The cancer patient had exhausted his options. Enter immunotherapy.

The treatment, which recruits the immune system to kill tumors, has become cancer patients' greatest hope. Six Chicago hospitals—including U of C, Rush and Northwestern—are on the forefront of testing whether it works on the rarest types.

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A year after doctors removed a tumor from Kevin Hill's body, his nightmare seemed to fade. At 26, he was happy, healthy and alive. He would touch the foot-long scar that stretches from his chest to
side and remember the baby-sized mass, the pain, the weeks away from his two young daughters. He was still here. "I'm blessed," he'd say.

Life became busy again, nearly normal. One week, roughly a year after he was first diagnosed, Hill filled out paperwork for a lunchroom job at Chicago Public Schools and had a Friday checkup scheduled at Rush University Medical Center. Suddenly, the nightmare returned: Doctors told him his adrenal cancer had metastasized into countless tumors speckled across his lungs.

Doctors tried to destroy the tumors with chemotherapy, which wiped Hill out. He slept 21 hours a day. Six weeks into treatment, he was gaunt and constantly nauseated. Dr. Nicklas Pfanzelter, an oncologist treating Hill at Rush, saw that his patient could barely stand. It wasn't working; Hill's tumors were the same size. Pfanzelter ordered the chemotherapy to stop.

There may be one last chance for survival, Pfanzelter told Hill: immunotherapy.

In less than a decade, immunotherapy has become cancer treatment’s greatest hope. Since early 2017, six Chicago hospitals—including Rush and Northwestern University—have been at the forefront of testing whether immunotherapy can effectively treat patients with rare tumors like Hill's. The University of Chicago Medical Center was the first in this market to offer this kind of treatment, rolling it out in mid-2017.

Hill's cancer, adrenal cortical carcinoma, is diagnosed in fewer than 500 Americans each year. Immunotherapy had never been tested to treat it.

"The population is so small that it's in no drug company's interest to design drugs for these patients," says Pfanzelter, the DART (Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors) trial investigator at Rush. "They would never make their R&D back."
DART, the first federally funded immunotherapy trial for rare cancers, was launched in January 2017 to examine the therapy's effect on disparate rare tumors. It's managed and funded by SWOG, a National Cancer Institute-supported organization that conducts and designs cancer trials.

Hill's recovery is one of the earliest known success stories for DART, which has been testing immunotherapy on patients at hundreds of hospitals across the U.S.

At the trial's outset, DART investigators planned to enroll 300 patients, but 526 had signed on as of September, with 404 joining in the past 12 months. Including Hill, 21 adrenal cortical carcinoma patients have enrolled.

The hope of immunotherapy for patients with rare cancers comes from its efficacy in treating cancers with larger sample sizes. It has proved effective in treating lung cancer, kidney cancer and melanoma—a 2018 study found that late-stage melanoma patients lived a median four years longer after immunotherapy.

It works by recruiting the immune system to destroy tumors. In a healthy body, the immune system dispatches T-cells to fight viruses, bacteria and cancer. But cancer cells are good at abusing the system and can prevent T-cells from recognizing them, allowing cancer to grow and spread. Immunotherapy unleashes the brakes on T-cells, allowing them to recognize and kill cancer.

Dr. Young Kwang Chae, an assistant professor of medicine at Northwestern University and one of DART's principal investigators, says that DART researchers are analyzing the first round of results and have no plans to close enrollment.

Patients with rare cancer make up roughly 20 percent of diagnoses, Chae says, but they often have no standard of care and little hope for survival. "That's really depressing," he says. "As a collection, they're not rare."

'ALMOST MIRACULOUS'

Every other Friday, Hill is injected with immunotherapy drug nivolumab at Rush's immunotherapy infusion center. Every third treatment, doctors add another immunotherapy drug to his regimen.

The drugs are injected into a port implanted under Hill's skin. After the first eight weeks of immunotherapy, his tumors had shrunk in size by half. Eight weeks later, the tumors had almost entirely disappeared. Perhaps tiny specks remain, Pfanzelter says, but they're negligible.

Pfanzelter has watched the life expectancy of his melanoma patients rise from months to years after immunotherapy was approved by the FDA. But Hill is "patient zero" for rare tumors, Pfanzelter's first indication that DART may serve its purpose. "It has improved my job satisfaction
significantly," he says. "Someone with this cancer usually lives months, but he has no evidence of cancer in his body."

But the doctor worries that Hill is an outlier, as immunotherapy often has unequal effects for patients with the same cancer. For example, Pfanzelter had enrolled another adrenal cortical carcinoma patient in the DART trial. Unlike Hill, that patient did not survive.

Why immunotherapy works so well for one person and not another is the treatment's biggest mystery. Tumors that are immunogenic—able to produce an immune response—tend to respond to immunotherapy, but Chae says that even immunogenic tumors don't respond each time. He hopes the DART trial can help solve the mystery by studying the tumors, blood and DNA of patients with rare cancers. "We need to learn which tumor is going to respond so that we can develop better immunotherapy," Chae says.

Pfanzelter believes that a few successful cases from DART could open the floodgates of FDA approval, giving other patients with rare cancer the same chance Hill had: treatment and potential survival. "Immunotherapy is a revolution in oncology," Pfanzelter says. "We haven't had a treatment like this where you could rationally hope that it might impact all these disparate types of tumors."

Hill, now 27, has been receiving bimonthly immunotherapy treatments for nearly a year and a half. Pfanzelter says that he plans to keep him on the trial for two years total, as long as the DART protocol allows. Now, Hill is feeling well enough to work again. He secured a job as lunchroom porter at Chicago Public Schools—the same job he was hired for before his second diagnosis.

Pfanzelter remains amazed by Hill's progress. "It's almost miraculous," he says. "Now, the question is how long he'll do this well."

**Letter to the Editor**

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