

Setting the Body's 'Serial Killers' Loose on Cancer

After a long, intense pursuit, researchers are close to bringing to market a daring new treatment: cell therapy that turbocharges the immune system to fight cancer.

By ANDREW POLLACK AUG. 1, 2016

BETHESDA, Md. — The young surgeon was mystified. A fist-size tumor had been removed from the stomach of his patient 12 years earlier, but his doctors had not been able to cut out many smaller growths in his liver. The cancer should have killed him, yet here he lay on the table for a routine gallbladder operation.

The surgeon, Dr. Steven A. Rosenberg, examined the man's abdominal cavity, sifting his liver in his fingers, feeling for hard, dense tumors — but he could find no trace of cancer.

It was 1968. Dr. Rosenberg had a hunch he had just witnessed an extraordinary case in which a patient's immune system had vanquished cancer. Hoping there was an elixir in the man's blood, Dr. Rosenberg got permission to transfuse some of it into a patient dying of stomach cancer. The effort failed. But it was the beginning of a lifelong quest.

“Something began to burn in me,” he would write later, “something that has never gone out.”

Half a century later, Dr. Rosenberg, who turns 76 on Tuesday and is chief of

surgery at the National Cancer Institute here, is part of a small fraternity of researchers who have doggedly pursued a dream — turbocharging the body's immune system so that more cancer patients can experience recoveries like his long-ago patient's.

Dr. Rosenberg, Dr. Carl H. June of the University of Pennsylvania and Dr. Michel Sadelain of Memorial Sloan Kettering Cancer Center have been at the forefront of this research for decades, laboring in separate labs in an intense sometimes-cooperative, sometimes-competitive pursuit to bring to fruition a daring therapy that few colleagues believed would work. Now, versions of the therapy for a limited number of blood cancers are nearing approval by federal regulators, and could reach the market as early as next year.

The technique, known as cell therapy, gives each patient an individualized and souped-up version of their own immune system, one that “works better than nature made it,” as Dr. June puts it.

The patient's T-cells, the soldiers of the immune system, are extracted from the patient's blood, then genetically engineered to recognize and destroy cancer. The redesigned cells are multiplied in the laboratory, and millions or billions of them are put back into the patient's bloodstream, set loose like a vast army of tumor assassins.

This is an unusual pharmaceutical — a drug that is alive and can multiply once inside the body. Dr. June calls these cells “serial killers.” A single one can destroy up to 100,000 cancer cells.

The killer cells are genetically engineered to produce a complex protein, an amalgam of pieces from different parts of the immune system that is unlike anything seen before.

“I call it a Frankenstein-like molecule,” said Dr. Renier J. Brentjens, the director of cellular therapeutics at Memorial Sloan Kettering Cancer Center.

This radical, science-fictionlike therapy differs sharply from the more

established type of immunotherapy, developed by other researchers. Those off-the-shelf drugs, known as checkpoint inhibitors, release a molecular brake on the immune system, freeing it to fight the cancer much as it fights infections by bacteria or viruses.

Cell therapy, in contrast, is brewed specially for each patient, one of the many challenges the field faces in broadening its use. So far, the number of patients treated with cell therapy is in the hundreds, not thousands. And for now it works only for certain types of blood cancers, not common malignancies like breast and lung cancer. Researchers are also still working out how to control potentially lethal side effects. Just recently, a clinical trial was briefly halted after three patients died of brain swelling.

Still, cell therapy has produced complete remissions in some patients who were out of treatment options, stirring excitement among doctors and patients and setting off a race among companies to bring the treatments to market.

Getting to this point has taken decades of painstaking work, with many false starts and setbacks.

“It was conceivable we were pursuing a ghost,” Dr. Rosenberg recalled.

Patient No. 67

The son of Orthodox Jews who immigrated from Poland to New York and ran luncheonettes, Steven Rosenberg was about 6 years old when his family learned that many relatives, including six of his father's nine siblings, had been murdered in the Holocaust.

“I saw so much evil in the world that early on I decided I wanted to do something that would help people, not hurt people,” he said in an interview here. He received a medical degree from Johns Hopkins and a doctorate in biophysics from Harvard.

From the start, he was a workaholic. At one point he tried to call off his

relationship with Alice O'Connell, whom he would later marry, because he was afraid it would distract him from research.

"I loved the night," Dr. Rosenberg wrote in his book, "The Transformed Cell," published in 1992. "I remember the exhilaration of working through the night in the lab, drinking thick pasty coffee that had been on the burner for hours, walking out into the sunrise." He added: "To be alone and out on the edge like that, there was no feeling like it in the world."

When Dr. Rosenberg arrived at the National Cancer Institute in 1974, his first attempt at immunotherapy was to give patients T-cells harvested from pigs. That failed.

He then began giving patients interleukin-2, or IL-2, a protein made by the body that spurs T-cells to proliferate. In some cases he treated patients with their own white blood cells that had been incubated in IL-2. The treatments sometimes set off such a violent immune system reaction that patients had to be placed in intensive care.

From 1980 to 1984, he treated 66 patients without success. Then, in late 1984, he encountered patient No. 67, Linda Taylor, a Navy officer with melanoma whose personnel file carried the stamp "death imminent."

Ms. Taylor is still alive; her case and others catapulted Dr. Rosenberg and IL-2 onto the cover of Newsweek and the front pages of newspapers. Some of his colleagues at the National Cancer Institute began referring to him as Stevie Wonder, thinking he had developed a swelled head.

But IL-2's vaunted prowess fizzled, helping only a few percent of patients with melanoma or kidney cancer.

Dr. Rosenberg then tried to surgically remove tumors and extract the T-cells that had already penetrated them, so-called tumor-infiltrating lymphocytes. He multiplied those cells in the lab and infused them back in the patient, along with shots of IL-2. He limited his focus to melanoma, the skin cancer that seemed most

susceptible to immune attack.

The treatment eventually achieved remissions in about 10 percent to 25 percent of patients. But it was labor-intensive and its application to other cancers unclear.

There had to be a better way. Indeed, one approach was taking shape across the street from Dr. Rosenberg, at the Naval Medical Research Institute in Bethesda.

Research Turns Personal

The Navy was not Carl June's desired career choice. Accepted at Stanford in 1971, he instead chose the Naval Academy to avoid the draft and Vietnam. The Navy sent him to medical school and for training in bone-marrow transplantation, geared toward treating people irradiated by nuclear weapons.

When the Cold War ended, the Navy lost interest.

Dr. June turned to working with T-cells at the Naval Medical Research Institute in the mid-1980s. He and a colleague, Dr. Bruce Levine, found a way to multiply T-cells in huge numbers outside the body, a method still used today. And in the mid-1990s, working with Cell Genesys, a gene therapy company, Dr. June began trying to genetically modify patients' T-cells to kill H.I.V., the virus that causes AIDS.

But when his wife, Cindy, the mother of the couple's three children, developed ovarian cancer in 1996, Dr. June's research turned personal.

Dr. June had tried everything to save her, including the primitive immune therapies under development. But Ms. June died in 2001.

"A lot of other scientists would have been disillusioned by the failure, in his case the personal tragedy," said Sean Parker, the internet billionaire who is funding some of Dr. June's work.

Instead, Dr. June, who had moved to the University of Pennsylvania, stopped treating patients, and devoted himself to creating cell therapies for cancer.

“Things that were back burner on cell therapy became front burner,” he said.

Following a ‘Pipe Dream’

In the 1980s, scientists began experimenting with gene therapy, putting new genes into cells of the body to treat disease. Michel Sadelain, while still a graduate student studying immunology at the University of Alberta, told colleagues that he thought the technique could be used to supercharge T-cells to fight cancer.

“At the time it sounded very pipe dream,” said Douglas Green, who was one of Dr. Sadelain’s doctoral thesis advisers and is now chairman of immunology at St. Jude Children’s Research Hospital.

But Dr. Sadelain, he continued, “believed in his approach and he pursued it relentlessly.”

After earning his Ph.D., Dr. Sadelain headed for the Whitehead Institute for Biomedical Research in Cambridge, Mass., to learn how to do gene therapy, using disabled viruses that could not cause disease to deliver genes into cells. By 1992, he had demonstrated that he could genetically engineer mouse T-cells.

He then moved to Sloan Kettering. In 2003, he and his colleagues — including his partner and now wife, Isabelle Rivière — showed that genetically engineered T-cells could eradicate certain cancers in mice.

How is this done? To fight cancer, T-cells have to recognize cancerous cells.

Each T-cell in the body has unique receptors, sort of like claws that jut out from its surface. T-cells patrol the body looking for protein fragments that indicate a cell might be infected by a bacterium or virus. If one of its claws latches on to such a fragment, the T-cell destroys the cell displaying it.

But cancer cells are mutated versions of the body’s own cells, not outsiders. T-

cells do not always recognize them as something to kill.

So scientists like Dr. Sadelain decided to put a new claw on the T-cells, one that could recognize cancer by latching on to a telltale protein on cancer cells.

The new claws came from another part of the immune system known as antibodies. Drug companies already knew how to make antibodies with claws that bind to specific proteins in the body.

But the claw was not enough. Once a claw binds to a target protein, it needs a molecule to signal the T-cell to go into killing mode. Yet another signal helps sustain the killing. The DNA instructions for all three components are inserted into the patient's T-cells.

Since this concoction is part antibody and part T-cell, it is a chimera, like the monster of Greek mythology that is part lion, part goat and part serpent. The claw is called a receptor and the protein it binds to on the cancer cell, the target, is called an antigen. So the whole construct is called a chimeric antigen receptor, or CAR, and the use of it to treat cancer is called CAR T-cell therapy, or CAR-T.

Dr. Sadelain was not alone in this work. Zelig Eshhar, an Israeli scientist, is credited with developing one of the first crude CARs around 1989. Dr. Rosenberg, always on the lookout for new types of immunotherapy, invited Dr. Eshhar to be a visiting scientist in his laboratory at the National Cancer Institute.

Another early developer was Dr. Dario Campana of St. Jude Children's Research Hospital.

As scientists worked to perfect the formula in the 1990s and early 2000s, there was quite a bit of sharing. Cancer cell therapy was still mostly an academic exercise; it was highly uncertain whether it would ever really work.

Dr. June, after hearing a presentation by Dr. Campana at a conference in 2003, requested a sample of Dr. Campana's CAR. Dr. Sadelain shared his design with both Dr. June and Dr. Rosenberg. The most prominent CAR developed at the

National Cancer Institute owes a lot to Dr. Sadelain, Dr. Rosenberg said.

But the science proved difficult and the research money scarce. Pharmaceutical companies showed little interest, preferring mass-produced drugs, one size fits all, rather than a treatment that would be made separately for each patient.

Again, a death from cancer propelled the field forward. In 2001, a 44-year-old woman, Kimberly Lawrence Netter, succumbed to breast cancer. Her father-in-law, Edward Netter, a wealthy financial services entrepreneur, and his wife, Barbara, formed the nonprofit Alliance for Cancer Gene Therapy, which issued some of its first grants to Dr. June and Dr. Sadelain. Dr. June also got support from the Leukemia and Lymphoma Society.

“Without that,” Dr. June said of the charities, “we would not have had a clinical trial.”

Successes Draw Attention

As the first decade of this century neared its end, the three pioneers were ready for the big moment — testing their treatments in patients. They scrambled to be the first to announce peer-reviewed results.

Dr. Rosenberg and colleagues published first, in the journal *Blood* in 2010. They described a single patient with lymphoma whose tumors shrank after treatment. (The patient later received more therapy, and has been free of cancer since.)

But the approach really attracted attention the next year when Dr. June reported that two of three patients with chronic lymphocytic leukemia went into complete remission.

One of them, Doug Olson, a chemist from Tinicum Township, Pa., left the hospital and immediately bought a sailboat. He also took to running half-marathons.

“It was like this weight that had been sitting there was gone,” said Mr. Olson, who is free of cancer nearly six years later.

Bill Ludwig, a retired captain in the New Jersey Department of Corrections, had already paid for his funeral when he started treatment in August 2010. Once his genetically engineered T-cells were unleashed in his system, Mr. Ludwig’s lungs started to fail, his legs ballooned to twice their size, his blood pressure dropped and he began hallucinating.

When he emerged from the ordeal, doctors searched for cancer. Detecting none, they ordered another test, certain of error. But there was no mistake. Five pounds of tumor had been destroyed.

Mr. Ludwig, now 71, and his wife bought an R.V. “We’re trying to make up for lost time,” he said. He has celebrated the high school graduations of five grandchildren and welcomed his first great-grandchild.

As for Dr. June, Mr. Ludwig said: “It’s hard to describe someone who basically saved your life. He lost the one he loved, and turned around and saved me years later.”

Money and Rivalries

The 2011 publication of Dr. June’s results transformed the field.

Novartis, the big Swiss pharmaceutical company, licensed the rights to the therapies created in Dr. June’s lab at the University of Pennsylvania, throwing aside concerns that treatments manufactured for individual patients would not be good business. That set off a commercial rush, flooding the field with cash after years of doubt.

While various companies are in pursuit, three are in the lead. They hope to win approval from the Food and Drug Administration to bring the first CAR treatments to market as early as 2017 or 2018, although it is not yet clear how easy it will be to get regulatory approval for such a novel therapy.

The companies are teamed with academic pioneers: Novartis with Penn; Kite Pharma with the National Cancer Institute; and Juno Therapeutics with Sloan Kettering, the Fred Hutchinson Cancer Research Center in Seattle and Seattle Children's Hospital.

Somewhat predictably, success provoked jostling and envy. Rather than being allies against a disbelieving world, the pioneers now had something worth fighting over — credit, and the gleam of a possible Nobel Prize.

While the Sloan Kettering researchers had done some of the early genetic engineering, they did not publish strong results in five patients until 2013. By then, they had been scooped by Dr. Rosenberg with one patient and Dr. June with three.

The spotlight further shifted to Dr. June because of his success with Emily Whitehead, a little girl whose miraculous recovery in 2012 made her the poster child for cell therapy. When Mr. Parker, the internet entrepreneur, announced in April that he would spend \$250 million to start a new cancer immunotherapy institute, Emily, now 11, appeared on stage at the launch extravaganza with Lady Gaga.

Dr. June's 2011 publications did not cite Dr. Rosenberg's paper from the previous year, prompting Dr. Rosenberg to write a letter to The New England Journal of Medicine. Dr. June's publications also did not acknowledge that the genetic construct he had used was the one he had obtained from Dr. Campana of St. Jude.

St. Jude sued the University of Pennsylvania. Novartis sided with Penn, and Juno Therapeutics with St. Jude.

The suit was settled last year, with Novartis agreeing to pay \$12.25 million plus possible future payments and royalties. Within days, Dr. June sent a correction and letter of regret to The New England Journal of Medicine, acknowledging that the CAR used in his groundbreaking 2011 study, and in treating Emily Whitehead, was "designed, developed and provided" by St. Jude.

Reasons for Caution

Patrick M. Coughlin, who teaches anatomy at the Commonwealth Medical College in Scranton, Pa., now explains the immune system to his classes by telling how one man overcame cancer. Only gradually does it become clear that he is referring to himself.

Now 63, Mr. Coughlin noticed a mass the size of a softball in his abdomen in summer 2013. It was a form of non-Hodgkin's lymphoma. Three different types of chemotherapy and a bone-marrow transplant all failed to help him. Desperate, he came to the National Institutes of Health campus here last year for the cell therapy developed by Dr. Rosenberg's team.

The battle between Mr. Coughlin's genetically engineered immune cells and the cancer was brutal. For four days he had a fever as high as 105, chills and bed-soaking sweats. Even his brain malfunctioned — at one point he could not count to 10 or write his wife's name.

But when the battle ended, the cancer was no longer there. "If I had gotten this thing five years ago," he said of his disease, "I'd be dead."

Yet for all the excitement, there are reasons for caution. The CAR therapy works now only for patients with some B-cell lymphomas and leukemias, which account for only about 80,000 of the 1.7 million cases of cancer diagnosed in the United States each year. It has not been successfully used to treat malignancies of the lungs, breast, prostate, colon or other organs.

"The solid tumors that kill over 90 percent of people do not respond to anything we have now," Dr. Rosenberg said.

Because it is personalized, cell therapy is likely to be frightfully expensive — probably hundreds of thousands of dollars per patient, though the companies bringing these treatments to market have not yet said how much they would charge.

Producing the re-engineered cells is lengthy and complex. Some patients have died during the two to four weeks it took to genetically modify and multiply their cells.

And the therapy itself can be arduous. First, patients get chemotherapy to wipe out many of their existing T-cells to make room for the engineered ones. Once those enter the body, they can set off a ferocious immune response as well as temporary neurological problems like memory loss, seizures and hallucinations.

Recently Juno Therapeutics had to temporarily halt its clinical trial after three patients died from brain swelling. The problem arose when the company added a second chemotherapy drug to the regimen preparing the patients for the cell infusion. The authorities allowed the trial to resume without that chemotherapy drug.

Still, some patients find themselves hoping they get violently ill, since that is a sign the treatment is working.

“Every morning my wife would ask me how I’m feeling,” said Myles Stiefvater, a copier salesman from Newark, Del., who had the treatment in 2014. When he said he felt O.K., they were disappointed.

Researchers are also finding, to their dismay, that remissions do not always last. The therapy has had its biggest success in acute lymphoblastic leukemia, producing complete remissions for 60 percent to more than 90 percent of patients. Yet up to half of those patients eventually suffer a relapse.

In some cases, the tumor evolves so that it no longer displays on its surface what the claw binds to, making it invisible to the engineered cells. In other cases, the engineered cells might not last long enough in the body, giving the cancer a chance to resurge.

Karen Shollenberger, a student at Drexel University with acute lymphoblastic leukemia, thought she was in the clear after being in remission for nine months after a CAR-T treatment.

But in September, as the school year was beginning, the cancer returned.

“My high hopes for the rest of the term were crushed,” Ms. Shollenberger wrote on her blog in October.

She entered a new trial testing a new CAR therapy directed at another protein on B-cells. Again the cancer went into remission, and she returned to school.

But fear lurked in her: What if the new therapy also stopped working? That indeed happened recently. Her best hope now is a bone-marrow transplant.

“Each relapse is increasingly terrifying as the options continue to shrink,” said Ms. Shollenberger, 22. But, she said, the cell therapies have given her nearly two good years.

The big thrust now is to expand the use of cell therapy to additional types of cancer.

The key is to find protein targets that the engineered T-cells can latch on to to kill cancer cells. Ideally, such a protein should be on all the tumor cells, so the entire cancer would be eradicated. But it should not be on healthy cells, or they would also be destroyed, causing side effects.

“T-cells are very powerful,” said Dr. Campana, formerly of St. Jude and now at the National University of Singapore. “In the same way they can eliminate cancer, they can also kill you.”

A protein called HER2, for instance, is found on many breast and other tumors, making it a seemingly good target. But it is also found in tiny amounts in the lungs. When Dr. Rosenberg’s team infused killer T-cells aimed at HER2 into a patient, she went into respiratory distress within 15 minutes and died five days later.

The treatments work for the blood cancers because there is a good target. But finding these for the most common cancers has been difficult.

One problem is that CARs, because of how they are made, can bind only to proteins on the surface of cancer cells. But most proteins made by these cells, or by any cell for that matter, are inside the cell, out of reach.

There is an alternative approach that is gaining interest. Patients' immune cells can be engineered to make what are called T-cell receptors, or TCRs. These can recognize proteins inside the cancer cells.

Some experts say TCRs, which have a far wider array of potential targets, represent the best hope of using cell therapy to treat solid tumors. There have been hints of effectiveness already in treating one of those, a type of sarcoma.

It might turn out that the best target for each patient will be unique to that person. Scientists are now experimenting with using DNA sequencing and other techniques to find the best mutated protein in each person's tumor at which to aim the claw.

"Think of how dauntingly personalized this is," Dr. Rosenberg said. "We are using their own cells to treat a unique mutation in their own tumor."

He said this approach might allow cell therapy to be used for most patients.

Many other improvements are on the runway.

Dr. Sadelain and Juno are working on "armored CARs" that not only bind to the target but produce immune-stimulating chemicals. Cellectis, a French company, has treated two babies with an off-the-shelf CAR treatment that does not require each patient's cells to be processed. Bellicum Pharmaceuticals is working on genetic switches that dim or shut off the CAR if the treatment is endangering the patient.

"We're in the Model T version of the CAR now," said Dr. Levine, now the director of the cell production facility at the University of Pennsylvania. "What's coming along are Google CARs and Tesla CARs."

Still in Pursuit

In February, the Novartis-Penn Center for Advanced Cellular Therapeutics opened on the ninth floor of a Penn medical building, paid for mainly by \$20 million from Novartis. It has gleaming new laboratory space, clean rooms with the capacity to manufacture therapy for 400 patients a year, and a great view of downtown Philadelphia. On the wall are photographs of patients with success stories, like Doug Olson running a half-marathon and, of course, Emily Whitehead.

Dr. June, who remarried and had two more children, now jets off regularly to attend conferences and give talks. A world map hanging outside his office is titled “Where in the World Is Carl June?” It has pins stuck in every location he has been, and a picture of him on a bicycle pinned to his location at the moment.

In the last two years he has visited more than 150 cities in more than 20 countries. This year alone he has accumulated more than 200,000 airline miles. Despite that schedule, he runs ultramarathons and participated in July in the Death Ride, a grueling bicycle race in California.

Dr. Rosenberg still arrives at the National Cancer Institute nearly seven days a week. The walls outside his office are covered with signed photographs of the hundreds of fellows who have trained under him, many of them now leaders in immunotherapy. Every five years, they gather for a reunion, to reminisce and honor their mentor.

Arie Belldegrun, who was a fellow in the 1980s, now runs Kite, the company commercializing the National Cancer Institute’s CAR technology. He recounted what happened when he tried to get Dr. Rosenberg to join the company.

“He sits quietly, quietly, quietly, and then he asks, ‘Arie, why don’t you ask me what I want to do?’

“He said: ‘Every day that I go to work, I’m as excited as a kid coming to a new place for the first time. If you ask me what I want to do, I want to die on this desk one day.’”

But not before he conquers cancer.

“I want to end this holocaust,” Dr. Rosenberg said in the interview. “I think I’m finally getting the hang of what it will take to widely apply this to cancers.”

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A version of this article appears in print on August 2, 2016, on page A1 of the New York edition with the headline: Setting Body's 'Serial Killers' Loose on Cancer.

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