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An Immune System Trained to Kill Cancer

By Denise Grady
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PHILADELPHIA — A year ago, when chemotherapy stopped working against his leukemia, William Ludwig signed up to be the first patient treated in a bold experiment at the University of Pennsylvania. Mr. Ludwig, then 65, a retired corrections officer from Bridgeton, N.J., felt his life draining away and thought he had nothing to lose.

Doctors removed a billion of his T-cells — a type of white blood cell that fights viruses and tumors — and gave them new genes that would program the cells to attack his cancer. Then the altered cells were dripped back into Mr. Ludwig's veins.

At first, nothing happened. But after 10 days, hell broke loose in his hospital room. He began shaking with chills. His temperature shot up. His blood pressure shot down. He became so ill that doctors moved him into intensive care and warned that he might die. His family gathered at the hospital, fearing the worst.

A few weeks later, the fevers were gone. And so was the leukemia.

There was no trace of it anywhere — no leukemic cells in his blood or bone marrow, no more bulging lymph nodes on his CT scan. His doctors calculated that the treatment had killed off two pounds of cancer cells.

A year later, Mr. Ludwig is still in complete remission. Before, there were days when he could barely get out of bed; now, he plays golf and does yard work.

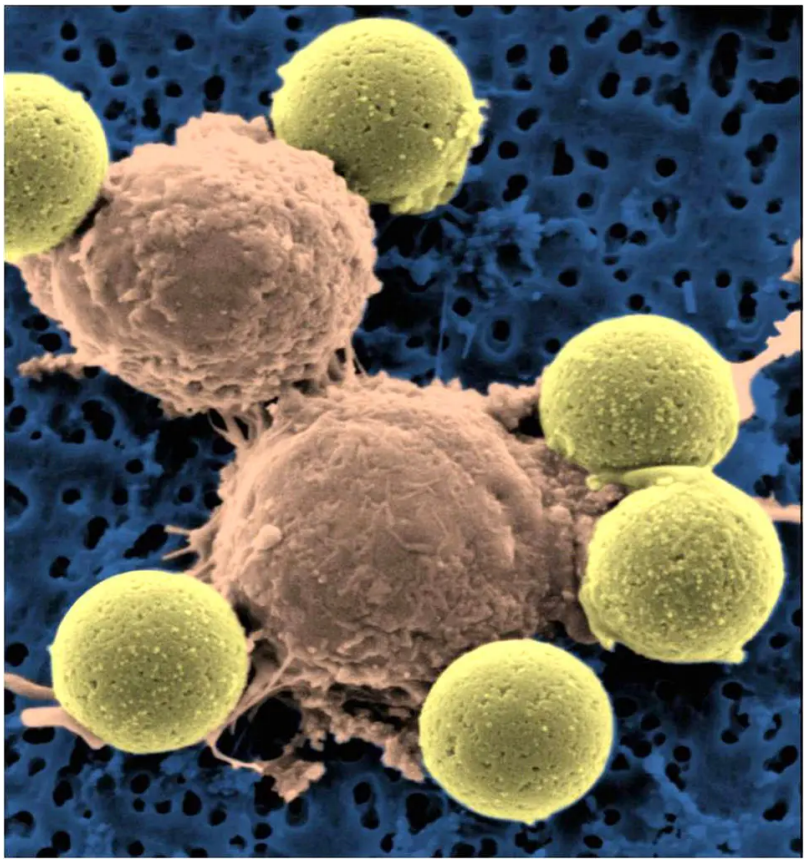
"I have my life back," he said.

Mr. Ludwig's doctors have not claimed that he is cured — it is too soon to tell — nor have they declared victory over leukemia on the basis of this experiment, which involved only three patients. The research, they say, has far to go; the treatment is still experimental, not available outside of studies.

But scientists say the treatment that helped Mr. Ludwig, described recently in The New England Journal of Medicine and Science Translational Medicine, may signify a turning point in the long struggle to develop effective gene therapies against cancer. And not just for leukemia patients: other cancers may also be vulnerable to this novel approach — which employs a disabled form of H.I.V.-1, the virus that causes AIDS, to carry cancer-fighting genes into the patients' T-cells. In essence, the team is using gene therapy to accomplish something that researchers have hoped to do for decades: train a person's own immune system to kill cancer cells.

Two other patients have undergone the experimental treatment. One had a partial remission: his disease lessened but did not go away completely. Another had a complete remission. All three had had advanced chronic lymphocytic leukemia and had run out of chemotherapy options. Usually, the only hope for a remission in such cases is a bone-marrow transplant, but these patients were not candidates for it.

Dr. Carl June, who led the research and directs translational medicine in the Abramson Cancer Center at the University of Pennsylvania, said that the results stunned even him and his colleagues, Dr. David L. Porter, Bruce Levine and Michael Kalos. They had hoped to see some benefit but had not dared dream of complete, prolonged remissions. Indeed, when Mr. Ludwig began running fevers, the doctors did not realize at first that it was a sign that his T-cells were engaged in a furious battle with his cancer.



Tiny magnetic beads force the larger T-cells to divide before they are infused into the patient. University of Pennsylvania

Other experts in the field said the results were a major advance.

“It’s great work,” said Dr. Walter J. Urba of the Providence Cancer Center and Earle A. Chiles Research Institute in Portland, Ore. He called the patients’ recoveries remarkable, exciting and significant. “I feel very positive about this new technology. Conceptually, it’s very, very big.”

Dr. Urba said he thought the approach would ultimately be used against other types of cancer as well as leukemia and lymphoma. But he cautioned, “For patients today, we’re not there yet.” And he added the usual scientific caveat: To be considered valid, the results must be repeated in more patients, and by other research teams.

Dr. June called the techniques “a harvest of the information from the molecular biology revolution over the past two decades.”

Hitting a Genetic Jackpot

To make T-cells search out and destroy cancer, researchers must equip them to do several tasks: recognize the cancer, attack it, multiply, and live on inside the patient. A number of research groups have been trying to do this, but the T-cells they engineered could not accomplish all the tasks. As a result, the cells’ ability to fight tumors has generally been temporary.

The University of Pennsylvania team seems to have hit all the targets at once. Inside the patients, the T-cells modified by the researchers multiplied to 1,000 to 10,000 times the number infused, wiped out the cancer and then gradually diminished, leaving a population of “memory” cells that can quickly proliferate again if needed.

The researchers said they were not sure which parts of their strategy made it work — special cell-culturing techniques, the use of H.I.V.-1 to carry new genes into the T-cells, or the particular pieces of DNA that they selected to reprogram the T-cells.

The concept of doctoring T-cells genetically was first developed in the 1980s by Dr. Zelig Eshhar at the Weizmann Institute of Science in Rehovot, Israel. It involves adding gene sequences from different sources to enable the T-cells to produce what researchers call chimeric antigen receptors, or CARs — protein complexes that transform the cells into, in Dr. June’s words, “serial killers.”

Mr. Ludwig’s disease, chronic lymphocytic leukemia is a cancer of B-cells, the part of the immune system that normally produces antibodies to fight infection. All B-cells, whether healthy or leukemic, have on their surfaces a protein called CD19. To treat patients with the disease, the researchers hoped to reprogram their T-cells to find CD19 and attack B-cells carrying it.

FULL OF LIFE William Ludwig, 66, in his RV parked at his home in New Jersey. Jessica Kourkounis for The New York Times

Various research groups have used different methods. Viruses are often used as carriers (or vectors) to insert DNA into other cells because that kind of genetic sabotage is exactly what viruses normally specialize in doing. To modify their patients' T-cells, Dr. June and his colleagues tried a daring approach: they used a disabled form of H.I.V.-1. They are the first ever to use H.I.V.-1 as the vector in gene therapy for cancer patients (the virus has been used in other diseases).

The AIDS virus is a natural for this kind of treatment, Dr. June said, because it evolved to invade T-cells. The idea of putting any form of the AIDS virus into people sounds a bit frightening, he acknowledged, but the virus used by his team was "gutted" and was no longer harmful. Other researchers had altered and disabled the virus by adding DNA from humans, mice and cows, and from a virus that infects woodchucks and another that infects cows. Each bit was chosen for a particular trait, all pieced together into a vector that Dr. June called a "Rube Goldberg-like solution" and "truly a zoo."

"It incorporates the ability of H.I.V. to infect cells but not to reproduce itself," he said.

To administer the treatment, the researchers collected as many of the patients' T-cells as they could by passing their blood through a machine that removed the cells and returned the other blood components back into the patients' veins. The T-cells were exposed to the vector, which transformed them genetically, and then were frozen. Meanwhile, the patients were given chemotherapy to deplete any remaining T-cells, because the native T-cells might impede the growth of the altered ones. Finally, the T-cells were infused back into the patients.

Then, Dr. June said, "The patient becomes a bioreactor" as the T-cells proliferate, pouring out chemicals called cytokines that cause fever, chills, fatigue and other flulike symptoms.

The treatment wiped out all of the patients' B-cells, both healthy ones and leukemic ones, and will continue to do for as long as the new T-cells persist in the body, which could be forever (and ideally should be, to keep the leukemia at bay). The lack of B-cells means that the patients may be left vulnerable to infection, and they will need periodic infusions of a substance called intravenous immune globulin to protect them.

So far, the lack of B-cells has not caused problems for Mr. Ludwig. He receives the infusions every few months. He had been receiving them even before the experimental treatment because the leukemia had already knocked out his healthy B-cells.

One thing that is not clear is why Patient 1 and Patient 3 had complete remissions, and Patient 2 did not. The researchers said that when Patient 2 developed chills and fever, he was treated with steroids at another hospital, and the drugs may have halted the T-cells' activity. But they cannot be sure. It may also be that his disease was too severe.

The researchers wrote an entire scientific article about Patient 3, which was published in The New England Journal of Medicine. Like the other patients, he also ran fevers and felt ill, but the reaction took longer to set in, and he also developed kidney and liver trouble — a sign of tumor lysis syndrome, a condition that occurs when large numbers of cancer cells die off and dump their contents, which can clog the kidneys. He was given drugs to prevent kidney damage. He had a complete remission.

What the journal article did not mention was that Patient 3 was almost not treated.

Because of his illness and some production problems, the researchers said, they could not produce anywhere near as many altered T-cells for him as they had for the other two patients — only 14 million ("a mouse dose," Dr. Porter said), versus 1 billion for Mr. Ludwig and 580 million for Patient 2. After debate, they decided to treat him anyway.

MAJOR ADVANCE Dr. Bruce Levine lifted cells from a freezer in his lab in Philadelphia last week. Special cell-culturing techniques may have contributed to the lab's success. Jessica Kourkounis for The New York Times

Patient 3 declined to be interviewed, but he wrote anonymously about his experience for the University of Pennsylvania Web site. When he developed chills and a fever, he said, "I was sure the war was on — I was sure C.L.L. cells were dying."

He wrote that he was a scientist, and that when he was young had dreamed of someday making a discovery that would benefit mankind. But, he concluded, "I never imagined I would be part of the experiment."

When he told Patient 3 that he was remission, Dr. Porter said, they both had tears in their eyes.

Not Without Danger to Patients

While promising, the new techniques developed by the University of Pennsylvania researchers are not without danger to patients. Engineered T-cells have attacked healthy tissue in patients at other centers. Such a reaction killed a 39-year-old woman with advanced colon cancer in a study at the National Cancer Institute, researchers there reported last year in the journal Molecular Therapy.

She developed severe breathing trouble 15 minutes after receiving the T-cells, had to be put on a ventilator and died a few days later. Apparently, a protein target on the cancer cells was also present in her lungs, and the T-cells homed in on it.

Researchers at Memorial Sloan Kettering Cancer in New York also reported a death last year in a T-cell trial for leukemia (also published in Molecular Therapy). An autopsy found that the patient had apparently died from sepsis, not from the T-cells, but because he died just four days after the infusion, the researchers said they considered the treatment a possible factor.

Dr. June said his team hopes to use T-cells against solid tumors, including some that are very hard to treat, like mesothelioma and ovarian and pancreatic cancer. But possible adverse reactions are a real concern, he said, noting that one of the protein targets on the tumor cells is also found on membranes that line the chest and abdomen. T-cell attacks could cause serious inflammation in those membranes and mimic lupus, a serious autoimmune disease.

Even if the T-cells do not hit innocent targets, there are still risks. Proteins they release could cause a "cytokine storm"— high fevers, swelling, inflammation and dangerously low blood pressure — which can be fatal. Or, if the treatment rapidly kills billions of cancer cells, the debris can damage the kidney and cause other problems.

Even if the new T-cell treatment proves to work, the drug industry will be needed to mass produce it. But Dr. June said the research is being done only at universities, not at drug companies. For the drug industry to take interest, he said, there will have to be overwhelming proof that the treatment is far better than existing ones.

"Then I think they'll jump into it," he said. "My challenge now is to do this in a larger set of patients with randomization, and to show that we have the same effects."

Mr. Ludwig said: “I don’t recall anybody saying there was going to be a remission. I don’t think they were dreaming to that extent.”

The trial was a Phase 1 study, meaning that its main goal was to find out whether the treatment was safe, and at what dose. Of course, doctors and patients always hope that there will be some benefit, but that was not an official endpoint.

Mr. Ludwig thought that if the trial could buy him six months or a year, it would be worth the gamble. But even if the study did not help him, he felt it would still be worthwhile if he could help the study.

When the fevers hit, he had no idea that might be a good sign. Instead, he assumed the treatment was not working. But a few weeks later, he said that his oncologist, Dr. Alison Loren, told him, “We can’t find any cancer in your bone marrow.”

Remembering the moment, Mr. Ludwig paused and said, “I got goose bumps just telling you those words.”

“I feel wonderful,” Mr. Ludwig said during a recent interview. “I walked 18 holes on the golf course this morning.”

Before the study, he was weak, suffered repeated bouts of pneumonia and was wasting away. Now, he is full of energy. He has gained 40 pounds. He and his wife bought an R.V., in which they travel with their grandson and nephew. “I feel normal, like I did 10 years before I was diagnosed,” Mr. Ludwig said. “This clinical trial saved my life.”

Dr. Loren said in an interview, “I hate to say it in that dramatic way, but I do think it saved his life.”

Mr. Ludwig said that Dr. Loren told him and his wife something he considered profound. “She said, ‘We don’t know how long it’s going to last. Enjoy every day,’ ” Mr. Ludwig recalled.

“That’s what we’ve done ever since.”

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