The T-Cell Army

Can the body's immune response help treat cancer?

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In the summer of 1890, an adventurous seventeen-year-old from New Jersey named Elizabeth Dashiell travelled across the United States by train. During the journey, she caught her hand between the seats of a Pullman car. The hand became swollen and painful, and, when it didn't heal after she returned home, Dashiell consulted William Coley, a young surgeon in New York City. Unable to determine a diagnosis, he made a small incision below the bottom joint of her pinkie finger, where it connected to the back of her hand, to relieve the pressure, but only a few drops of pus drained out. During the following weeks, Coley saw Dashiell regularly. In the operating room, he scraped hard, gristly material off the bones of her hand. But the procedure gave only fleeting relief. Finally, Coley performed a biopsy that showed that Dashiell had sarcoma, a cancer of the connective tissue, which was unrelated to her initial injury. In a desperate attempt to stop the cancer's spread, Coley followed the practice of the time and amputated Dashiell's arm just below the elbow. But the sarcoma soon reappeared, as large masses in her neck and abdomen. In January, 1891, she died at home, with Coley at her bedside.

After Dashiell's death, Coley was distraught, and searched through the records of New York Hospital for similar cases. He found one patient who stood out from the grim stories. Eleven years earlier, Fred Stein, a German immigrant who worked as a housepainter, had a rapidly growing sarcoma in his neck. After four operations and four recurrences of the cancer, a senior surgeon declared Stein's case "absolutely hopeless." Then an infection caused by streptococcal bacteria broke out in red patches across Stein's neck and face. There were no antibiotics at the time, so his immune system was left to fight off the infection unaided. Remarkably, as his white blood cells combatted the bacteria, the sarcoma shrank into a bland scar. Stein left the hospital with no infection and no discernible cancer. Coley concluded that something in Stein's own body had shrunk the cancer.

Coley spent the next decade hoping to replicate Stein's extraordinary recovery. In "A Commotion in the Blood," published in 1997, Stephen S. Hall describes how Coley inoculated cancer patients, first with extracts of streptococcal abscesses, termed "laudable pus," and later with purer cultures of the microbes. He claimed several successes, but the medical establishment did not embrace his approach, because his results could not be reliably reproduced. His primary critic, the pathologist James Ewing, believed that the new technique of radiation was the only scientifically sound way to treat cancer.

Coley's work was financially supported by John D. Rockefeller, Jr., a classmate of Dashiell's brother who had considered Elizabeth his "adopted sister." But Rockefeller also donated to Ewing's research. While Coley told stories of miraculous recoveries, Ewing presented numbers

that consistently demonstrated the power of radiation. Ultimately, Rockefeller chose Ewing as his scientific adviser. Rockefeller's support led to the creation of what is now the Memorial Sloan-Kettering Cancer Center, one of the foremost institutions studying and treating malignancies. The idea that the body's immune system could play a crucial role in eradicating cancer was largely discarded. One doctor at the time called Coley's hypothesis "whispers of nature."

In the last hundred years, progress in the treatment of cancer has come mostly from radiation and chemotherapy. Previously fatal blood-cell cancers, such as childhood leukemia and Hodgkin's disease, are now curable. But solid tumors, which grow in the lungs, the colon, and the breast, have stubbornly resisted treatment once they spread beyond their initial site.

In 1971, the Nixon Administration declared a "war on cancer," promising Americans that within ten years the disease would be beaten. At the time, many researchers believed that cancer was caused by a virus that speeded up a cell's metabolism, resulting in uncontrollable growth. After all, they had discovered some hundred viruses that caused cancer in amphibians, birds, and mammals. In the early seventies, interferon, a drug that had been developed from a protein released by white blood cells during a viral infection, was widely thought to be a possible cure for cancer; in 1980, it appeared on the cover of *Time*. The tumors of mice shrank dramatically when treated with the drug. But in patients interferon failed to cure solid tumors, and melanoma responded only occasionally.

Over the next decade, other proteins produced by the body as part of its immune response were made into drugs, most notably one called interleukin-2. In 1988, Armand Hammer, the ninety-year-old oil-company magnate who chaired Ronald Reagan's cancer panel, sought to raise a billion dollars, with the aim of curing cancer by his hundredth birthday. He touted interleukin-2 as an immune booster that could achieve the goal. But most solid tumors were impervious to it, too.

In the past fifteen years, as tumors have been found to contain genetic mutations that cause them to grow unrestrained, the focus of research has shifted to cancer's genome. Targeted therapies, which are designed to disarm these mutations, are now at the forefront of care. The first successful targeted therapy was Gleevec, which caused rapid remissions in chronic myelogenous leukemia, with few and mild side effects. Herceptin, a targeted therapy that attacks HER-2, a protein that is found in some twenty to thirty per cent of breast-cancer cases, has also been effective.

Advances such as these caused Coley's approach to fade into obscurity. Harold Varmus, a Nobel laureate and the director of the National Cancer Institute, told me that until very recently, "except for monoclonal antibodies, every therapy that exploited the immune system was pretty abysmal. There weren't any good ideas about why immune therapy failed." But now patients who did not respond to available therapies have shown dramatic and unexpected responses to a new series of

treatments that unleash the immune system. Coley's theories are suddenly the basis for the most promising directions in cancer research. In March, 2011, the National Cancer Institute announced that it would fund a network of twenty-seven universities and cancer centers across North America to conduct trials of immune therapies. Mac Cheever, the director of the program, who is at the Fred Hutchinson Cancer Research Center, in Seattle, described it as a way to speed the practical work of developing treatments. "All of the components needed for effective immunotherapy have been invented," he said.

Jim Allison, the director of the tumor-immunology program at Memorial Sloan-Kettering, began his career as a researcher at the University of Texas Cancer Center, in 1978. At the time, he was taken with the idea that the T-cell could be directed against cancers. T-cells are a potent type of white blood cell that destroy cells infected with microbes that they recognize as foreign. The immune system uses a variety of white blood cells to fight disease. Some, like neutrophils and macrophages, engulf and chew up microbes. In contrast, T-cells attack the microbe from the outside, with a fusillade of enzymes. Cancers disarm the immune system, producing proteins that cause T-cells to either quickly become exhausted and die or blithely overlook the tumor. Allison's research focussed on why T-cells failed either to recognize cancer as being aberrant or to attack it, as they do with microbes.

Allison's mentors discouraged him from pursuing research on T-cells. "Tumor immunology had such a bad reputation," he told me when we met in December at his laboratory at Sloan-Kettering, which overlooks the East River. Allison, who is sixty-three years old, is a thickset man with a stubbly beard and a gravel voice. "Many people thought that the immune system didn't play any role in cancer." Treatments like interferon and interleukin-2 had led scientists on a roller coaster of hype followed by disappointment. Immune therapy was also tainted by popular claims that following a certain diet or reordering your mind could be natural immune-boosting ways to cause tumors to disappear, with none of the miserable side effects of chemotherapy and radiation.

But Allison started looking at how the immune system fights disease, using mice as study models, and capitalized on a critical discovery: T-cells require two signals to attack a target effectively. The first signal, he said, was "like the ignition switch," and the second "like the gas pedal." When working against a microbe, both signals were operative. But, in the presence of cancer, "T-cells don't get those signals to attack," he explained. Allison started to wonder what it would take to reliably activate the immune system against cancer.

In 1987, researchers in France discovered a protein called cytotoxic T-lymphocyte antigen-4, or CTLA-4, which protruded from the T-cell's surface. "There was a real race among a number of labs to figure out its function," Allison recalled. A scientist at Bristol-Myers Squibb, using results from his lab, contended that CTLA-4 increased the activity of T-cells and the immune system. But Allison and Jeffrey Bluestone, an immunologist, obtained results from independent experiments that contradicted that conclusion. Allison and Bluestone believed that CTLA-4

actually acted as a brake on the T-cells, and Allison thought that it might be keeping the immune system from attacking tumors. “Jeff and I were kind of in the wilderness for a while,” Allison said. “Before this, people just thought that T-cells died on their own.” He speculated that treatments designed to activate the immune system might have failed because the treatments were actually stimulating CTLA-4. As Allison put it, “We ought to free the immune system, so it can attack tumor cells.”

Allison’s postdoctoral researchers implanted cancer cells under the skin of mice, some of which were then treated with an antibody that blocked CTLA-4. After several weeks, the cancers disappeared. One of the researchers showed Allison the data in early December, 1995. Allison was astounded. The lab was about to go on Christmas break, but he wanted to repeat the experiment immediately. “I told the researcher that he should inject the tumors into a new group of mice, and have a control group that didn’t get the antibody. And I’d measure the tumors myself,” Allison recalled. “So it was really a blinded experiment, because I didn’t know what was what.” A week later, Allison measured the cancers. “The tumors were still growing, and I’m starting to despair. And then, in half of the mice, the tumors just seemed to stop, but in the other half of the group they kept going. And then the ones in which it stopped, the cancer started disappearing and just went away.” Allison added, “It immediately confirmed our original assumption that this could be good for any kind of cancer.”

For two years, as Allison continued his experiments on mice, he approached pharmaceutical and biotech companies for help in developing the treatment for patients, but he was repeatedly turned away: “People were skeptical of immunology and immune therapy. They would say, ‘Oh, anybody can treat cancer in mice.’ Sometimes they’d say, ‘You think you can treat cancer by just removing this negative signal on a T-cell?’ ”

Allison also learned that Bristol-Myers Squibb had filed for a patent asserting that CTLA-4 stimulated T-cell growth. “If that was the case, you would never, ever think about injecting an antibody that blocked CTLA-4 into a cancer patient, because it would make things worse,” he said. “People were scared of putting that into a patient.” But Allison persisted, telling industry executives that Bristol-Myers Squibb was wrong. Finally, he persuaded a small company called Medarex to invest in the approach.

Among its first trials on humans, in 2001, Medarex included patients with malignant melanoma, because it was one of the few cancers that had occasionally responded to immune-based treatments like interferon or interleukin-2. In pilot studies, patients were treated with the antibody to CTLA-4, and, as in mice, the cancers continued to grow for some weeks, before a few of the tumors shrank. In 2004, Bristol-Myers Squibb formed a partnership with Medarex to collaborate on the drug. A subsequent trial showed scant impact after twelve weeks. Many of the tumors got bigger, and in some patients new lesions appeared. Pfizer was also testing an antibody to CTLA-4, and concluded that it was a failure; the trial was stopped early.

Months after the end of the Bristol-Myers Squibb study, however, several of the clinicians involved, including Jedd Wolchok, of Memorial Sloan-Kettering, and Stephen Hodi, of the Dana-Farber Cancer Institute, in Boston, realized that the tumors had either stopped growing or begun to shrink. Wolchok and his colleagues prevailed upon Bristol-Myers Squibb to include over-all survival rates of patients after several years. (Because the established criteria for judging the effectiveness of chemotherapy drugs are based on the first months of treatment, the trial had been considered a failure.) "It was pretty courageous," Allison said, "because it would take a long time to finish the study." In June, 2010, the results were presented at the annual meeting of the American Society of Clinical Oncology. Although the drug had extended the patients' lives a median of only four months, nearly a quarter of the patients were alive two years into the trial. Their predicted survival had been seven months. "This is a drug unlike any other drug you know," Allison said. "You are not treating the cancer—you are treating the immune system. And it was the first drug of any type to show a survival benefit in advanced-melanoma patients in a randomized trial."

Allison's results astounded cancer specialists. *Nature* published a review in December, 2011, and noted that the antibody to CTLA-4 "provides realistic hope for melanoma patients, particularly those with late stage disease who otherwise had little chance of survival. More broadly, it provides clear clinical validation for cancer immunotherapy in general." I asked Harold Varmus why Allison had had success where other researchers in immunotherapy had failed. "We need to understand what we do," he said. "Jim made things understandable."

"You've got to be careful about using the word 'cured,' because some patients have residual tumors," Allison said. "But it doesn't matter, because their cancers are not growing. And, in others, tumors just pop up and then go away. So it's become something of a chronic condition," rather than a death sentence. Allison moved to Sloan-Kettering to be closer to the clinical trials conducted by Wolchok and others. "I just wanted to be the advocate who is keeping it in everybody's face," he said.

In the fall of 2003, Sharon Belvin was a twenty-two-year-old student teacher with plans to marry the following June. She ran between four and five miles a day, and began to notice that her chest hurt after her morning workout. The student health service thought that she might have viral bronchitis, picked up from the children in her class. But her symptoms did not improve, and she was given other diagnoses, including asthma and pneumonia. Before long, she found it uncomfortable even to walk. On a visit to her mother, Belvin saw the family physician, who found a lump on her clavicle. A biopsy showed that she had metastatic melanoma. "It shocked me," Belvin told me. "I was never a sunbather. And I never had any lesions on my skin." A week before her wedding, she completed her evaluation. A body scan "lit up like a Christmas tree," she recalled. "I ended up having chemotherapy on Monday, Tuesday, and Wednesday, and got married on Saturday." During four months of therapy, the tumors shrank a bit. Then they began to grow again. An MRI showed that the melanoma had spread to her brain. Belvin went to Sloan-Kettering, where the brain tumor was treated with radiation. After recovering from the

procedure, she received interleukin-2, to stimulate her T-cells. The therapy caused such a severe reaction that “my skin peeled off over my body,” Belvin said. “I was so violently ill, I don’t remember half of what happened.” Worse yet, the treatment failed to stop the cancer’s growth. “The doctor told me, ‘If you are going to take a vacation, you’d better do it now.’ ” Belvin and her husband went on a Caribbean cruise.

When she got back, Belvin returned to the hospital and had twelve litres of fluid drained from her chest. Then Wolchok offered Belvin treatment with the antibody to CTLA-4, which was still an experimental therapy. “By that point, I had told my husband, ‘If this doesn’t work, I don’t know how much more I can take,’ ” she recalled. Wolchok gave her an informed-consent release that listed all the possible side effects. “It was pages and pages of this could happen to you and that could happen to you. I didn’t read one page. I just signed at the bottom and said, ‘Give it to me.’ ”

The antibody was infused through one of Belvin’s veins, and she had a drastic reaction: her body shook and she experienced drenching sweats, as well as an immune attack on her thyroid gland. “I thought I was dying, the rigors were so bad,” she recalled. After four treatments given every three weeks, Belvin went for a set of scans. “I remember how Dr. Wolchok came in with this huge smile on his face, and he was like, ‘This is great!’ He was just floored.” The massive tumors in her lungs had shrunk significantly.

Wolchok did not want to raise Belvin’s hopes too much. But “every single scan that I had after that time, the tumors kept shrinking,” she said. Eight years after her diagnosis, she still has no signs of the cancer.

Belvin’s case is remarkable, but it contradicts the popular notion that boosting the immune system is a “natural” way to treat cancer, free of the harsh side effects associated with chemotherapy or radiation. The results of immunotherapy can include an attack on the skin, intestines, lungs, liver, thyroid, pituitary gland, kidneys, and pancreas. When T-cells are stimulated to an intensity that destroys cancer cells, they can also cause collateral damage to normal tissue. Wolchok told me, “You may need to cross the line to toxicity for the immune system to be effective against a cancer. It’s not a free ride.” Because Belvin’s thyroid gland was destroyed by the therapy, she now requires replacement hormones.

Steven Rosenberg, the chief of surgery at the National Cancer Institute, who played a key role in developing interleukin-2, also conducted some of the early studies with the antibody to CTLA-4. He noted that the bowel often became severely inflamed with the treatment: “You have, like, eight litres of diarrhea a day. The colitis is atrocious, and would be lethal in almost everybody. If you don’t put those patients on corticosteroids immediately, they’ll die.”

“In the field of oncology, the bar is set so low,” Rosenberg told me. He welcomes the outcomes for patients like Belvin, but is cautious about the long-term benefits of similar treatments. “I believe that the antibody to CTLA-4 will cure some patients with melanoma, although the

follow-up is short." But unless all detectable cancer disappears, he said, "the tumors are going to grow back eventually."

Rosenberg has pioneered a different strategy, called "adoptive cell transfer," in which T-cells are taken from a patient's tumor and given immune stimulants such as interleukin-2, which cause them to replicate. Then they are put back into the body. In the latest of three trials of patients with melanoma who underwent adoptive cell transfer at the National Cancer Institute, nine of twenty-five patients have been in complete remission for more than five years. Across all three trials, five patients who had received earlier, unsuccessful treatment with the antibody to CTLA-4 are in remission.

Sam Breidenbach, who runs a construction company in Wisconsin, was one of those five. In September, 1999, his wife noticed a small mole on his back. He went to the hospital at the University of Wisconsin in Madison, and was told that he had melanoma. It was caught early, and the doctors, after removing it, said that the cancer did not appear to have spread. But three years later, while playing volleyball, he lunged to spike the ball, and felt a pull at his left flank. "It was this roly-poly little nodule on my left hip, at the top of the bone"—a metastasis from the original melanoma. "A local oncologist just basically said, 'You'll be lucky to live five years,' " Breidenbach recalled. He returned to the hospital in Madison, where he was given high doses of interferon. "For the first month, I was just totally dead. I couldn't do anything." The treatment was ineffective. Within months, the melanoma had appeared in the lymph nodes of his left groin.

Breidenbach found out about Rosenberg through his daughter, who was in a violin class with a girl whose father had been treated for melanoma at the National Cancer Institute. Breidenbach contacted Rosenberg, who treated him with an experimental melanoma vaccine. Breidenbach did not respond to the treatment, and the melanoma spread to his liver and lungs. In the summer of 2003, after being treated with the antibody to CTLA-4, he developed excruciating pain in his abdomen—pancreatitis, caused by the toxicity of the immune response. "It was so brutal that they had to stop the treatment," Breidenbach said. "They were basically out of any other ammunition to throw at me." His doctor at the University of Wisconsin told him that he couldn't expect to live more than four to six months. One oncologist suggested chemotherapy, but "I knew the numbers, and my wife and I said, 'If this is really the remaining time I have on the planet, why make it miserable?' "

Over the week of Thanksgiving, Rosenberg called and told him that his research team had studied his T-cells in the laboratory. "Your cells are jumping out of the petri dish," Rosenberg said. He explained that Breidenbach's T-cells could be stimulated to recognize and attack melanoma. "Dr. Rosenberg basically told me to get on the plane on Monday and expect to be here for three weeks." Breidenbach's T-cells had been removed and manipulated in Rosenberg's lab. Upon his arrival at the N.I.H., they were returned to his body through a catheter entering the vein to his heart. "All the doctors were grinning in the operating room," he told me. "I felt like it was 'Dr. Strangelove.' " Breidenbach developed a fever of a hundred and four degrees, and his

skin erupted in a rash. He went home on Christmas Eve, barely able to walk, but within a month the numerous metastases had started to shrink. Today, none of the melanoma remains. “My T-cells, they were fiery,” Breidenbach concluded. But there was one permanent side effect of the treatment. Along with the cancer, the manipulated T-cells attacked the normal cells with melanin, causing vitiligo, in which skin loses its pigment, and his hair to turn white.

Rosenberg believes that melanoma has a unique relationship with the immune system: there are so many mutations in the tumors that T-cells have an easier time recognizing them as foreign. This characteristic makes developing immune therapies easier. “An intense natural immune response just doesn’t exist for other kinds of cancers,” he said.

But Rosenberg thinks that he has the key to a more wide-ranging approach. “With six hundred thousand Americans dying every year with cancer, we need something for the common cancers,” he said. He acknowledges that targeted drugs, such as Gleevec, can be effective, but he points out that most targeted therapies quickly wane in their efficacy. A recently developed therapy for melanoma dramatically shrank more than half of tumors, but nearly all patients relapsed within a year. A study published in March suggested that as a cancer spreads in the body—from the kidney to the liver and the lungs—the mutations occur in non-uniform ways, so that DNA in liver deposits may differ from DNA in tumors in the lung. This protean progression means that a drug targeted to one mutation may not work against cancer cells throughout the body.

In Rosenberg’s view, with adoptive cell transfer, these malignancies would all appear equally foreign to the immune system. He is refining the treatment for other cancers by skimming patients’ blood and then inserting a gene into their T-cells that targets a different protein, called NY-ESO. The protein, which was identified at Memorial Sloan-Kettering, is normally absent in tissues after fetal development, except in the testis, but it reappears in about a third of all common cancers. “I think adoptive cell transfer is going to be the secret to applying immune therapy to the treatment of many human cancers,” Rosenberg said. “When T-cells are genetically engineered to target NY-ESO, there is no difference between melanoma and breast cancer or prostate cancer, or colon cancer, ovarian cancer, sarcoma, and so on.”

Varmus agrees that this approach might make a wider array of tumors susceptible to therapy, and in early trials Rosenberg’s strategy has been promising. In 2008, Anita Robertson, a sixty-three-year-old accountant from Long Beach, California, had a large sarcoma growing in her hip, a type of tumor similar to the one that killed Elizabeth Dashiell. In July, 2010, after treatment with genetically altered T-cells, Robertson was discharged from the N.I.H. hospital. A CAT scan in September showed that the sarcoma had begun to shrink; it is now more than fifty per cent smaller. Once immobile and in pain from the cancer, she now can drive, shop, and attend church.

Using a similar approach, researchers at the University of Pennsylvania have eradicated chronic lymphocytic leukemia in three patients who were no longer responding to other therapies. This

month, Rosenberg reported remissions in eight of nine patients with advanced lymphoma, and in three of those patients the cancer disappeared completely.

"We've got much, much better now with adoptive cell transfer," Rosenberg told me, "but it's not widely available." The treatment has to be individually designed for each patient, which makes it enormously expensive, and so less valuable to pharmaceutical companies. "They want a drug, and they don't care if you spend five hundred million dollars developing the first vial, as long as they can produce the second vial for a dollar," Rosenberg said. Because his work is experimental, it has been supported by federal funds. Eventually, however, these therapies will be priced by calculating how much they offset the costs of conventional treatments. Although the new procedures could run to hundreds of thousands of dollars, they might still prove less costly than the money spent on chemotherapy, hospitalization, and hospice care for the many patients who currently cannot be cured.

Jedd Wolchok, however, argues that common cancers may not require adoptive cell therapy. He talks about the "three 'E's" in immune therapy: elimination, equilibrium, and escape. Therapy should aim for total elimination of the cancer, but "we need to think about immune-system equilibrium," in which the cancer, though present, does not grow or spread. After decades of frustration and failure in the clinic, most scientists are wary of predicting whether immune therapy will be able to completely cure the majority of cancer patients. Tumors have mutated to escape the effects of radiation, chemotherapy, and targeted agents; the body's immune responses may not be unique.

Though CTLA-4 is still the focus of much research, scientists have now identified at least five other inhibitors on T-cells. Initial studies show that treatments directed at these inhibitors can shrink some of the most deadly tumors, including those of the lung and the colon. Mario Sznol, an oncologist at Yale, has conducted clinical trials with an antibody directed against one of the inhibitors, a protein called PD-1. "I believe that in the future we can customize immune therapy to the individual patient," he said. Doctors will examine the specific characteristics of a tumor, and then treat patients with the appropriate antibody.

Allison's laboratory is an open space that occupies a large part of the fifteenth floor of the Zuckerman Research Building, at Sloan-Kettering. The day I visited, postdoctoral fellows and graduate students were analyzing data on their computers from recent experiments. In a corner was an intravital microscope, which can show cells and tissues in a living animal. Allison demonstrated how an anesthetized mouse is injected with the antibody to CTLA-4. Previously, the T-cells of the mouse had been labelled with a fluorescein dye and sensitized to a protein from a tumor. Using the intravital microscope, "you can actually watch the T-cells move into the lymph node," Allison said. They appeared as bright-green circles coursing through thin gray vessels. "And then the T-cells jump—they leave the lymph node and attack the tumor."

In another part of the lab, a postdoctoral fellow had arranged a series of mice that had been inoculated with melanoma. Some served as controls, and black masses an inch or more grew on their flanks. Others had received the antibody to CTLA-4, or to PD-1, or a combination. “The most dramatic regression is seen with the combination,” Allison said, pointing to the flanks of mice where the tumors had shrunk to small black dots. Clinical trials in patients have begun with combining one antibody against CTLA-4 and another against PD-1, in order to remove two distinct brakes on the T-cell.

Last year, the antibody to CTLA-4, marketed under the name Yervoy, was approved by the Food and Drug Administration to treat melanoma. It was a vindication for immune therapy, and an important step in the treatment of cancer. Yet this branch of research has also uncovered how far we have to go to understand the mutations that make cancer the most protean of diseases. “The future is about thoughtful combinations, different antibodies, perhaps with targeted therapies,” Wolchok told me. “There won’t be a single silver bullet for everyone.” ♦