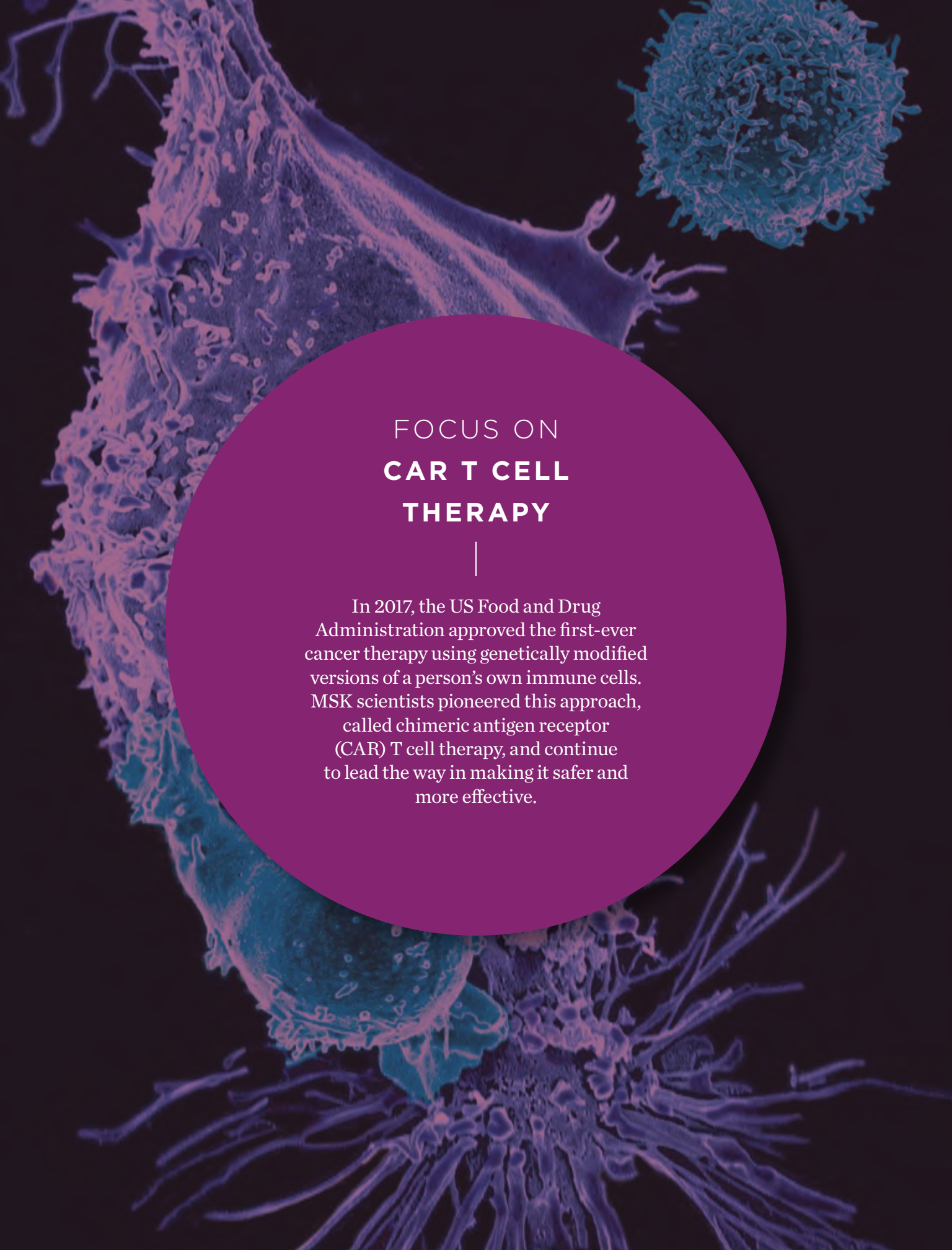
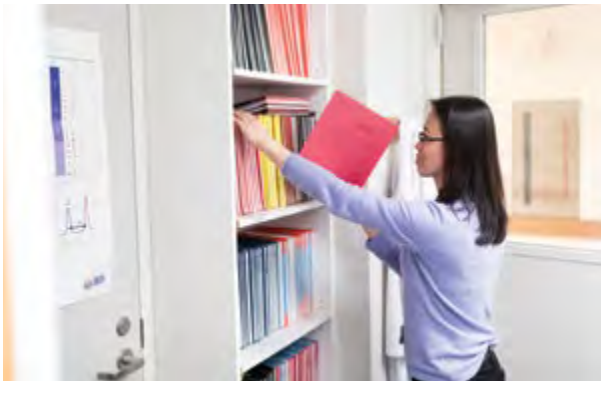


FOCUS ON
CAR T CELL THERAPY

In 2017, the US Food and Drug Administration approved the first-ever cancer therapy using genetically modified versions of a person's own immune cells. MSK scientists pioneered this approach, called chimeric antigen receptor (CAR) T cell therapy, and continue to lead the way in making it safer and more effective.

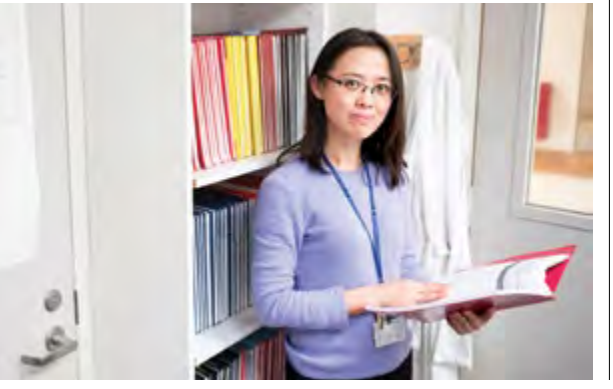
It takes many people to bring CAR T cells, like the one shown in the photo at left, to life. Xiuyan Wang manufactures these cells for use in patients on MSK clinical trials.

CAR AND DRIVERS



> I remember one of the patients very vividly. He was an ALL patient. The primary investigator from the clinical trial came to us and said, 'The family wants to meet the people who are making the magic cells.' So we met with them. The son was very happy to see us. He said it helped his father to feel like we would treat his cells with the utmost care."
>
> –XIUYAN WANG

Left: Xiuyan Wang and senior research specialist Jolanta Stefanski in the lab where they manufacture CAR T cells for use in patients on MSK clinical trials. *Below*: Each of the colorful folders carefully organized in Dr. Wang's office represents a life — an MSK patient who's received CAR T therapy.



CREATING "LIVING DRUGS"

Against one wall of Xiuyan Wang's office is a floor-to-ceiling bookcase stuffed with thick colored folders. Each one represents a patient treated at MSK with an experimental immune treatment called CAR T cell therapy.

The folders are color coded: orange for chronic lymphocytic leukemia, black for non-Hodgkin lymphoma, blue for acute lymphoblastic leukemia (ALL), red for ovarian cancer. There are about 300 binders in total.

"You see the shelf is kind of bulging already," Dr. Wang says, pointing.

As Assistant Director of the Cell Therapy and Cell Engineering Facility, Dr. Wang is responsible for manufacturing CAR T cells, a type of "living drug," for infusion into patients on clinical trials. A CAR is a designer protein that scientists genetically engineer into a person's own immune cells, turning them into souped-up cancer fighters.

Dr. Wang is part of a large orchestra of players who collaborate to bring these living therapies to life. But you might say she's the maestro, since she's the one making these sensitive, powerful cells.

The process is delicate. Immune cells called T cells are removed from a patient's blood, the CAR gene is delivered to the cells, and then they're grown in incubators until they multiply into the billions. The cells are then infused back into the patient, in the hope that these genetically modified versions will find and destroy the cancer.

"I remember one of the patients very vividly," Dr. Wang says. "He was an ALL patient. The primary investigator from the clinical trial came to us and said, 'The family wants to meet the people who are making the magic cells.' So we met with them. The son was very happy to see us. He said it helped his father to feel like we would treat his cells with the utmost care. We actually treat every patient's cells with the utmost care."

Dr. Wang is well aware that the cells that pass through her hands can represent someone's best and last treatment option. For many people, the best that CAR therapy offers is a significantly longer life, and sometimes, an outright cure.

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A TRANSFORMATIVE THERAPY

MSK investigators have played a pioneering role both in developing the technology of CAR T cells and in showing that it is an effective treatment for people with different types of cancer. They built the first effective CAR T cells in 2002 and began treating patients with them in 2007. A trial of CAR T cells in adults with ALL opened at MSK in 2010. MSK investigators published the results of that trial in early 2018 in the *New England Journal of Medicine* (*NEJM*).

These findings showed conclusively what anecdotal reports had already documented: Some people with terminal cancer could be cured with genetically engineered T cells made to detect and kill their cancer cells. The study also helped to identify the factors influencing who had the best results from the treatment, including that people with less disease benefited the most. Compared with patients who had a greater amount of disease, those in the low-disease category lived significantly longer and experienced fewer life-threatening side effects.

"This is the longest follow-up study of people with ALL treated with CAR therapy," says Jae Park, a medical oncologist and principal investigator of the adult ALL clinical trial. "It confirms the power of CAR T cells as an effective cancer therapy in adults with ALL."

Ultimately, he says, these findings show that it may make sense for people to receive CAR T cell therapy as a first treatment, rather than after other options have failed.

"This study represents the culmination of 20 years of research at MSK," says Michel Sadelain, Director of the Center for Cell Engineering and a pioneer of CAR therapy. "These data strongly support the use of this CAR therapy for adults with relapsed ALL and predict better outcomes when used earlier in the course of the disease."

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>
> –MICHEL SADELAIN

Michel Sadelain and colleagues were the first to show that CAR T cells could kill cancer cells. The roots of CAR T therapy stretch back nearly to the beginning of Dr. Sadelain's career as an immunologist.

GLEN'S STORY

The scientists also sought the answer to another conundrum. Many patients on CAR T therapy receive bone marrow transplants (BMTs) afterward as a preventive measure to keep the cancer from returning. But if people received CAR T cell therapy earlier, before a relapse, and had better outcomes, might they be able to forgo a BMT altogether?

Like many people who come to MSK, Glen Blum had already been treated at another hospital for a cancer that was proving stubbornly hard to beat.

His journey began several years ago, when lingering back pain led to a blood test, a biopsy, and eventually a diagnosis of ALL. This aggressive cancer, which grows in the bone marrow, had already damaged several of his vertebrae. Mr. Blum received conventional treatment with both chemotherapy and radiation, which helped for a while. But as is often the case with ALL, the cancer came roaring back. And when it did, it was resistant to further treatment with the usual drugs.

THE CAR T PIT CREW

Center for Cell Engineering (CCE)

DIRECTOR: Michel Sadelain

This multidisciplinary center is composed of basic scientists, translational researchers, and clinicians with an interest in developing cell therapies. CCE scientists help design and test new cell therapies, including better and safer CARs.

Cell Therapy and Cell Engineering Facility

DIRECTOR: Isabelle Rivière

This clinically certified, state-of-the-art manufacturing facility is where CAR T cells are made for use in MSK clinical trials.

Cellular Therapeutics Center

DIRECTOR: Renier Brentjens

This group of clinician-scientists takes the lead in caring for the patients treated with CAR T cells as part of clinical trials at MSK. The clinical data obtained from these trials are an important part of improving CAR T treatments.

Bone Marrow Transplant Service

DIRECTOR: Sergio Giralt

Members of this service are responsible for caring for patients treated with FDA-approved CAR T therapies. The doctors and nurses on this team are skilled at dealing with immune-related complications.

That's when Mr. Blum's doctor recommended that he enroll in a clinical trial of CAR T cell therapy at MSK. The goal of this treatment would be to shrink his cancer to a point where he would be eligible for a potentially lifesaving bone marrow transplant.

"The way they explained it to me is that the treatment would get my own immune cells to see the cancer cells as foreign and eliminate them," says Mr. Blum, who is now 32 and lives in East Harlem in New York City. "Then the bone marrow transplant was a secondary step so that I wouldn't grow more cancer cells."

Historically, a BMT is often the last, best hope for a cure for a person with leukemia once initial therapy has failed. But the procedure is not without significant risks. To receive new bone marrow, people must first have their existing bone marrow destroyed with high-dose chemotherapy or radiation. Because the bone marrow is what produces blood cells, including the white blood cells that make up the immune system, people are vulnerable to infections while the new bone marrow grows. There is also the risk that immune cells from the donor marrow will start to attack the body's healthy cells.

The *NEJM* study suggests that getting a BMT after CAR therapy does not make an important difference in how well people do in the long term. This result is preliminary, however, and needs to be confirmed with further research.

According to Dr. Park, at this time the decision to recommend a BMT or not becomes a question of weighing different factors, including the number of previous treatments, the characteristics of the disease, the risks of the transplant, the risk of relapse, and the age of the patient.

"These are the practical conversations we're having with patients every day," he says. "And while we have not answered the question definitively, this study raises the possibility that — at least for some patients — CAR therapy could be an end point."

continued ▶

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>
> –GLEN BLUM

Glen Blum, a CAR T cell therapy patient who visits MSK regularly for follow-up appointments, plays pool in MSK's Charles Hallac Patient Recreation Center. The center was redone in 2017 and now includes tables for arts and crafts, a coffee and beverage bar, shelves of board games, and ample lounge space.

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>
> –JAE PARK

Top: Jae Park (*right*) is a principal investigator of CAR T clinical trials at MSK. *Above*: Isabelle Rivière (*left*), with Jinrong Qu, senior research assistant, leads CAR T manufacturing at MSK.

HOW TO ENGINEER A CAR

The process of building a safe genetically engineered T cell was neither easy nor straightforward. It took the expertise of numerous investigators working over a period of decades. Leading the manufacturing effort at MSK was Isabelle Rivière, an immunologist who trained in France and the United States and is now Director of the Cell Therapy and Cell Engineering Facility. Dr. Rivière, who has been at MSK since 1998, was the first to design a standard operating procedure for the manufacturing of CAR T cells. Or rather, *procedures* — there are currently 250.

"I can honestly say I don't think we knew what we were getting into," she says. "We were really establishing the field as we went."

After many years of effort, exploring many different variables, she succeeded in developing a protocol that works. It involves a precise series of steps that include capturing T cells with magnetized beads and growing them in baglike incubators rolling on an oscillating tray.

The engineered T cells target a marker on B cell leukemias called CD19. When the therapy was used in people with B cell ALL, the researchers knew they were onto something special.

"The most dramatic result was when we took the bone marrow of these patients a couple of weeks postinfusion, and the disease had completely vanished," she says. "That was really the eureka moment. We had to convince ourselves that this was real."

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>
> –ISABELLE RIVIÈRE

FIRST CARS HIT THE ROAD

Two CAR T cell therapies were approved by the FDA in 2017. One, made by the company Novartis, is for children and young adults with ALL. Another, made by Kite Pharma (now owned by Gilead Sciences), is for adults with non-Hodgkin lymphoma.

Pediatric oncologist Kevin Curran, a member of the Pediatric Bone Marrow Transplant Service who leads MSK's CAR T cell efforts in children and young adults, calls the treatment "revolutionary" and says it opens a whole new avenue of options for patients. "It gives them hope," he adds.

These approvals are "only the beginning," Dr. Curran says. "Just like a new model of an automobile comes out each year, there are going to be new models of CAR T cells that come out too. We think some of the ones we've built and are testing at MSK have the potential to be even better."

MSK is one of only a handful of cancer centers that have the experience and expertise necessary to administer CAR T cell therapies safely to patients.

"Our primary job is making sure that each person gets the very best care — whether that's CAR T cell therapy or another approach," says Sergio Giralt, Chief of the Adult Bone Marrow Transplant Service. "It's a great privilege to be among such an incredible group of professionals, who all do their utmost each day to return our patients to a life free of cancer."

continued ▶

Kevin Curran leads MSK's CAR T efforts in children with blood cancers.

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>
> –SERGIO GIRALT

Sergio Giralt oversees the care of patients receiving FDA-approved CAR T cell therapies at MSK.

GROUP EFFORT

Senior clinical research supervisor Yvette Bernal has been a crucial player in MSK's CAR T program from the beginning. In fact, her career path has closely mirrored the development of the therapy itself. She joined MSK as a physician office assistant in the Division of Hematologic Oncology in 2004. Then, about a decade ago, she became among the first on the CAR T crew when she began working with physician-scientist Renier Brentjens as he established the Cellular Therapeutics Center, the group that treats people receiving investigational CAR T therapies at MSK. She started as a research study assistant (RSA) and is now a supervisor for the RSAs on the team.

Ms. Bernal stresses the collaborative nature of the work, as well as the entire team's dedication to their common goal. The RSAs serve as liaisons between the different clinical, academic, and regulatory groups involved. They are certified in human subjects protection, which is an important part of every clinical trial. They work alongside doctors, nurses, and lab monitors to collect data. They also liaise with MSK's Institutional Review Board, which oversees all clinical trials, and the FDA, to ensure the highest level of adherence to the study protocol and to keep things running smoothly.

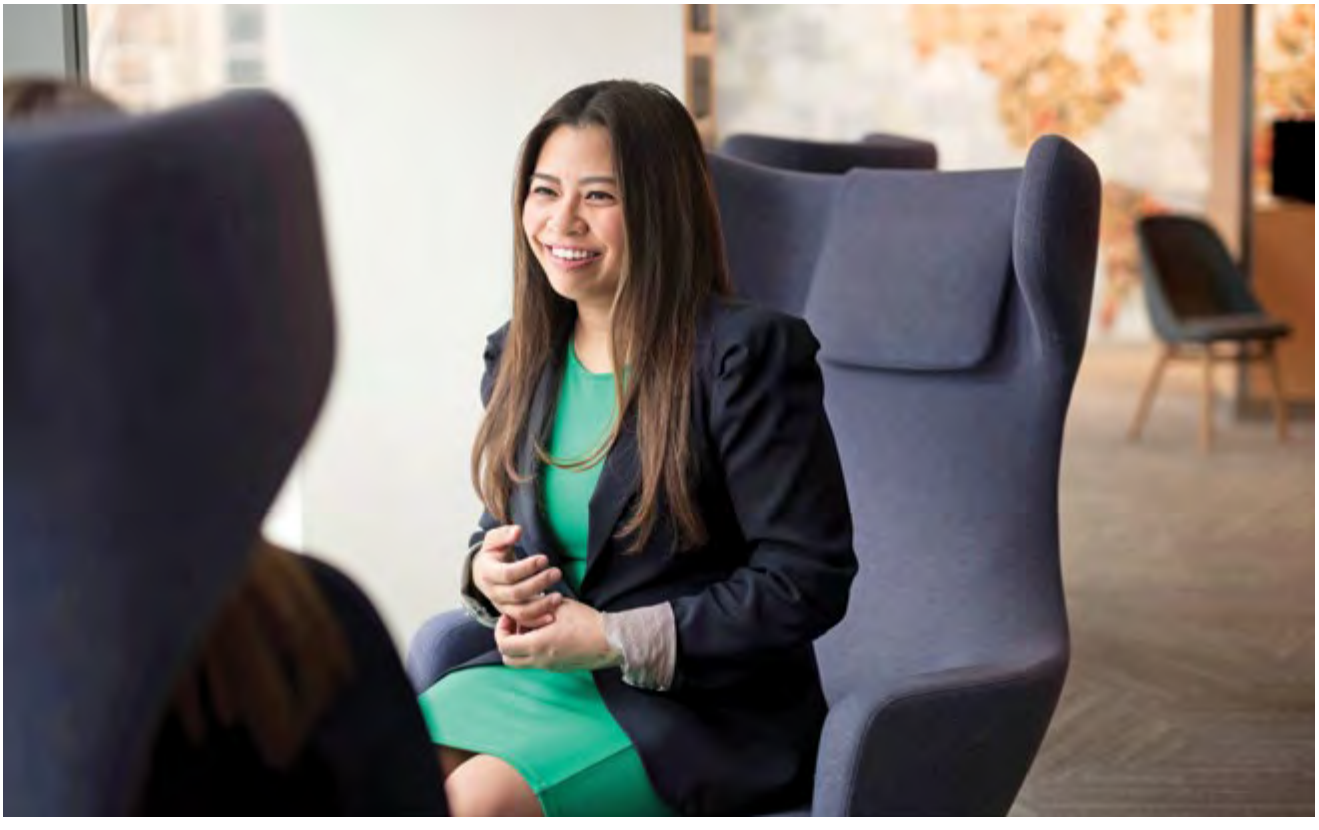
The RSAs "really are the backbone of the service," Ms. Bernal says. "They monitor the patients from the moment they walk through the door of MSK to the moment they are deemed cancer free."

Nurse practitioner Elizabeth Halton is also an integral longtime member of the group, and of MSK. She spent more than a decade working with the Leukemia Service before coming to the CAR T program. Like Ms. Bernal, she joined Dr. Brentjens when the first CAR T trials began at MSK in 2007, and she was instrumental in getting the CAR T program up and running. She and the other advanced practice nurses from the Leukemia Service on the 12th floor of Memorial Hospital first cared for people who received this powerful experimental therapy.

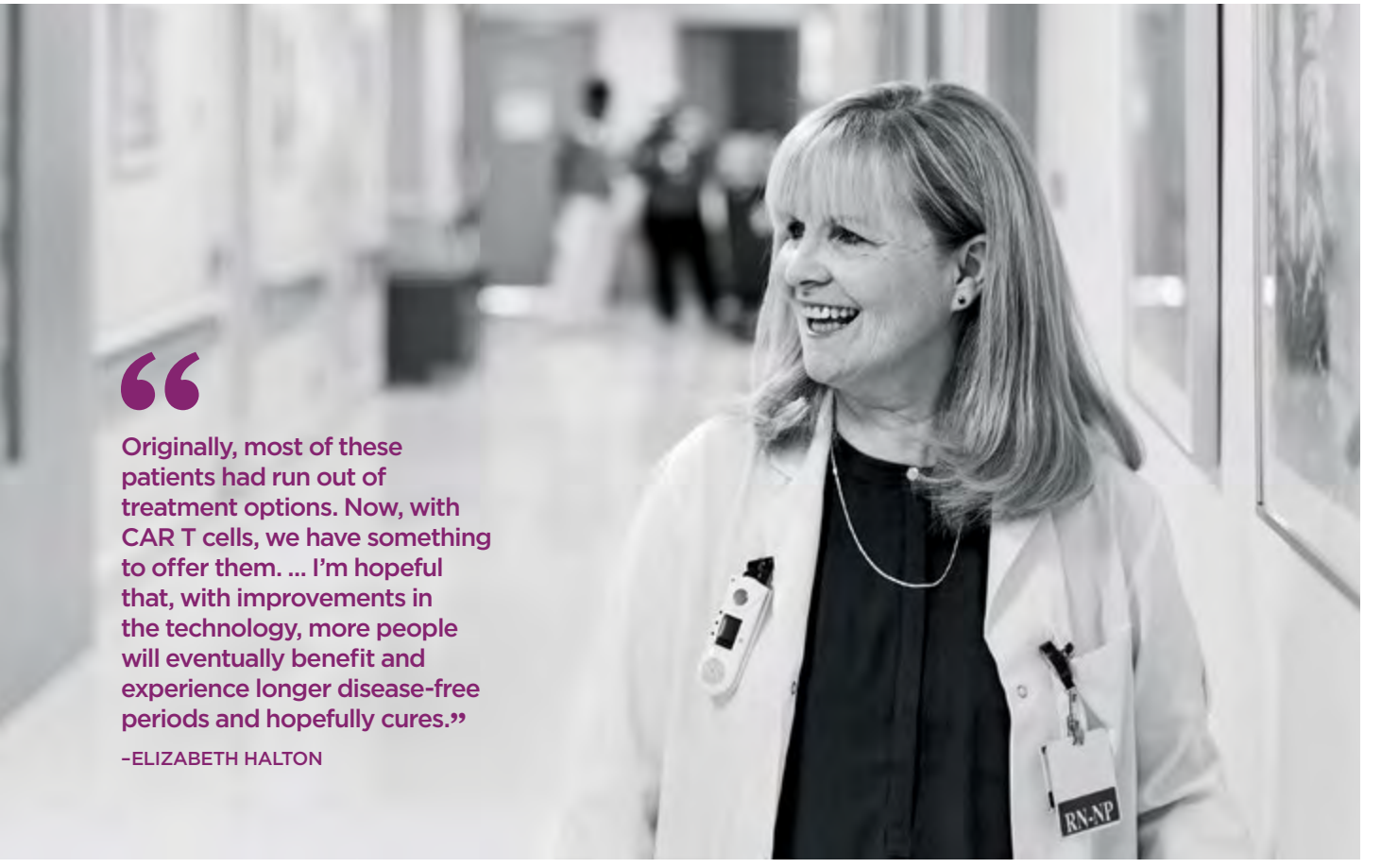
"It was an exciting but also an intimidating time," Ms. Halton says. "We did not know what to expect after infusing the CAR T cells."

She credits Dr. Park, in particular, for developing effective clinical measures to deal with the sometimes severe side effects of CAR therapy. "We called him in the middle of the night. Together, we learned what worked, what didn't — and then we tweaked it for the next patient," Ms. Halton says.

Looking back over the decade-plus it took to get where the treatment is today, Ms. Halton is quietly optimistic. "Originally, most of these patients had run out of treatment options. Now, with CAR T cells, we have something to offer them. And while it doesn't work for everyone, I'm hopeful that, with improvements in the technology, more people will eventually benefit and experience longer disease-free periods and hopefully cures."



Every clinical trial must follow a careful plan, called a protocol, that describes exactly what will happen during the study. Research study assistants (RSAs), including those on the CAR T team, help monitor and record data. Yvette Bernal oversees and trains these RSAs.



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>
> –ELIZABETH HALTON

GOING THE LAST MILE

As for Mr. Blum, though his results have been good, his experience with bone marrow transplantation after CAR T cell therapy demonstrates why doctors are eager to get to a point at which they can safely avoid it. About a month after the transplant, he got an infection that led to a severe case of pneumonia.

"I was in the ICU, and honestly, it was a really scary time," Mr. Blum says. "The doctors told my mother not to leave the hospital. They were worried I might not make it."

But thanks to CAR T cell therapy, he's just beginning a new life. It's been nearly two years since Mr. Blum had his BMT. He's since gotten married, and he and his wife, Ashley, took a trip to Jamaica to celebrate.

He says he always felt very well cared for at MSK. "That hospital is a piece of heaven," Mr. Blum says. "Everyone there has a heart three times the size of normal." ■

Top: Elizabeth Halton has been part of the CAR T program from the very beginning.
Above: Renier Brentjens, who helped pioneer CAR T therapy, is Director of the Cellular Therapeutics Center, the group of doctors, nurses, and staff who care for patients treated with CAR T cells as part of clinical trials at MSK.