successful human immunosurveillance. The reason these cases were noticed at all is unfortunate. The patients' immune responses caused rare autoimmune diseases known as PNDs—paraneoplastic neurologic syndromes. Doctors detected breast, ovarian, and small-cell lung tumors in the patients during PND diagnosis—tumors that were kept in check without anyone's notice until neurological problems compelled the patients to visit a hospital. Some patients had no sign of cancer whatsoever—they did, however, present antitumor antibodies, signs of battles won.

Some might consider this story a cautionary tale, a reason to rule out cancer immunotherapy as too dangerous. When the subject comes up, Finn acknowledges that immunotherapists must be selective in choosing their targets. In the same breath she says the Rockefeller group's findings are good news—proof that immunosurveillance exists.

Finn is not interested in talking about the legitimacy hurdles her field has scaled since Coley's day. She's focused on the future: one-stop shopping for diagnosis and treatment at a fraction of the time, expense, and inconvenience. As an alternative to colonoscopies, perhaps one day doctors will detect the smallest germs of cancer in blood samples, then immediately administer vaccines. And if cancer is detected in malignant stages, once the tumors are removed, perhaps doctors will prevent recurrence by boosting antibody levels as needed.

She thinks big.

In underdeveloped countries where widespread papilloma-virus infection causes cervical-cancer epidemics, it will be much easier for health workers to collect drops of blood from women than do pap smears. Then, they'll be able to zero in on women with the highest risk, manage their antibody levels with a vaccine, and save lives. Someday.

In the meantime, there's work to do. Finn sifts through manuscripts, rushes from one conference to another—advocating, goading. "All for the cause," she says. ■