

WINTER 2024

MSKNews

MEMORIAL SLOAN KETTERING CANCER CENTER

Fighting Cancer by Boosting the Immune System

How MSK is pushing the frontier
of immunotherapy to help
patients like Antonio



Memorial Sloan Kettering
Cancer Center

ALSO INSIDE

New hope for a young father

Turning immune cells into cancer fighters

A warm welcome in any language

Meeting baby Mya Grace

Dear MSK Community,

Every day we are inspired when our patients are given new hope, thanks to a lifesaving approach to cancer treatment that was pioneered at MSK — immunotherapy.

The premise is straightforward: Encourage a person's own immune system to overpower cancer cells and stop their growth. But developing new approaches demands exceptional ingenuity and perseverance. This issue of *MSK News* focuses on the many ways we are making immunotherapy help more people.

This type of therapy started here more than 100 years ago, when surgeon **William Coley** conducted the world's first successful experiments using it to treat cancer in the 1890s. He noticed that patients with bacterial infections sometimes saw their tumors shrink and began treating people with specially prepared bacteria.

Since those early days, MSK researchers and clinicians have made transformational contributions to immunotherapy. Most recently, MSK physician-scientist **Michel Sadelain, MD, PhD**, was awarded the prestigious **Breakthrough Prize in Life Sciences** for his pivotal research on CAR T cell therapy, a form of immunotherapy.

As you'll read, CAR T cell therapy reengineers the T cell — the foot soldier of the immune system. The result supercharges the immune system's ability to fight cancer, as do TIL therapy, checkpoint inhibitors, and other immunotherapies explored in this issue.

New and visionary philanthropic support from **Henry R. Kravis** in honor of his wife, **Marie-Josée Kravis**, Vice Chair of the MSK Board of Trustees, will enable us to remain at the forefront, through the creation of **The Marie-Josée Kravis Center for Cancer Immunobiology**. This center and other efforts span the research spectrum — from discovery science to patient care — and will produce advances to help people with cancer for decades to come.

In this issue, you will also see how we care for people in every way they need us. For **Beatriz Galvan**, that meant providing language interpretation, which gave her peace of mind during breast cancer treatment.

We are also pleased to mark important milestones for the **Sloan Kettering Institute** — which is celebrating its 75th anniversary — as well as for MSK's **Bone Marrow Transplant team**, which has been saving lives for half a century.

To conclude this issue, we'll introduce one of the newest members of the MSK community, **Mya Grace**, who was born in July 2023. Her mother, **Kelly Spill**, participated in a heralded MSK clinical trial using immunotherapy for rectal cancer, allowing Kelly to skip radiation treatments that typically make women infertile.

New life and new discoveries help make MSK what it is. We hope you enjoy reading about our quest to end cancer for life.



Sincerely,

Selwyn M. Vickers, MD, FACS
President and Chief Executive Officer

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CAR T cell therapy gave Guillaume Arnould another option, after other therapies for multiple myeloma failed.

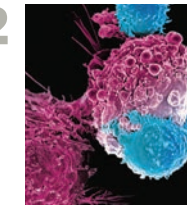
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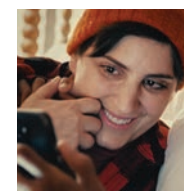
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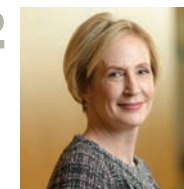
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Happy Birthday, Sloan Kettering Institute!
Scan here for 75 years of innovation.

Treating Cancer With Immunotherapy



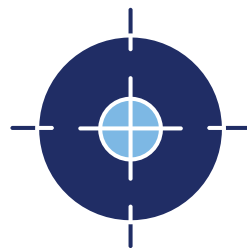
Immunotherapy works by enlisting and strengthening your body’s natural ability to fight cancer. Unlike other forms of cancer treatment, in which drugs or radiation target cancer cells directly, immunotherapy targets your immune system, boosting its innate power to fight the cancer.



Immunotherapy is one of the most promising approaches to cancer treatment, but how does it work and who can it help? We asked melanoma oncologist Michael Postow, MD, an expert in immunotherapy at Memorial Sloan Kettering Cancer Center (MSK), to address the most frequently asked questions.

1. How is the immune system able to fight cancer on its own?

Your immune system keeps you safe from many threats — not only infectious ones like bacteria and viruses, but also cancer. It does this by recognizing and attacking things that appear foreign or dangerous. Because cancer cells are genetically mutated, they look different to your immune system than healthy cells. Your immune system is constantly ridding your body of mutated cells that could lead to cancer.



2. How do cancer cells evade the immune system?

Occasionally, cancer cells trick the immune system into sparing them from attack. One way is to step on an immune cell’s brakes, which keep immune cells from attacking healthy cells. Cancer cells can also alter the tumor microenvironment in surrounding tissue to make it hostile to immune cells.

3. What are the types of immunotherapy?

There are three main types of immunotherapy:

Immune checkpoint inhibitors: These are drugs that release the brakes on immune cells, allowing them to go after cancer cells.

Adoptive cell-based therapies: Sometimes called living drugs, these are natural or engineered versions of a person’s own immune cells that are multiplied in the lab and given back to the person in large numbers. These therapies include CAR T and TIL. Having more of these cells in the body is like having a bigger army to naturally fight cancer.

Cancer vaccines: These are designed to either prevent or treat cancer, by training the immune system to identify dangerous cells that have telltale markers, called antigens. Recently, an MSK clinical trial showed that a personalized cancer vaccine may activate the immune system in patients with pancreatic cancer. But more research is needed.

4. Which cancers can be treated with immunotherapy?

Immunotherapy works well for cancers that have distinguishable markers that our immune system is able to recognize. There are several broad categories:



Cancers with many genetic mutations: These are easier for the immune system to detect because they look so different from normal cells. Some cancers, like melanoma and lung cancer, can develop many mutations from the genetic damage caused by sunlight and cigarette smoking, respectively. Other cancers, including certain types of colon cancer, may develop many mutations as a result of an underlying genetic condition.

Cancers with high levels of PD-L1 expression: PD-L1 is a protein that some cancers make that can step on an immune cell’s brakes and cause the immune response to shut down. Certain cancers with high amounts of this protein are considered good candidates for anti-PD-1 immunotherapy drugs such as pembrolizumab and nivolumab.

Cancers with distinctive markers on their surface: Certain blood cancers have markers on their surface that make them good targets for CAR T immunotherapy. The surface marker CD19 on B cell leukemias is a good example.

5. What are the side effects of immunotherapy?

The most common side effects result from the immune system overreacting to normal tissues in the body. They include skin problems like rash or itching, chills and other flu-like symptoms, gastrointestinal issues like diarrhea, and pain from joint inflammation. These side effects can be very dangerous if they involve vital organs, such as the lungs, and go untreated. MSK doctors are experts in caring for people with immune-related adverse events.

6. What percentage of cancer patients can immunotherapy help?

It varies by cancer type but, on average, immunotherapy helps:

Between **15% and 30%** of patients who have common solid tumors such as lung, bladder, and kidney cancer.

Between **45% and 60%** of patients with certain skin cancers and solid tumors that have a type of mutation called MMRd/MSI-high.

7. Why does immunotherapy stop working in some patients?

Immunotherapies may stop working when cancer cells evolve to evade immune cells, often by losing the specific marker or markers that the immune cells were using to identify it. This is called antigen escape or immune escape. Cancer and the immune system are in a constant battle to see which can get the upper hand; immunotherapy intends to strengthen the immune response to ensure it continues to control cancer as long as possible.

8. Is there anything patients can do to boost their own immune system?

There are no specific actions a person can take to ensure their immunotherapy is successful. However, some research indicates patients do better when they maintain a healthy gut microbiome by eating a diet high in plant fiber, avoiding unnecessary antibiotics, and avoiding probiotics.

The Art of Improving Immunotherapy

How Checkpoint Inhibitors Are Transforming Treatment

Antonio Lekhrajmal enjoys working in his art studio, five years after he was diagnosed with stage 4 stomach cancer.

Antonio Lekhrajmal knew his diagnosis of advanced stomach cancer — also called gastric cancer — was extremely serious.

He credits his doctor, Memorial Sloan Kettering Cancer Center (MSK) gastrointestinal oncologist Yelena Janjigian, MD, with being upfront with him. “She said that stage 4 stomach cancer is very hard,” he recalls. “But she told me, ‘Together, we’re going to do everything possible to help you.’”

Today, more than five years after his diagnosis, Antonio is thankful to be doing what he loves — spending time with his wife, Maria, and daughters and pursuing his artwork after nearly 30 years in the custodial department of the Livingston, New Jersey, school system.

The treatment that made the difference for Antonio and people facing similar cancers is the immunotherapy known as checkpoint inhibitors. As Chief of the **Gastrointestinal Oncology Service** at MSK, Dr. Janjigian is at the forefront of efforts to investigate how they can help more people.

In fact, clinical trials she led using checkpoint inhibitors were cited by the U.S. Food and Drug Administration when it approved this therapy as “the first treatment in more than a decade to show survival benefit for people with metastatic gastric cancer who are being treated for the first time.”

The success of these clinical trials joins a growing list of advances with checkpoint inhibitors that have been pioneered by MSK scientists and clinicians for more than two decades.

How Checkpoint Inhibitors Work

The cells of the immune system are so powerful that they contain a built-in brake to prevent them from attacking healthy cells by accident. Cancer cells, says Dr. Janjigian, “are normal cells gone rogue.” So they can sometimes trigger the brake, effectively disguising themselves as normal cells and deceiving immune cells into leaving them alone.

Checkpoint inhibitors expose the deception by preventing cancer cells from activating the brake. “They uncloak the cancer cells,” says Dr. Janjigian, “making them more visible to the immune system and allowing it to attack the cancer cells and suppress them from coming back.”

Dr. Janjigian adds, “The reason this works so well is that the immune system can continue doing surveillance and attacking cancer cells longer than other treatments like chemotherapy.”

Which Cancers Are Treated by Checkpoint Inhibitors?

Checkpoint inhibitors are remarkably powerful and adaptable — much like the immune system itself.

They can be used for local cancer that hasn’t spread, as well as for metastatic cancer. They can be combined with chemotherapy and used before or after surgery and radiation. And they strengthen other forms of immunotherapy, such as vaccines and cellular therapies like TIL.

In a small but impactful study at MSK, checkpoint inhibitors used alone made rectal cancer disappear entirely in a group of patients whose tumors had a specific genetic mutation. MSK researchers are now investigating this use of checkpoint inhibitors in other cancer types.

Checkpoint inhibitors have proved themselves effective in treating many forms of cancer, including melanoma, lung, bladder, kidney, and, recently, ovarian cancers. Dr. Janjigian says this form of immunotherapy is particularly useful in gastrointestinal (GI) cancers, including esophagus, colorectal, gastric, and liver cancers.

“These kinds of tumors are driven by several different genetic abnormalities and are very complex,” she says.

Using checkpoint inhibitors — in combination with other therapies — offers new options that can help address these complexities.

Making Checkpoint Inhibitors Work for More People

Dr. Janjigian stresses that immunotherapy, including checkpoint inhibitors, doesn’t work for everyone. In some cancers, only a small percentage of people see substantial improvement.

“Making this work for more people is the next big leap for researchers at MSK,” she says. Among the areas being investigated, Dr. Janjigian cites the “genetics of the tumor itself, as well as where it sits in the body and how easily it can be infiltrated by immune cells.” Perhaps most important, Dr. Janjigian explains, is the person’s own body: “How well does their immune system work in general, and how does that affect treatment?”

Dr. Janjigian says, “Understanding these factors is why it matters so much where you go for treatment. Using immunotherapy can affect the entire trajectory of a person’s care. Getting the right expertise is crucial.”

MSK’s Expertise

Antonio’s treatment involved regular infusions of checkpoint inhibitors along with chemotherapy. Together, this treatment shrank his tumor enough that it could be surgically removed by **Vivian Strong, MD**. Antonio says recovery from the treatment was challenging. But “after surviving cancer,” he says, “I know what’s really important in life, and I have Dr. Janjigian to thank.”

For her part, Dr. Janjigian is thankful to be able to offer checkpoint inhibitors. “I can now look people in the eye who have stage 4 disease and say there’s a possibility they will live with this disease, rather than live in fear.” •



“I can now look people in the eye who have stage 4 disease and say there’s a possibility they will live with this disease, rather than live in fear.”

—Yelena Janjigian, MD

Immunotherapy research at MSK receives essential philanthropic support from the **MSK Giving** community, including **The Carrie Blessing Fund; The Endeavor Foundation, Inc.;** and the **Parker Institute for Cancer Immunotherapy.**

Dr. Strong holds the **Iris Cantor Chair.**

New Hope for a Young Father With Multiple Myeloma

Shortly after finding out his wife was pregnant with their son, Guillaume Arnould got terrible news about his own health: He had multiple myeloma, a rare blood cancer. He was just 33 years old. The following six years were a grueling succession of stem cell transplants, chemotherapy, and radiation. Yet the cancer was relentless.

“It was devastating for me and my family each time I relapsed,” says Guillaume. “You’re living with that sword of Damocles above your head all the time, and you don’t know when it’s going to fall.”

Initially treated at another New York hospital, Guillaume says his doctor advised that his best hope

would be Memorial Sloan Kettering Cancer Center (MSK). He had his second stem cell transplant under the care of hematologist-oncologist Sergio Giralt, MD, using cells from a donor — his younger brother, who flew over from France, where Guillaume grew up. The treatment was arduous, but it seemed to work — until it didn’t.

Three years ago, the disease was on the march again. Guillaume wondered if he had run out of options. Like most cancers, multiple myeloma becomes harder to treat every time it comes back. Guillaume despaired at the thought of saying goodbye to his wife, Ruth, and Tristan, then 6.



With his disease currently in check, Guillaume is back to enjoying life with his wife, Ruth, and son, Tristan.

“You start panicking because you have basically tried everything on the myeloma menu at that point — is there anything left?” Guillaume says.

Thanks to MSK, there was.

CAR T Cell Therapy for Multiple Myeloma

Dr. Giralt told Guillaume about a clinical trial testing a new treatment called chimeric antigen receptor (CAR) T cell therapy. Often called a living drug, the treatment involves removing immune cells called T cells from the blood and inserting a new gene into those cells, which enables them to recognize the cancer.

The clinical trial, led by MSK multiple myeloma specialist Sham Mailankody, MBBS, took a novel approach: It was targeting an antigen on the surface of the myeloma cells called GPRC5D. Previous CAR T cell therapies for multiple myeloma had targeted a different antigen — called BCMA. But BCMA-targeted therapies don’t work for everyone, especially those who have received many previous treatments.

“One of MSK’s great strengths is our ability to develop new immunotherapy treatment options for people who, like Guillaume, appear to have exhausted all other available therapies,” Dr. Mailankody says.

Indeed, there was exciting research underway in an MSK lab, which reported in 2019 that GPRC5D could be a promising multiple myeloma target. Scientists used a specialized staining technique to reveal GPRC5D antigens all over the surface of myeloma cells. Soon thereafter in 2020, MSK launched a phase 1 clinical trial at MSK, led by Dr. Mailankody.

“It’s a testament to the clinical, translational, and laboratory teams at MSK that we were able to take that pre-clinical lab data and open the first human study very quickly,” Dr. Mailankody says.

The Clinical Trial That Renewed Hope for Guillaume

Guillaume jumped at the chance to join the trial. “We didn’t think twice. I was absolutely convinced that they were doing what was best for me and my family,” he says.

In January 2021, Guillaume received his CAR T cells, which had been engineered to attack this new target. Although he needed chemotherapy first, it was a milder dose than for his previous stem cell transplants. After seven years of being in hospitals, Guillaume had built up a tolerance for the pain and discomfort, and he made sure to exercise diligently throughout treatment.

“I discovered CrossFit and I love it — I work out almost every day,” he says. “It is important to have something to clear your mind and get it off the cancer.”

Guillaume was able to return to work as a fund manager in April 2021. His disease is currently stable. Guillaume is checked regularly with scans and other tests in Manhattan and at MSK Westchester, not far from his home in Larchmont, New York.

The Future of Immunotherapy for Multiple Myeloma

Targeting GPRC5D continues to offer promise for patients with multiple myeloma. In September 2022, Dr. Mailankody reported encouraging results from the phase 1 trial in *The New England Journal of Medicine*. In addition, a new trial has opened at MSK, to give BCMA- and GPRC5D-targeted CAR T cell therapies together, for patients with advanced myeloma.

“We are continuing to explore possible combination approaches with this therapy, as well as understand how resistance may develop,” Dr. Mailankody says.

More than two and a half years after the cutting-edge treatment, Guillaume continues to enjoy life with Ruth and Tristan, now 9. “I owe so much to my family in their continuous support through these challenging years and helping me to keep up my fighting spirit and not give up,” Guillaume says. “I’m also extremely grateful to Dr. Giralt, Dr. Mailankody, and all the nurses and support staff at MSK. Their devotion and passion are inspiring.” •

Dr. Giralt and his colleagues’ research receives essential philanthropic support from the MSK Giving community, including the A.C. Israel Foundation, Inc.

Dr. Giralt holds the Melvin Berlin Family Chair in Multiple Myeloma.

Winning the Race Against Solid Tumors



By the summer of 2022, Roberto Romero was running out of options to treat the melanoma he'd been coping with since 2015. He'd already had several surgeries and many rounds of drug treatment. But the cancer — which started as a dark spot under a toenail — continued to grow and was now invading his organs.

So when Roberto learned about a new immunotherapy targeting solid tumors like his, he leaped at the chance to receive the experimental treatment at Memorial Sloan Kettering Cancer Center (MSK). “I thought, ‘If I can do it and it works for me, that would be great,’” says Roberto, 51. “And even if it doesn’t help me, it could still help others.”

This approach is part of a class of treatments called TIL (pronounced “till”)

therapy. TIL stands for tumor-infiltrating lymphocytes, a specialized type of white blood cell in the immune system. The concept is simple yet revolutionary: Take these immune cells from within the tumor — where they have already been doing their best to fight the cancer — grow them into large numbers, and then put them back into the patient. Like a small group of soldiers that’s been multiplied into a bigger army, they become a stronger force to seek and destroy the cancer.

“The idea behind TIL therapy is that these cells already know how to find the cancer,” says **melanoma oncologist and cellular therapist Alexander Shoushtari, MD**, a leader in TIL research. “By multiplying the number of TILs in the body, we give the immune system a better chance of fighting the disease.” The particular TIL treatment that Roberto received is called lifileucel.

Early results show the treatment has been effective for Roberto and several other MSK patients. A phase 2 clinical trial involving many hospitals found that 36% of patients responded to the therapy. Nearly a year after treatment, Roberto’s tumors are continuing to shrink. He’s resumed his passion for distance running and his jobs working in information technology at a university and teaching English to Spanish-speaking immigrants.

Cell Therapy Takes a Team of Experts

TIL therapy is a type of cell therapy, meaning living cells are injected into a patient to treat their disease. It’s similar to another cell therapy — chimeric antigen receptor (CAR) T cell therapy, which treats some blood cancers and was pioneered at MSK. But TIL therapy may work better against solid tumors, in part because TIL cells can recognize a broad range of “markers” found on solid tumors, explains **melanoma surgeon Charlotte Ariyan, MD, PhD**, one of Dr. Shoushtari’s collaborators.

One benefit of the TIL approach is that it can be effective even when surgically removing all the tumors is not an option. “We operate only on the tumor that’s easiest to access,” Dr. Ariyan explains. “That’s because patients have to recover from surgery and be ready to receive the TIL therapy relatively quickly.”

For Roberto, the process began just before Christmas in 2022. MSK **surgeon Edmond Bartlett, MD**, performed surgery



Dr. Alexander Shoushtari is a leader in TIL research at MSK.

to remove a tumor from the lining of Roberto’s abdomen near his colon. After he recovered, he was given high doses of chemotherapy to prepare his body for the TILs, which were sent to be grown in the lab of the company that makes lifileucel. Ten days later, his TILs were infused through a port in his chest to circulate throughout his system and hunt down additional tumors. He was then given an immune-stimulating drug called interleukin-2 to further boost his immune system.

The first few weeks were difficult. He had high fevers and could not have visitors due to his weakened immune system. Except for the nurses who cared for him around the clock, Roberto spent the holidays in isolation in his room decorated with a small tree and twinkling lights. “I wanted it to feel festive despite what I was going through,” he says.

As he recovered, he spent hours walking the halls and riding a stationary bicycle in his room. By the end of January, he was home. By February, he was already back at work. To his astonishment and great relief, scans showed his tumors were

shrinking. “It’s pretty amazing, because there were moments during my treatment when I didn’t think I was going to make it out of the hospital,” he says.

TIL Therapy May Work for Other Cancers

Like other immunotherapies pioneered at MSK, Dr. Shoushtari believes TIL therapy may be effective against many types of cancer. “These melanoma studies are a powerful proof of concept for this class of treatment,” he says. TIL therapy studies are already underway at MSK for lung cancer, as well as for other types of melanoma, including melanoma that has spread to the brain.

In March 2023, Roberto started jogging again. Vowing to run the New York City Marathon, he joined Fred’s Team to raise money for research at MSK.

“Dr. Shoushtari tells me I make recovery look easy, but I know it’s not easy for most patients,” Roberto says. “I’m fortunate that I was in good shape before treatment. And I’m grateful for the care that I received from everyone at MSK.” •

Melanoma research at MSK receives essential philanthropic support from the **MSK Giving** community, including **Betsy and Philip Allen**, the **Hazen Polsky Foundation**, the **Heineman Russell Family Foundation**, the **Melanoma Research Alliance**, **Nonna’s Garden Foundation**, **Allan H. Selig**, **Sephora**, and **The Shore Family Fund**.

Dr. Ariyan holds the **Carol Bassok Lowenstein Endowed Chair**.

Training Cells To Become Cancer Fighters

This electron microscopic image shows CAR T cells (blue) attacking cancer cells (pink). Courtesy of Dr. Prasad Adusumilli.

Giving one dose of a treatment that will stay in a patient's body to help it continue to fight cancer may seem like mission impossible. But it's not. This type of immunotherapy, called CAR T cell therapy, is one of the most exciting fields in cancer treatment today.

Think of it as creating “cellular assassins,” trained to eliminate cancer cells. T cells from a patient's own immune system are removed and then outfitted in the lab with special tools that recognize specific targets on the surface of a cancer cell. When these armed cells are put back into the patient, they patrol the bloodstream like elite soldiers on search-and-destroy missions attacking those targets, leaving minimal collateral damage, and resuming the action if the cancer cells return.

For more than two decades, scientists at Memorial Sloan Kettering Cancer Center (MSK) have been pioneers in this field.

They've invented as many as 20 CART technologies so far. MSK discoveries have made CAR T cell therapy especially effective in treating patients with blood cancers, including certain leukemias and lymphomas, as well as multiple myeloma.

But there are major hurdles currently keeping CAR T cell therapy from helping more patients:

- The cells can take weeks to prepare and are expensive because they are engineered individually for each patient.
- Many people don't respond to the treatment, or the cancer returns after it works. It also can have serious side effects in the short term.

- CAR T cells haven't worked well against solid tumors, which make up the vast majority of cancers.

Every day, across MSK, scientists and clinicians are working to overcome the obstacles for this treatment, whose full name is “chimeric antigen receptor T cell therapy.” The “antigen” is a protein that exists in abundance on cancer cells but not normal cells. CAR T cells are engineered to selectively target these antigens, destroying the cancer.

“By investigating how T cells are wired and what receptors make them work, our laboratories can keep pushing the limits of this revolutionary treatment,” says physician-scientist Michel Sadelain, MD, PhD, who first engineered T cells 30 years ago. As Director of the Center for Cell Engineering and through his lab at the Sloan Kettering Institute, Dr. Sadelain has continued leading the field.

His lab is one of more than a dozen throughout MSK focused on improving CAR T cell therapy in the following ways:

Helping T Cells Keep Up the Fight

The T cells can lose their potency over time — a phenomenon known as T cell exhaustion — but Dr. Sadelain's lab found a way to keep up the fight by inserting a molecule called 1XX into the T cell genome at a precise location called TRAC. His team used the new gene-editing technology CRISPR for this groundbreaking feat of engineering.

The laboratory advance is now coming to fruition in patients. In early 2023, MSK launched a clinical trial, led by hematologic oncologist Jae Park, MD, to test these fortified CAR T cells against a type of lymphoma. The translation from lab to clinic was made possible by Isabelle Rivière, PhD, and the Cell Therapy and Cell Engineering Facility at MSK. “If the cells are more potent and last longer, we ultimately would need fewer of them, which could make manufacturing easier and less expensive,” Dr. Park says.

Overcoming Resistance

Another major challenge for CAR T is that cancers develop resistance to the treatment by making less of the target antigens. This problem, known as antigen escape, enables the cancer to come roaring back. But Dr. Sadelain and colleagues used CRISPR to boost the sensitivity of the T cells to antigens by at least tenfold, enabling the CAR T cellular assassins to finish the job, even with fewer targets guiding their way.

These redesigned cells are called HLA-independent T cell receptor (HIT) T cells.

“This could really expand the field,” Dr. Sadelain says. “We may no longer be limited to targeting antigens that are abundant for CAR T cells to work.”

Penetrating Solid Tumors

A major reason CAR T cell therapy hasn't worked on solid tumors is that they are often difficult for T cells to penetrate. Like a moat around a fortress, tumors are also surrounded by cells and molecules that hinder the T cells until they run out of steam.

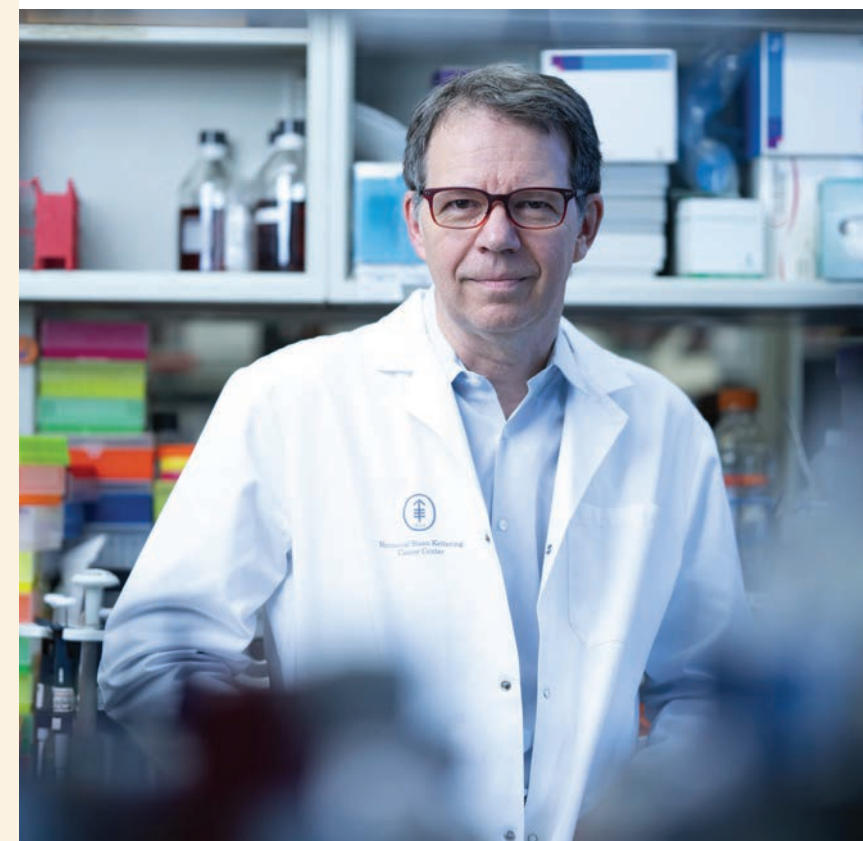
But the laboratory of physician-scientist Prasad Adusumilli, MD, is trying to solve this problem in multiple ways, including:

- Delivering CAR T cells directly into the chest cavity for tumors caused by mesothelioma, a rare cancer in the lining surrounding organs.
- Using low-dose radiation to help CAR T cells penetrate tumors.
- Genetically engineering the CAR T cells to contain a “decoy receptor” that foils cancer cells from blocking the immune cells until they become exhausted.
- Co-opting one of cancer's own weapons by adding a mutation in a gene called c-KIT to the CAR T cells. When given to animals with human tumors from mesothelioma, lung, and prostate cancers, these new tricked-out cells appeared to be more effective than conventional T cells.

Another approach to make CAR T work for solid tumors is by turning the cell into a “micropharmacy.” An entirely new type of CAR T cell has been designed by physician-scientist David Scheinberg, MD, PhD, Chair of the Center for Experimental Therapeutics, in collaboration with chemical biologist Derek Tan, PhD, Chair of the Chemical Biology Program.

These cells can activate a toxic drug payload directly at a tumor, killing both tumor cells that contain the cancer marker as well as those cancer cells nearby that do not have the marker. Fittingly, the name for these cells is SEAKER (Synthetic Enzyme-Armed KILLER).

“These cells combine the target-seeking power of immune cells with the ability to generate a potent anti-cancer drug right at the site of a tumor. It's a one-two punch on the cancer,” Dr. Scheinberg says.



Dr. Michel Sadelain recently received the prestigious Breakthrough Prize in Life Sciences for his pioneering work to develop CAR T cell therapy.

Peering Inside Cancer Cells

Currently, CAR T therapies can only engage target proteins located on the outside of cancer cells, a feature that limits their effectiveness and safety, especially against solid tumors. **MSK physician-scientist Christopher Klebanoff, MD**, is focused on an innovative, next-level approach.

His team is researching ways to genetically reprogram T white blood cells to recognize mutated cancer-causing proteins located on the inside of cancer cells — using a technique called T cell receptor therapy. This approach engineers T cells to enable them to survey the interior of cells in search of rogue proteins that are unique to tumors.

“We’re using a genetic engineering approach to help supercharge T cells in a new way,” says Dr. Klebanoff. “It’s akin to giving immune cells X-ray vision.”

Making CAR T Cell Therapy Easier for Patients — and More Accessible

The need for CAR T cells to be custom-made for each patient makes the treatment expensive and time-consuming. That’s why researchers are striving to make standardized CAR T cells. An “off-the-shelf” therapy would use cells taken from healthy donors — known as an allogeneic transplant — which then would be genetically modified and stored in large batches, ready for treatment.

“CAR Ts may never be widely used if they have to be made one at a time, per patient,” Dr. Scheinberg says. “We really want something that’s



Dr. Christopher Klebanoff is creating new T cell therapies that detect and selectively eliminate cancer cells while leaving healthy tissues unharmed.

waiting in a freezer — you order it, it’s thawed, and you infuse it into the person the next morning.”

Multiple myeloma specialist **Sham Mailankody, MBBS**, has reported encouraging results using donor CAR T cells to treat multiple myeloma in a small group of patients. These cells were modified using a virus.

In the lab, a more precise engineering technique may be able to prevent the downside of using donor CAR T cells — a serious side effect called graft-versus-host disease, which occurs when donor cells attack the patient’s normal cells. But by using CRISPR technology, MSK researchers are studying how to tweak the CAR T cells to disable the part that triggers this side effect.

In turn, to keep a patient’s immune cells from attacking donor CAR T cells, Dr. Scheinberg’s lab has developed new cells that could fend off this assault, using what he calls a “shield CAR T cell.”

“These CAR Ts are designed specifically to be off-the-shelf because that is where rejection is such an important issue,” says Dr. Scheinberg.

No doubt, making CAR T cell therapy a truly transformative cancer treatment requires the continued drive and ingenuity of MSK scientists. But the pace of discovery is picking up, thanks to new technologies like CRISPR. Scientists who once only imagined changing the genes of a cell are now able to do so. With exquisite precision, they can arm immune cells to continually attack cancer. It’s a mission that’s now possible. •

CAR T cell research at MSK receives essential philanthropic support from the **MSK Giving** community, including most recently **Cycle for Survival®**, **Mr. and Mrs. William H. Goodwin, Jr.** and **The Commonwealth Foundation for Cancer Research**, and **Wendy and Neil Sandler**.

Dr. Sadelain holds the **Stephen and Barbara Friedman Chair**.

Dr. Scheinberg holds the **Vincent Astor Chair**.

Dr. Tan holds the **Eugene W. Kettering Chair**.

Illuminating the Immune System

Dr. Chrysothemis Brown is shedding light on new types of immune cells and their role in cancer and other diseases.

When physician-scientist Chrysothemis Brown, MBBS, PhD, talks about the process of scientific discovery and the nuances of the immune system, the sincerity of her enthusiasm is unmistakable.



Along with being a dedicated researcher, Dr. Chrysothemis Brown excels as a mentor to trainees like Gayathri Shibu (right).

“What I love about science is the freedom and creativity,” Dr. Brown says. “And if you discover something, you’re the first person in the world to see it. It’s incredibly exciting and at the same time an enormous privilege.”

And already, the pediatrician and researcher, who founded her lab at Memorial Sloan Kettering Cancer Center (MSK) in early 2021, has had a number of these firsts.

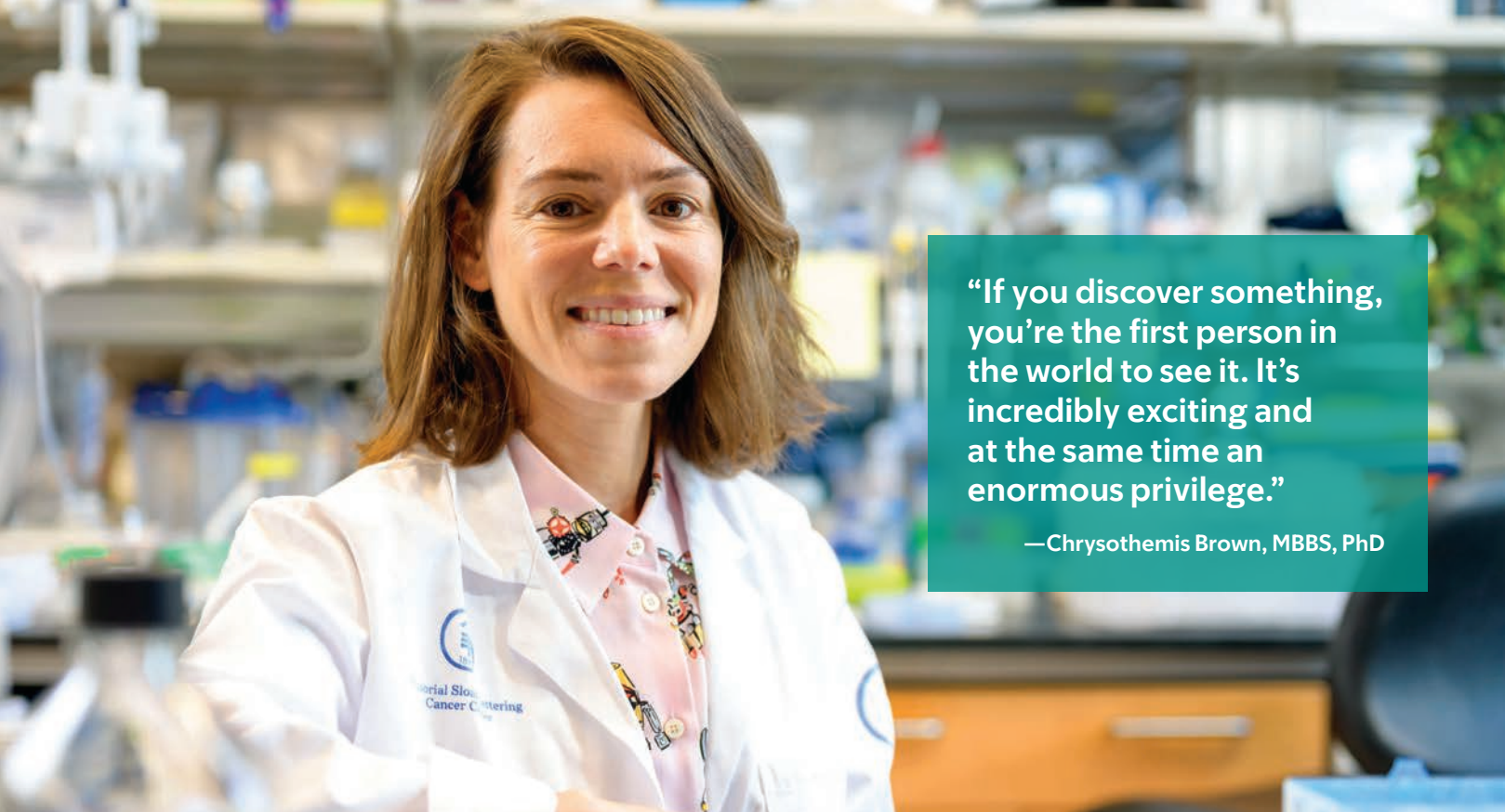
Notably, she co-led a research team that uncovered a new class of immune cells that play a key role in training babies’ immune systems not to attack the helpful bacteria in the digestive system.

“The immune system is very dynamic,” Dr. Brown says. “Not only can it change in hours in response to an infection but it also changes over the course of your lifetime.”

She and her colleagues identified a window in the early weeks of life where a “developmental wave” of these newly discovered immune cells rises and falls.

The study — a collaboration with mentor **Alexander Rudensky, PhD**, who chairs the **Immunology Program** at MSK’s **Sloan Kettering Institute** — appeared in *Nature*, one of the world’s premier scientific journals.

“This opened up a whole new area of investigation for us,” she says. “Basic questions like, ‘What causes this wave to start?’ And, ‘What causes it to stop?’



“If you discover something, you’re the first person in the world to see it. It’s incredibly exciting and at the same time an enormous privilege.”

—Chrysothemis Brown, MBBS, PhD

“But what’s also interesting is that we found that these cells can reemerge in adulthood in the context of cancer — so now we wonder whether tumors co-opt this developmental program to suppress the immune response against cancer. That’s something that we’re very actively working on,” she says.

Beyond cancer, Dr. Brown’s research within MSK’s **Human Oncology and Pathogenesis Program** is also helping to illuminate autoimmune disorders, like arthritis. (MSK’s foundational biology research frequently has applicability in areas beyond cancer.)

The Path of a Rising Star

Dr. Brown was born in London and grew up in Cambridge, England, where her parents’ careers in medicine and research inspired her own pursuit of science. As a teen, she spent summers working in her father’s lab studying the genetic underpinnings of hypertension.

She fell in love with immunology during medical training at Oxford University and then pursued doctoral work at King’s College London, where she studied the role of vitamin A as a regulator of the immune system.

“I spent three and a half years working on that, and we made an interesting discovery that showed how vitamin A

influences T cell differentiation. And that really opened my eyes to just how much the immune system can be modulated by, for example, dietary metabolites.”

Wanting to probe deeper into the regulation and development of the immune system, Dr. Brown did her post-doctoral research in the lab of Dr. Rudensky, a world-renowned immunologist.

“She is fearless as a scientist, ready to take on big, important questions with no hesitation,” Dr. Rudensky says. “Her agility in scientific pursuits is really her trademark — pivoting as observations lead to new insights and focusing in on the most exciting, novel, and promising paths.”

A Generous Mentor Herself

Yoselin Paucar Iza, a graduate student in Dr. Brown’s lab, said that as a mentor, Dr. Brown champions her trainees’ curiosity, supports their strengths, and nurtures their weaknesses.

“What we’ve learned from her is to really be guided by what the science is telling us,” Paucar Iza says. “And it’s clear she’s never scared to go into areas that

our lab may not already have expertise in, or to ask the tough questions that others might shy away from because of how challenging they are.”

Not only has Dr. Brown been the recipient of prestigious awards — including recently being named a **Pew Scholar in the Biomedical Sciences** — but trainees in her lab also have received notable recognitions.

This year, Dr. Brown and Paucar Iza were jointly awarded a **Gilliam Fellowship from the Howard Hughes Medical Institute**, a program committed to advancing equity and inclusion in science. And lab member **Gayathri Shibu** received a **Marie-Josée Kravis Women in Science Endeavor Graduate Fellowship**.

“Science can be really tough, and there’s a lot of failure baked in,” Dr. Brown says. “So you have to enjoy the process itself and not lose your confidence in what you’re doing when you hit a snag. That’s why I try to really be a cheerleader for everyone in the lab and make a fun environment that also supports their freedom and creativity.” •

The work of **Dr. Brown** and **Dr. Rudensky** is supported by the **MSK Giving** community, including the **Parker Institute for Cancer Immunotherapy**.

Dr. Brown is a **Josie Robertson Investigator**.

Life Lessons

People with cancer often wonder: How do you live to the fullest during one of life’s most frightening experiences?

Unforgettable lessons in finding joy and meaning — even in the darkest moments — are found in the documentary *American Symphony*. The film tells the story of Suleika Jaouad, an Emmy Award-winning and *New York Times* best-selling writer, advocate, and cancer survivor, and her husband, Jon Batiste, a Grammy- and Oscar-winning musical phenom and former band leader of *The Late Show With Steven Colbert*.

The movie — directed by Oscar-nominated and Emmy Award-winning filmmaker **Matthew Heineman** — was originally intended to document Jon’s first symphony, which premiered at New York’s famed Carnegie Hall.

But cancer has its own timetable.

In February 2022, Suleika received a bone marrow transplant (BMT) at Memorial Sloan Kettering Cancer Center (MSK), 13 years after she was first treated for acute myeloid leukemia. “Only weeks after I learned of my leukemia relapse,” she says, “we started filming from sunrise to long past sunset.”

Over the next seven months, she recalls, “We rode out the highest highs and lowest lows of our lives.” Cutting back and forth between music rehearsals and Suleika’s inpatient room at MSK influenced the film, she says. “[The movie] morphed from a straightforward music documentary into one about love and art and survival — about what happens when the human spirit is tested again and again.”

For decades, the staff of MSK’s **BMT Service** have devoted themselves to helping people not only survive, but thrive. This year, the service marks an exceptional milestone: the 50th anniversary of the first successful BMT ever performed using cells from a donor who was not related to the patient. Since that breakthrough procedure led by **Richard O’Reilly, MD** (who continues to work at MSK), more than 100,000 people around the world have received transplants from unrelated donors.

Half a century later, the transplant team continues to help people like Suleika. As for the movie, it has been picked up for distribution by **Netflix** and **Michelle and Barack Obama’s Higher Ground Productions**. Netflix plans to release the film November 29, 2023. •



The new documentary *American Symphony* captures intimate moments between Suleika Jaouad and her husband, Jon Batiste. Photo courtesy of *American Symphony*.

A Warm Welcome at MSK

Beatriz Galvan was cared for in every way she needed after a breast cancer diagnosis.

Beatriz Galvan treasures spending time with her granddaughter, Mía Camila, after being successfully treated for breast cancer at MSK.

The phone call was startling. Beatriz Galvan was not expecting to hear from her doctor on a Sunday. The 62-year-old grandmother from Bayville, Long Island, had just had a long-overdue checkup and her first-ever mammogram to screen for breast cancer. Her doctor asked to see her first thing Monday morning.

Beatriz had not been feeling well for some time. She felt a mass in her breast the year before, but was focused on supporting her family in her native country of Colombia through the devastating loss of her brother to stomach cancer and her father to prostate cancer.

That Monday morning, as they sat in her doctor's office, Beatriz and her husband, Octavio, received even more devastating news. She had breast cancer. Beatriz, who speaks little English, felt lost and terrified. "I had no job, no insurance," she says. "What was I going to do?"

Facing Barriers to Cancer Care

Sadly, Beatriz's circumstances are not unique. According to the Centers for Disease Control and Prevention, cancer is the leading cause of death for Hispanic or Latino people in the U.S. They face challenges that make it harder for them to get medical care than for non-Hispanic white people.

There are many contributing factors, such as language barriers, misinformation and lack of awareness about cancer prevention and early detection, and not having timely access to screening services or treatment.

"Other barriers include lack of health insurance and childcare, the cost of paying for treatment, housing and food insecurity, transportation concerns, and having a job that doesn't allow you to attend frequent appointments,"

says **Lisa Diamond, MD, MPH**, a researcher in the **Immigrant Health and Cancer Disparities (IHCD) Service** at Memorial Sloan Kettering Cancer Center (MSK). "Identifying these challenges when a person first comes to MSK is a crucial part of care."

Accessing Compassionate Care Close to Home

After a friend recommended MSK, Beatriz was happy to learn there was an MSK location in Commack, near her home. Her daughter, Diana, called MSK and easily was able to make an appointment for her mother to see **breast oncologist Iris Zhi, MD, PhD**, and **breast surgeon Tracy-Ann Moo, MD**, right away. Beatriz was also referred to MSK's **Financial Assistance Program** to apply for additional support beyond Medicaid to help cover her care.

Dr. Zhi explained that Beatriz had locally advanced cancer in the right breast. She would need four months of chemotherapy to first shrink the tumor, then surgery to remove it, followed by five weeks of radiation. She would then have to take medicine (endocrine therapy) for 10 years to reduce the risk of the cancer coming back.

Beatriz wondered if she could handle all that treatment, but she says she trusted Dr. Zhi's expertise and was impressed with the warm, friendly environment at the **MSK Commack Nonna's Garden**



"When you speak to [patients] in their own language, [it] plays a huge role in making them feel welcome."

—Lisa Diamond, MD, MPH



Beatriz is grateful her daughter, Diana, could be by her side during her care at MSK.

Foundation Center. “From the person who greeted us in reception to the staff who work in the doctors’ offices, everyone was so kind and attentive, and it made me feel good,” she says. “The doctors and nurses calmed my nerves, and I felt a lot of peace there.” It also helped that Beatriz’s daughter, Diana, was welcome to participate in every discussion.

“I’m grateful for my daughter’s support,” adds Beatriz. “She never left my side and encouraged me every step of the way.”

Communicating With the Care Team

Beatriz’s MSK care team made sure there was an interpreter present in person or over the phone or video during all her appointments. “They kept us informed

and ensured that we understood everything we needed to know about my treatment,” says Beatriz.

Dr. Diamond says providing qualified, competent interpreters must be a priority at a cancer hospital. “Conversations about cancer are emotional and complicated, and patients see numerous clinicians throughout their experience,” explains Dr. Diamond.

Her research focuses on how the quality of care and outcomes improve when a provider is truly fluent in the language a patient speaks — called “language concordance.” This work has led MSK to launch a new program for bilingual employees to test the strength of their language skills before they speak with patients in that language in the clinical setting.

“Patients completely open up and change their demeanor when you speak to them in their own language,” Dr. Diamond says. “That plays a huge role in making them feel welcome, and it’s the right thing to do.”

‘Impossible Not To Get Well’

After Beatriz finished her course of chemotherapy, Dr. Moo confirmed that the tumor was small enough to be removed. Beatriz had the operation and then underwent radiation therapy.

“The care at MSK is wonderful, and the staff is well prepared and very professional. I never met anyone who made me feel bad or that I didn’t belong because I was Latina,” she says. “I believe that when a person as sick as I was finds so much compassion and support in one place, it’s impossible not to get well.”



Community outreach team members (from left) Gabriela Rebolo and Josana Tonda working at the MSK Ralph Lauren Center.



The MSK Mobile Health Unit and its bilingual staff bring services directly to communities in New York.

Improving Access to Clinical Trials

After surgery and radiation, Beatriz agreed to participate in a clinical trial. She underwent MSK’s state-of-the-art genetic testing called **MSK-IMPACT®** to look for changes that fueled her cancer. The study is evaluating whether a new drug that targets those changes taken together with the endocrine therapy would further reduce the risk of her cancer returning.

“One of MSK’s strengths is our effort to enroll patients from underrepresented populations into clinical trials,” says Dr. Zhi. A recent study found that 13% of people with cancer are Hispanic, but only 3% to 6% of those who participate in clinical trials are Hispanic. Inclusivity in clinical trials is important so researchers can get a better picture of how a new treatment affects different ethnic groups.

Dr. Zhi and the care team took time to make sure Beatriz and her daughter understood everything that would be involved in the study so they could make an informed decision about participating. “I was happy to sign up so MSK could learn more and help more people like me,” says Beatriz.

“I was able to sit with Beatriz, listen to her concerns, answer all her questions about the study, and help her walk away feeling like I had her best interest at heart,”

says Dr. Zhi. “I think that human touch made a big difference for her.”

Reaching the Hispanic and Latino Community

For more than a decade, MSK’s IHCD Service has been working to break down barriers to cancer care among people in the Hispanic and Latino community and other ethnic groups. Programs include:

- **The Integrated Cancer Care Access Network (ICCAN)**, which connects medically underserved patients with services such as health insurance, transportation, childcare, financial assistance, and healthy groceries from hospital-based food pantries throughout the city.
- **Access to Telehealth (ActT)**, which provides phones and tablets to people with cancer and teaches them how to access their patient portal and use telemedicine services.
- **MSK’s traveling Mobile Health Unit (MHU)**, whose bilingual staff offers

health screenings, help with health insurance, and other resources.

“We take the time to listen and engage with people to understand their specific challenges, follow up with them, build trust, and offer culturally sensitive materials and interventions that support their needs,” says **Josana Tonda, IHCD Community Outreach Manager**. “Our work is important because when we break down healthcare barriers in underserved communities, we can save lives.”

Support Continues After Treatment Ends

Today, Beatriz feels well and continues to be monitored for cancer recurrence. She will soon transition to MSK’s **Survivorship Program** to support her overall health and well-being.

“I wake up every morning thankful for my family and my MSK doctors who got me through this dark storm,” says Beatriz. “They saved my life.” •

Cancer equity initiatives at MSK are supported by the **MSK Giving community, including Roger W. Ferguson, Jr. and Annette L. Nazareth; Jamie Nicholls and Fran Biondi; Raj and Indra Nooyi; The Ralph Lauren Corporate Foundation; and the Stavros Niarchos Foundation.**

Claire's Legacy

Claire Theobald's journey with breast cancer has taught her to cherish every small, beautiful moment of life.

It has also inspired her to include Memorial Sloan Kettering Cancer Center (MSK) in her estate planning by making a bequest to MSK in her will. Her hope, she explains, is to help other people facing breast cancer find the treatment options they need and get a second chance at life.



Despite the challenges of being a small-business owner and single mother of twins, Claire, 56, says that it's important to her to give back.

"I want my legacy to be about saving lives," she says.

A Shocking Diagnosis

Claire's twins were 11 years old and her business — a children's accessories company — was taking off when her yearly mammogram in 2012 revealed four tumors in her breasts.

She was devastated, angry, and scared.

"That winter was the lowest point of my life," she says. "My first question was whether I'd live to see my kids graduate from middle school." She didn't know how she'd have the time or energy to endure cancer treatment.

MSK on the Line

Claire called MSK for a consultation and began treatment soon after. "MSK's doctors, nurses, and staff didn't waste any time," she says.

When Claire had an allergic reaction to one of her medications, her doctors promptly identified the problem and provided three alternative treatment options. "I was awed by their expertise

as well as their warmth and kindness," she says. "It was so clear to me that I was in the place with the best care."

She persevered through chemotherapy, radiation treatment, and surgery. It was a long road, but she found strength from her care team and family every step of the way.

Giving Back for the Future

Today, Claire is cancer free. In May, she watched her son, Alex, graduate from college, and her daughter, Juliane, is set to graduate in 2024.

Claire now lives in Charleston, South Carolina, and her business, Beatrix New York, sells contemporary kids gear worldwide.

She is proud to support cancer research at MSK. Making a bequest is easy, she explains. She contacted the **Office of Gift Planning**, which guided her through the process step-by-step.

"By including MSK in my estate plans, I am helping ensure that people with cancer around the world will have access to lifesaving treatments for years to come," she says.

Contact the Office of Gift Planning at giftplanning@mskcc.org or **800-688-1827** to start your bequest to MSK. •

"I want my legacy to be about saving lives."

—Claire Theobald

Don't miss your chance to take part in Cycle for Survival, MSK's rare cancer fundraiser.

Together with its founding partner, Equinox, Cycle for Survival® will host team stationary-cycling events in 13 locations across the country in February and March 2024. Rides are filling up, so sign up today at: cycleforsurvival.org/register



It's Personal

Dr. Andrea Cercek was overwhelmed with joy meeting the 4-day-old baby of John Bonito and Kelly Spill, one of her patients who participated in a groundbreaking immunotherapy research trial.

“Would you like to hold my baby?”

Kelly Spill's question to Andrea Cercek, MD, is a familiar one from any proud parent. But as they sat together surrounded by Kelly's family on her porch in southern New Jersey, that simple question took on a much more poignant meaning.

As she gently cradled 4-day-old Mya Grace in her arms, Dr. Cercek knew it also marked an incredible step forward in a medical journey that has drawn attention around the world.

“The day was so emotional. I cried again and again,” remembers Dr. Cercek. “I can't put into words what it meant to hold Mya Grace. It was amazing.”

Just a few years earlier, Kelly feared her dream of a big family was shattered when she was diagnosed with rectal cancer at age 28. The news came shortly after the birth of her first child, Jayce. Kelly and her husband, John Bonito, were devastated.

“After Jayce was born, I knew I wanted another baby,” Kelly recalls. “But I was told at another hospital that the usual

treatment for rectal cancer was brutal — and that it would make carrying more children nearly impossible. It was one of the hardest things to hear.”

She learned about another option offered by Dr. Cercek and her colleague **Luis Diaz Jr., MD**, who are both gastrointestinal oncologists. They and their team were conducting a clinical trial to investigate if people like Kelly, whose rectal tumors have a specific genetic mutation, could be treated with a form of immunotherapy alone.

If successful, it would mean the participants would be spared the standard treatment of chemotherapy, radiation, and surgery.

“The standard treatment does well in terms of curing the patient,” explains Dr. Cercek. “But it can seriously alter quality of life, and infertility for women is almost inevitable because of radiation. We wanted to try to help.”

Kelly enrolled in the trial. She received infusions of a form of immunotherapy

called a checkpoint inhibitor, which helps the immune system recognize and attack cancer cells. (See page 6 to learn more.)

When the results of the trial were first reported, 18 people with rectal cancer had taken part in the trial. Remarkably, every single person, including Kelly, saw their tumor vanish without any additional chemo, radiation, or surgery — an outcome so rare it's been calculated at a trillion to one.

Months after stopping treatment, Kelly learned she was pregnant with Mya. “I look at her as a miracle,” says Kelly, who told Dr. Cercek, “She's here because of you.”

As Dr. Cercek was saying her good-byes with happy tears and smiles, she was embraced by Kelly's mother, while 3-year-old Jayce hugged Dr. Cercek's leg.

“Kelly's mom whispered, ‘Thank you for saving our family,’” recalls Dr. Cercek. “And that really drove home what this means for the next generation. For the people we treat, this is just the beginning.” •

This groundbreaking research was made possible by philanthropic support from the **MSK Giving** community, including **Cycle for Survival®**, **Jackie and Richard Emmet**, the **Frechette Family Foundation**, **Shelby Cullom Davis Charitable Fund Inc.**, and **Stand Up To Cancer**.

Dr. Diaz holds the Grayer Family Chair.



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