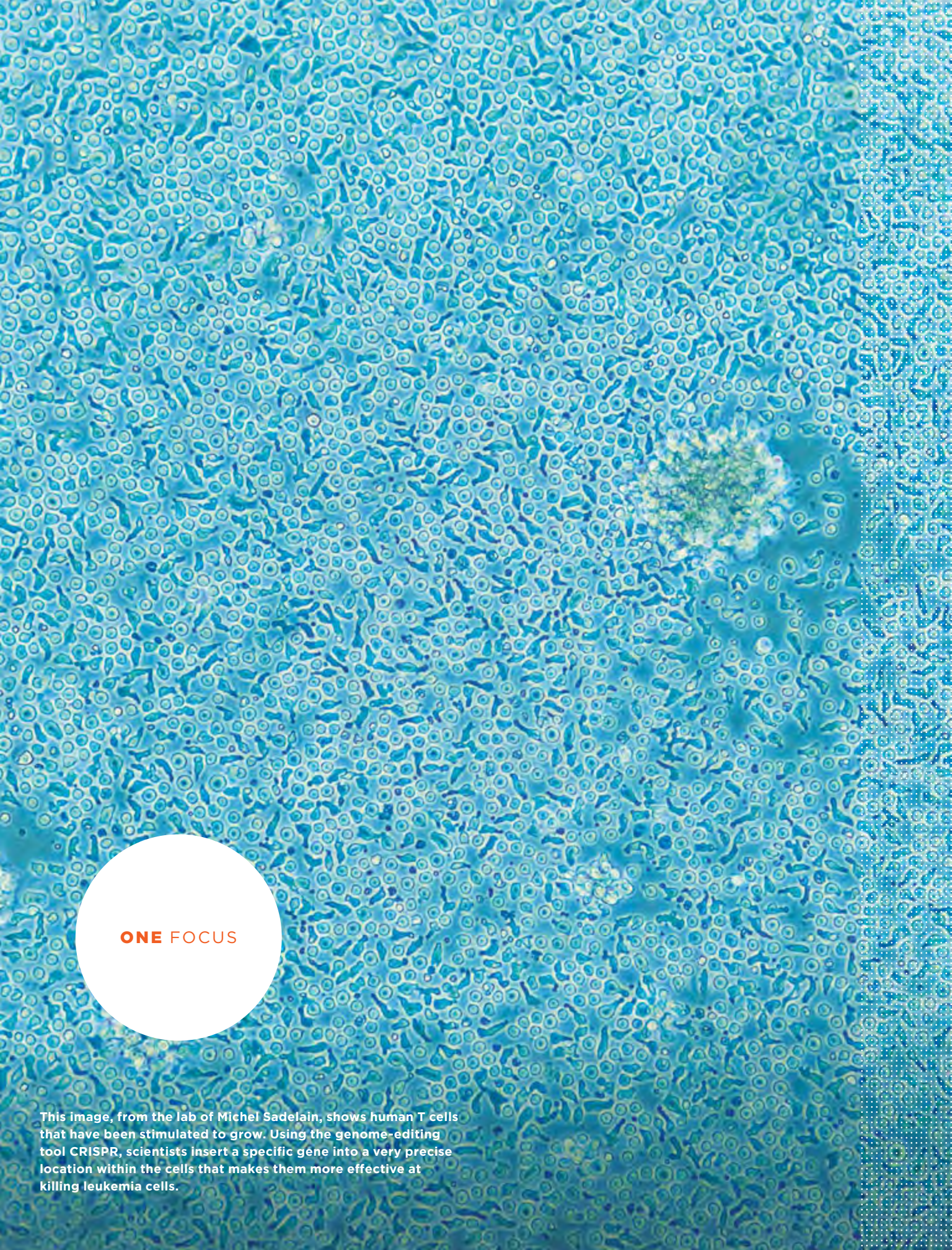
Memorial Sloan Kettering Cancer Center

2017 ANNUAL REPORT

# ONE MSK



**ONE** FOCUS

**This image, from the lab of Michel Sadelain, shows human T cells that have been stimulated to grow. Using the genome-editing tool CRISPR, scientists insert a specific gene into a very precise location within the cells that makes them more effective at killing leukemia cells.**

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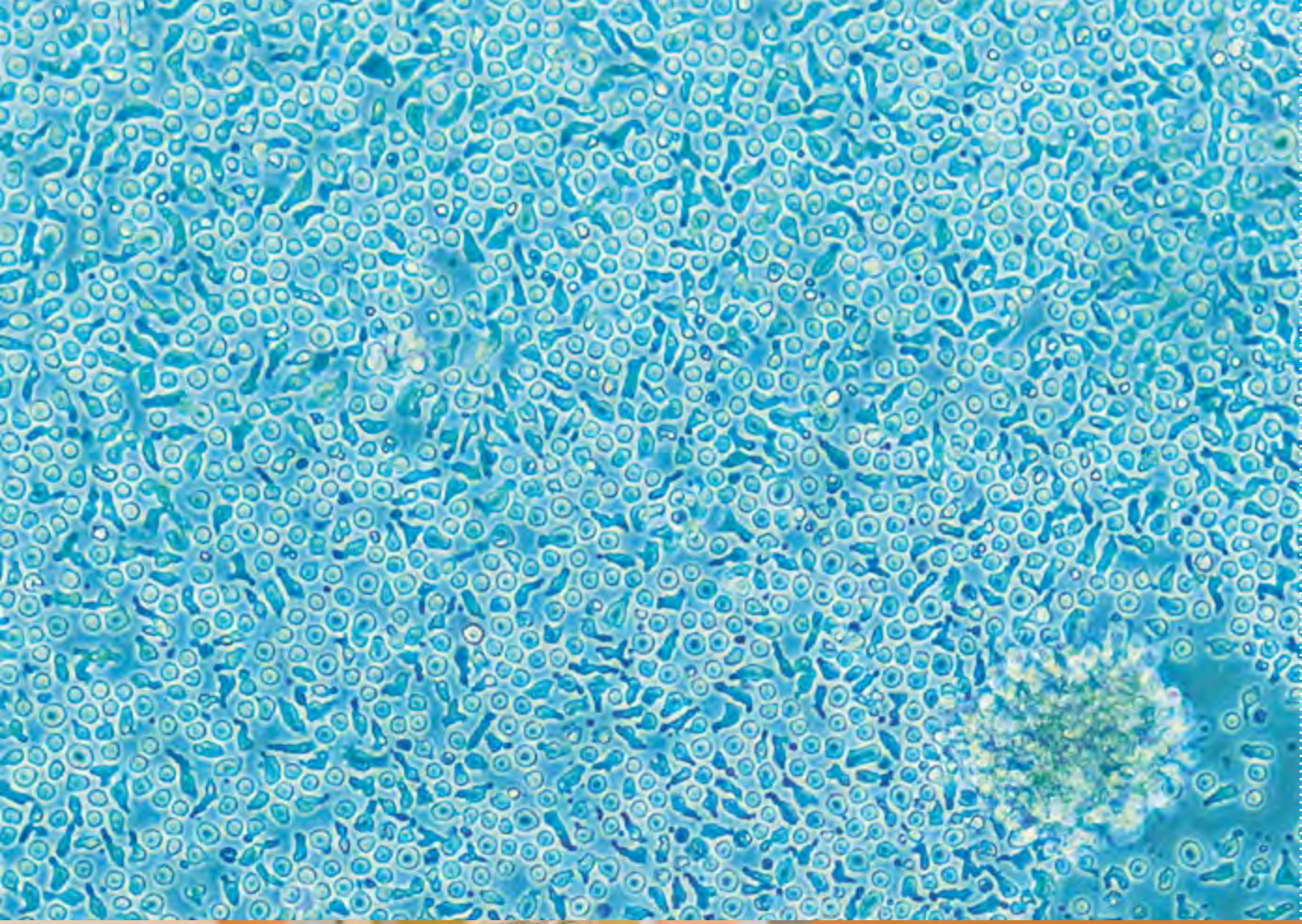
# THE INSIDE STORY

## A SNAPSHOT OF 2017 AT MSK



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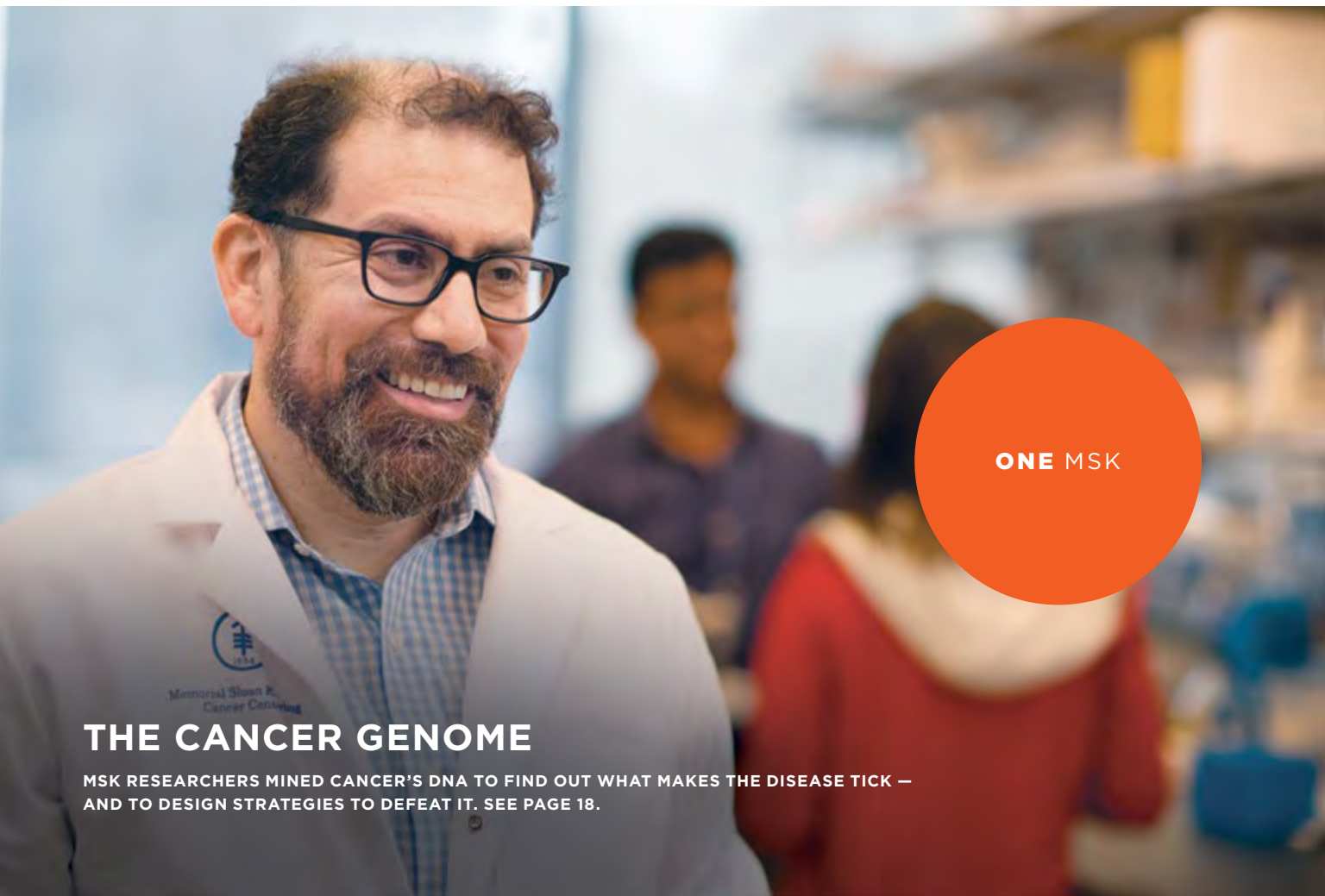


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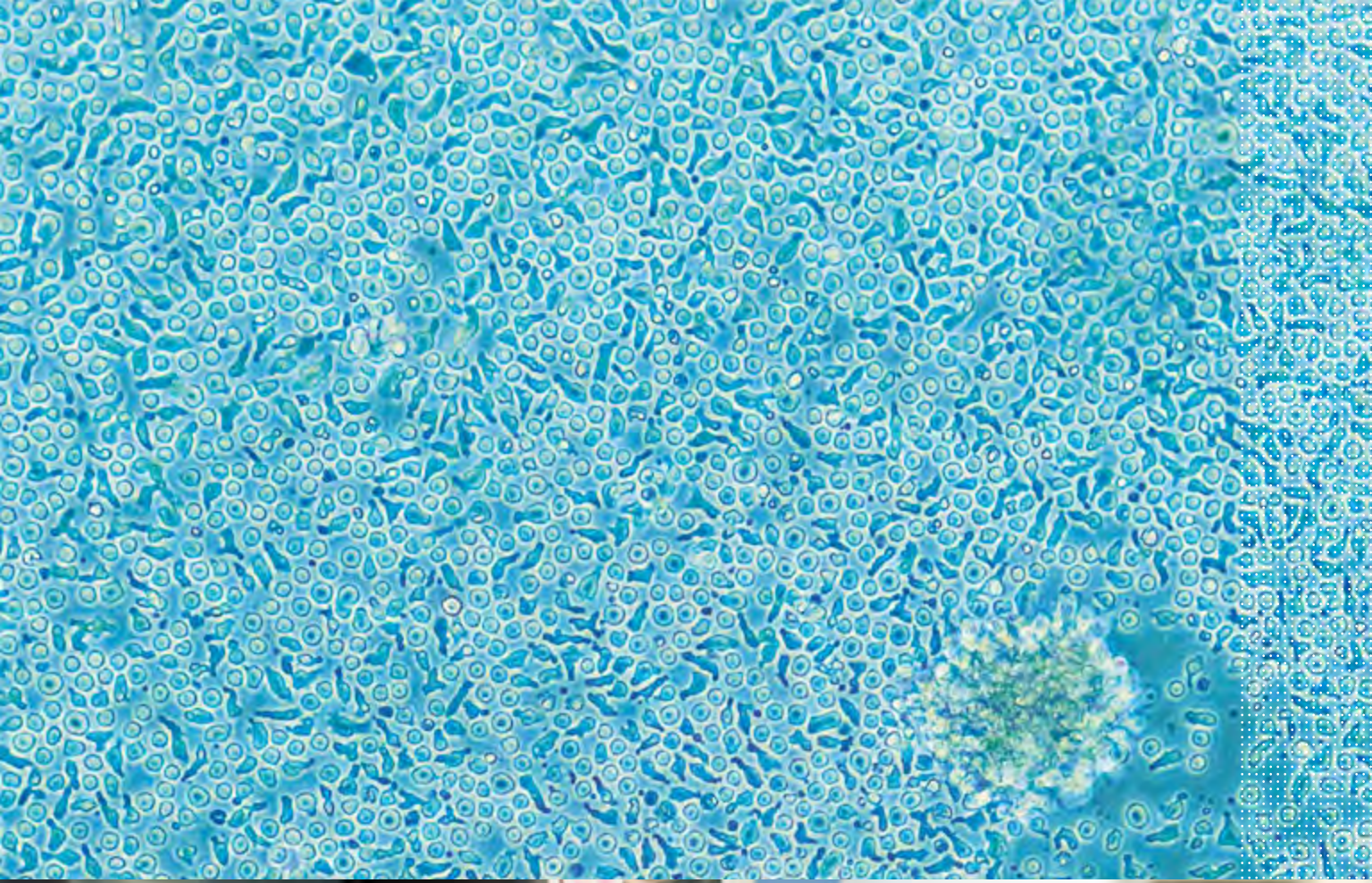

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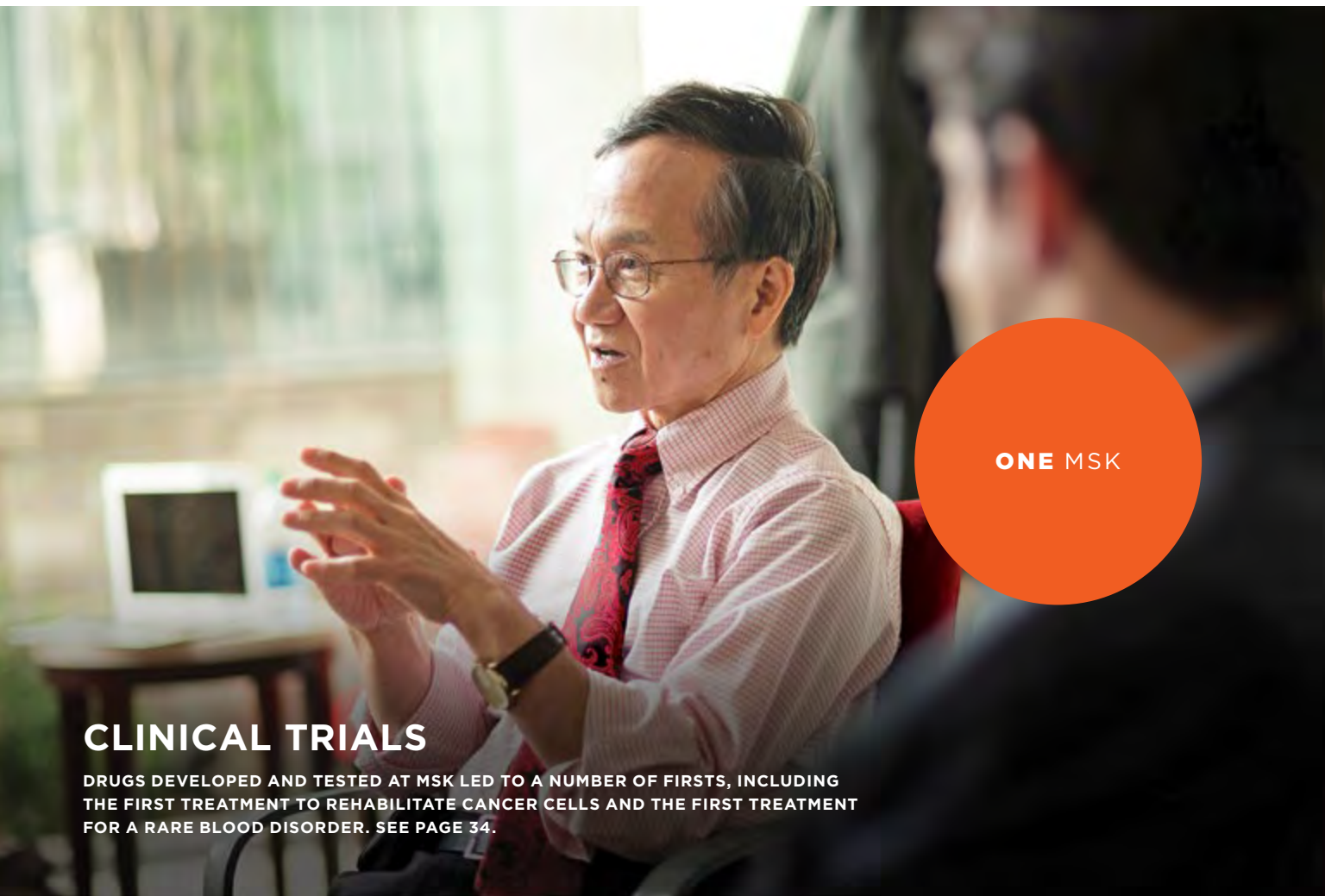


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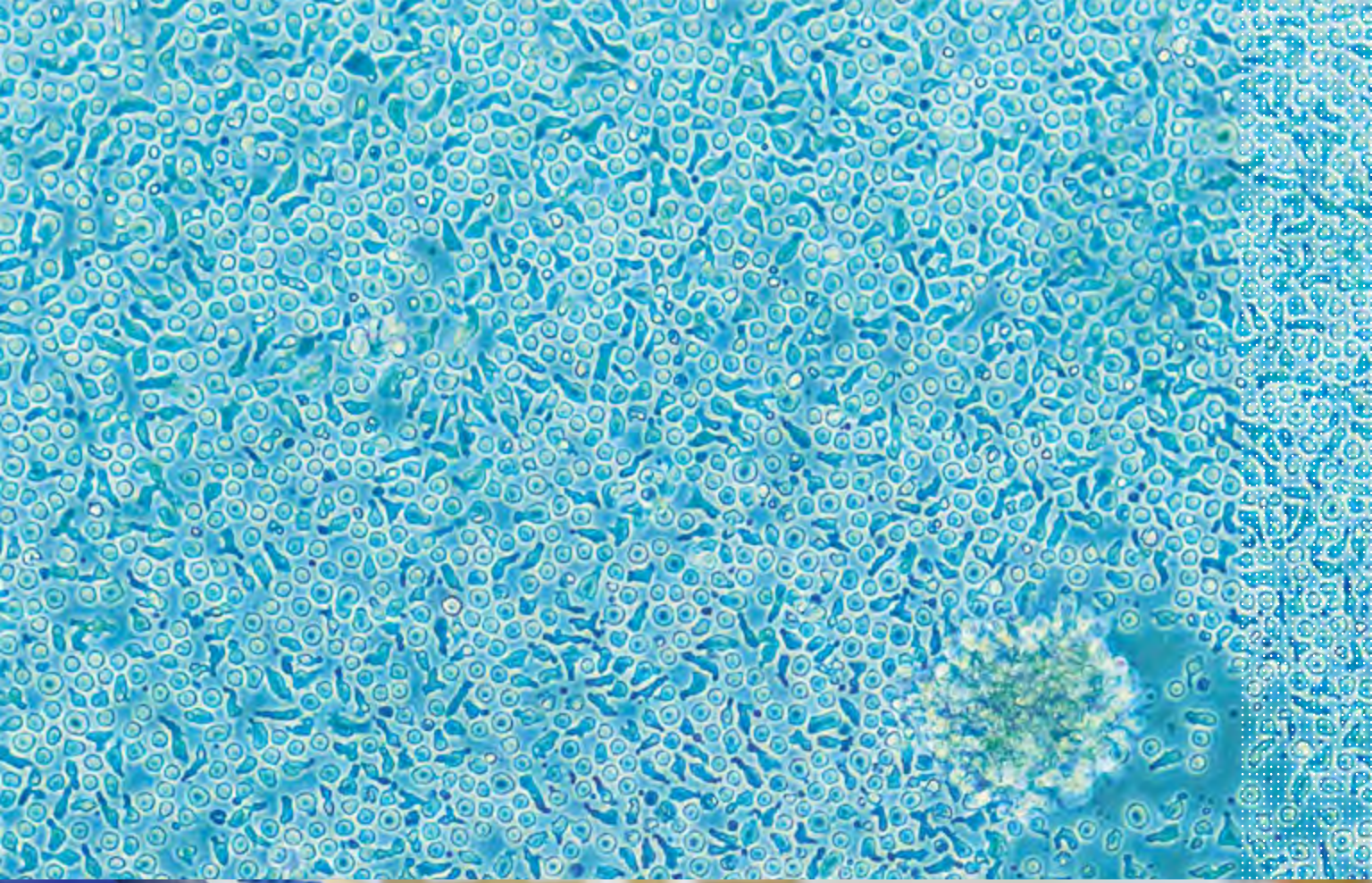

ONE FOCUS

## BASIC SCIENCE

SCIENTISTS IN THE SLOAN KETTERING INSTITUTE MADE FUNDAMENTAL DISCOVERIES ABOUT THE STRUCTURE OF PROTEINS, A MUTATION CAUSING A RARE CANCER, AND THE TRIGGERS DRIVING CANCER'S SPREAD. SEE PAGE 44.

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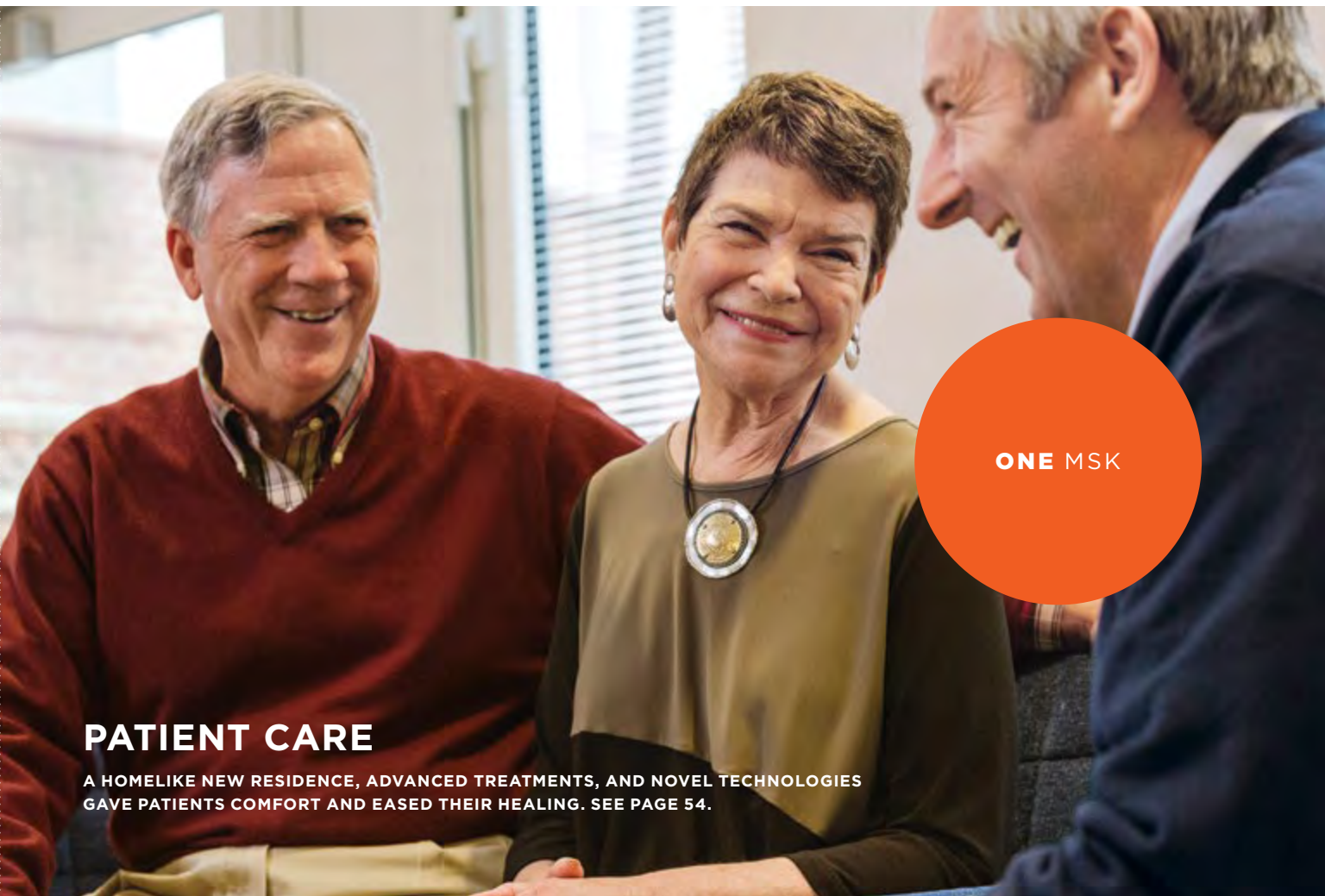


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**A HOMELIKE NEW RESIDENCE, ADVANCED TREATMENTS, AND NOVEL TECHNOLOGIES GAVE PATIENTS COMFORT AND EASED THEIR HEALING.** **SEE PAGE 54.**

**ONE** FOCUS

**SEE WHAT A TEAM OF REMARKABLE PEOPLE WITH AN UNMATCHED DEDICATION TO CHANGING CANCER CAN DO IN JUST ONE YEAR.**

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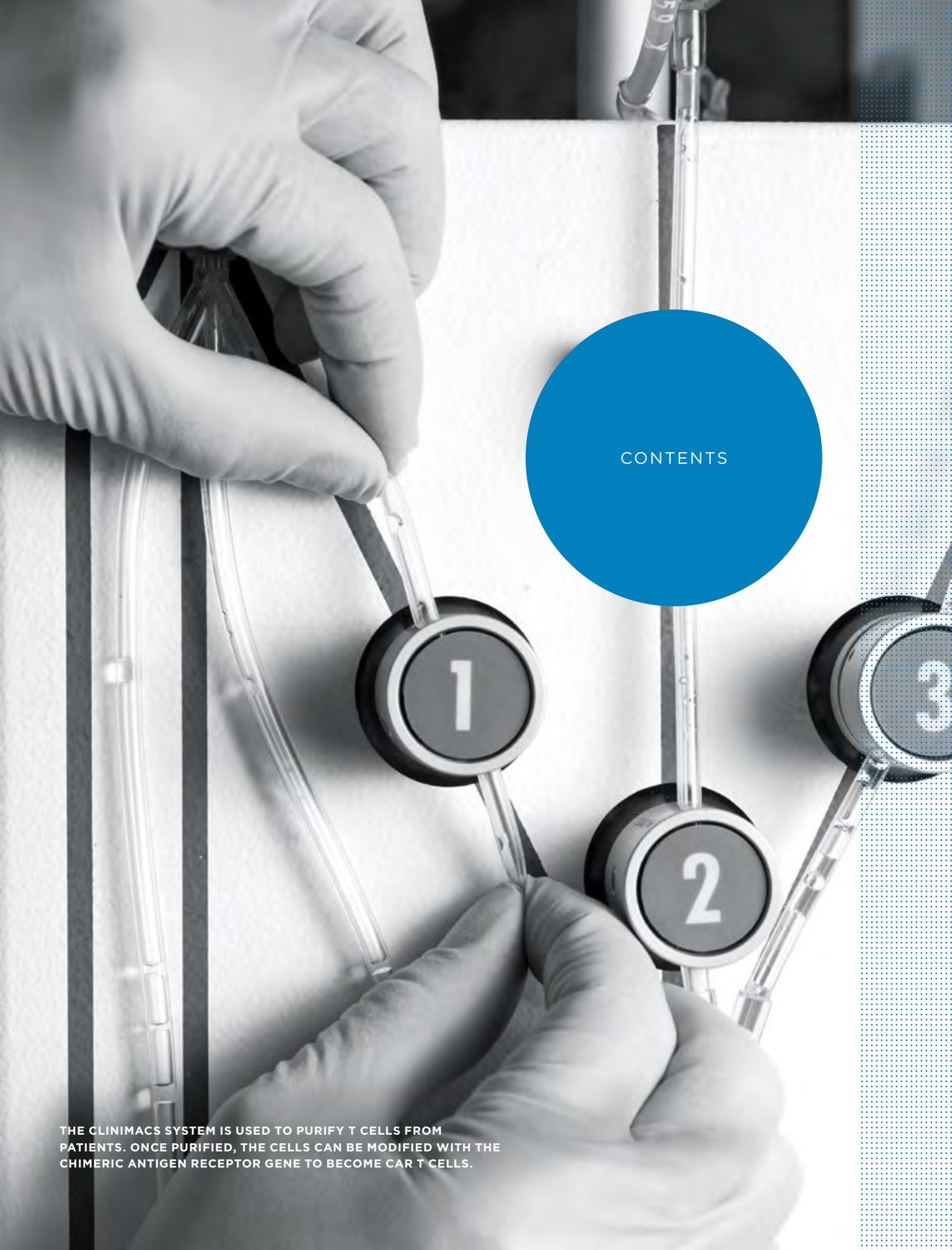


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**Craig B. Thompson**
President and
Chief Executive Officer

**Douglas A. Warner III**
Chair, Boards of Overseers
and Managers

## MESSAGE FROM THE CHAIRMAN AND THE PRESIDENT

Memorial Sloan Kettering's singular focus on cancer — as true today as it was more than 130 years ago — sets our organization apart in New York City, the nation, and the world. The impact of our collective efforts can be seen in the dedicated workforce of more than 17,000 people, in scientific research that fundamentally changes the understanding of biology, and in clinical innovation that delivers new treatments and better care to thousands of people every year. Woven together, these threads form "One MSK."

“Our commitment to basic research is both substantial and sustained, and resulted in discoveries that once again yielded accolades in 2017. The Nature Index ranked the work of our research faculty, and specifically the scientists at the Sloan Kettering Institute, as number one among cancer research organizations.”

Our commitment to basic research is both substantial and sustained, and resulted in discoveries that once again yielded accolades in 2017. The Nature Index ranked the work of our research faculty, and specifically the scientists at the Sloan Kettering Institute, as number one among cancer research organizations. In just two examples, Nikola Pavletich and Haijuan Yang mapped the structure of mTOR, a crucial growth regulator in cancer, in work enabled by a new cryo-electron microscope installed in 2017. And Scott Lowe, elected to the National Academy of Sciences in 2017, and colleagues used the gene-editing tool CRISPR to demonstrate how a specific genetic mutation causes a rare liver cancer in children and young adults. More about the work of the Pavletich and Lowe labs — as well as of other basic scientists — can be found later in this report.

Our researchers and clinicians have pioneered and continue to advance one of the most significant therapeutic developments in recent years: the engineered immune cells called CAR T cells. The therapy became commercially available in 2017 when the US Food and Drug Administration approved it for certain types of leukemia and lymphoma. Physician-scientist Michel Sadelain, along with researchers Renier Brentjens and Isabelle Rivière, were the first to devise this type of “living drug,” which employs a patient’s own immune cells to find and fight cancer. MSK is one of a handful of cancer centers to provide this therapy to patients, thanks to the unparalleled expertise of our doctors and nurses. You can learn more starting on page 8.

In 2017, the FDA reaffirmed MSK’s leadership in targeting molecular defects in cancer by authorizing MSK-IMPACT™, the first genetic-sequencing test of its kind to receive the designation. This test scans tumors for mutations in more than 460 genes linked to cancer. Developed by physician-scientist Michael Berger and others in the Marie-Josée and Henry R. Kravis Center for Molecular Oncology, MSK-IMPACT has analyzed the tumors of more than 20,000 MSK patients with advanced cancer. Its use has generated actionable information that has allowed many of those people to receive more targeted treatment. (For more on MSK-IMPACT, see page 26.)

MSK’s clinical trials program continues to transform research breakthroughs into lifesaving treatments that often become the new standard of care. In 2017, nearly a third of MSK patients were enrolled in more than 800 clinical trials. As you’ll read on page 34, MSK faculty distinguished themselves with FDA approvals of several therapies that are the first of their kind, including a drug that rehabilitates cancer cells rather than killing them and a targeted therapy developed simultaneously in children and adults.

**Kathryn Martin**
Chief Operating Officer

**José Baselga**
Physician-in-Chief and Chief Medical Officer, Memorial Hospital

**Joan Massagué**
Director, Sloan Kettering Institute

**James D. Robinson III**
Honorary Chair, Boards of Overseers and Managers

MSK further strengthened its expertise in clinical innovations in 2017 by recruiting Luis Diaz as Head of the Division of Solid Tumor Oncology in the Department of Medicine. While at Johns Hopkins Medicine, Dr. Diaz was the principal investigator of a key clinical trial of pembrolizumab (Keytruda®), the first drug approved by the FDA to target a specific genetic mutation in tumors. This work built on groundbreaking research by MSK's Jedd Wolchok and Timothy Chan. (See page 21 for more.)

Of course, our leadership in developing targeted therapies comes with the responsibility of addressing the challenges of these treatments. In 2017, MSK researchers strove to improve these new approaches on several fronts, from reducing toxicities to testing whether they can be made more precise.

A major challenge for some of the most promising cancer treatments is that currently only a small percentage of people have access to genetic testing and clinical trials. Diversity in participation is also crucial to the success of clinical trials and has been a continued goal. To address this, MSK has sought to extend availability by establishing relationships with medical facilities that share our dedication to high-quality research and patient care.

In 2017, our partnership with Hackensack Meridian Health in New Jersey made important progress, completing shared guidelines for patient care in several of the most common cancers as well as shaping a mutual research agenda to advance the next generation of cellular treatments, including CAR T cell therapy. The Miami Cancer Institute at Baptist Health South Florida became the latest member of the MSK Cancer Alliance, which continues to flourish. And we created a unique relationship with Norwalk Hospital in Connecticut: MSK Physicians at Norwalk Hospital, which has MSK doctors providing on-site care to patients at a non-MSK facility outside of New York State for the first time.

Our commitment to new models of patient care was also shown in bold relief against the skyline of Manhattan, with the David H. Koch Center for Cancer Care hitting its "topping-off" point on 74th Street. When it opens in 2019, this 23-floor, state-of-the-art facility will define the future of cancer care, focusing on outpatient procedures, innovative treatments such as immunotherapy, and early-stage clinical trials.

This same forward-thinking vision is found in the recently opened Center for Laboratory Medicine building in Manhattan, an environmentally friendly lab that has brought important efficiencies to the processing of 5,000 patient samples and 24,000 clinical lab tests every day.

Within ten years, projections are that nearly 80 percent of MSK's patients will never spend a day in the hospital. This fact drove the remarkable growth and success of our outpatient centers in the regional care network. In its first

> Of course, our leadership in developing targeted therapies comes with the responsibility of addressing the challenges of these treatments. In 2017, MSK researchers strove to improve these new approaches on several fronts, from reducing toxicities to testing whether they can be made more precise.”

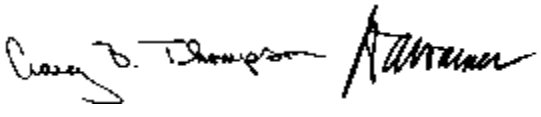
year of operation, MSK Monmouth saw patient volumes that were years ahead of schedule, with positive reviews from patients about both the facility and its exceptional team. MSK Bergen is on track to open in 2018, and MSK Nassau in 2019.

This increased demand for MSK’s superior clinical care across the region combined with sustained philanthropic support resulted in exceptional financial performance. Prudent management of MSK resources played a significant role because 2017 marked the end of royalty payments for a major clinical discovery made in the laboratory of Malcolm Moore. This loss required careful planning throughout the past several years to ensure the continued vitality of our research program.

Charitable gifts to MSK reached new levels in 2017, thanks to the leadership of Anne McSweeney, Special Advisor to the President, and Richard Naum, Senior Vice President for Development. During the past 15 years, they have helped ensure MSK’s ability to invest in promising areas of research and patient care. The Campaign for MSK, which they directed and which recently ended, surpassed its lifetime goal of $3.5 billion by $700 million. We wish them well in retirement. And Cycle for Survival continues to generate millions for research into rare cancers.

This past year also saw MSK faculty receive numerous individual awards and honors. Of particular note is Viviane Tabar’s election to the National Academy of Medicine and her appointment as Chair of MSK’s Department of Neurosurgery, after the retirement of Philip Gutin. Other highlights include the election of Maria Jasin, Scott Keeney, and Christopher Lima to the American Academy of Arts and Sciences, along with Marie-Josée Kravis, a member of MSK’s Board. Sasha Rudensky won the Crafoord Prize; Lorenz Studer was given the Ogawa-Yamanaka Stem Cell Prize; and Andrea Schietinger received a New Innovator Award from the National Institutes of Health.

Ultimately, though, these individual honors are a testament to the fact that we all share the same passion, conviction, and drive to conquer cancer. The profound energy and seriousness of purpose that all of our staff pour into improving the understanding, prevention, and treatment of cancer make us truly One MSK. ■



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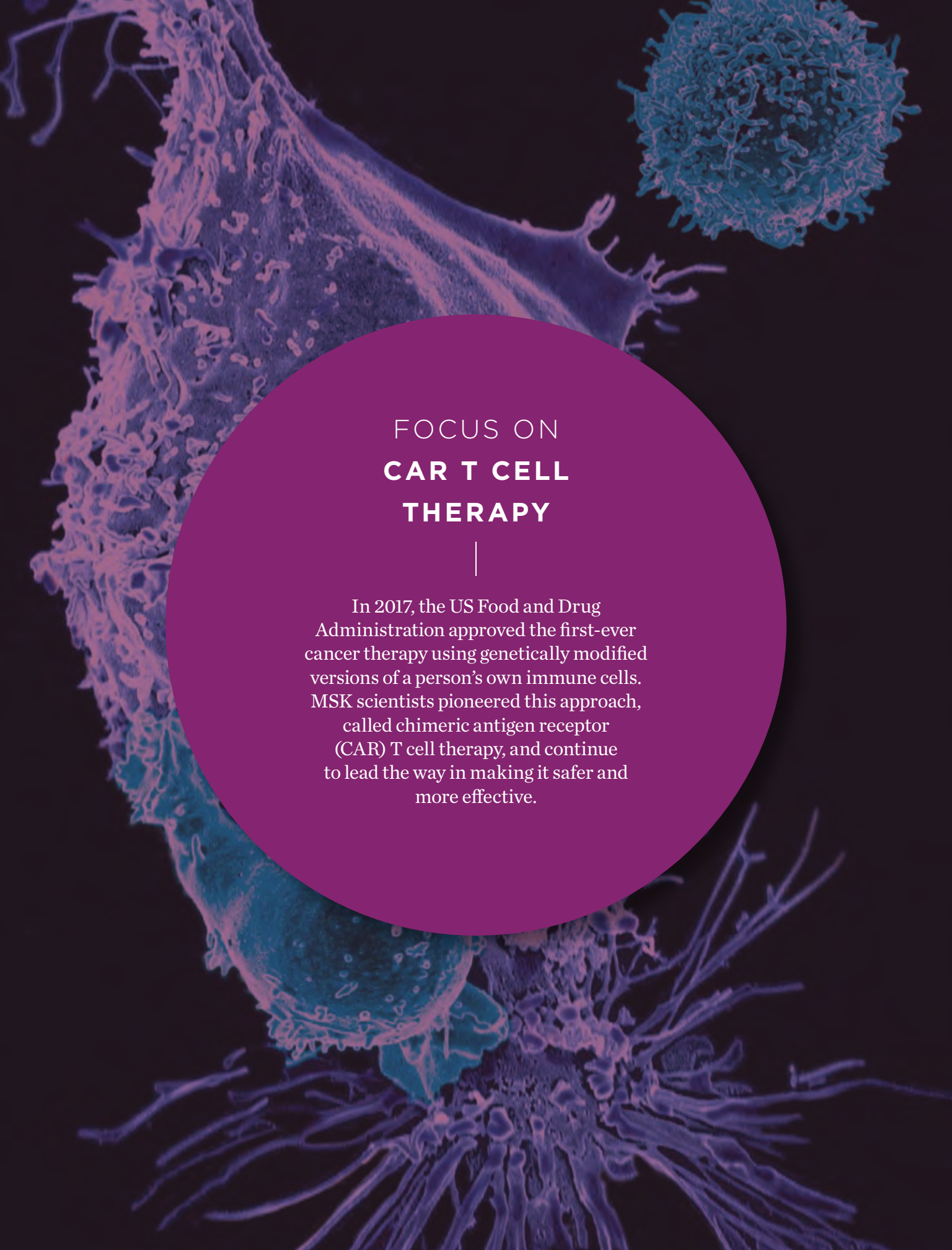
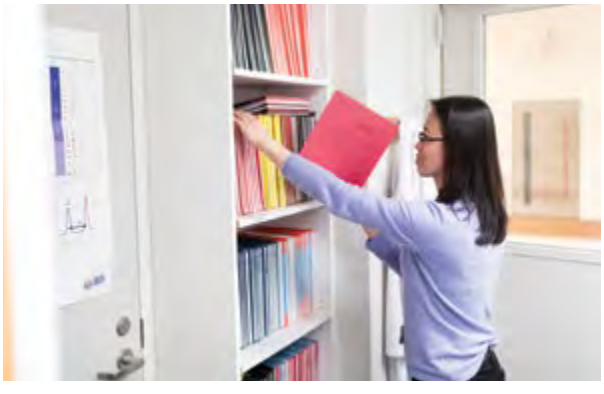


## FOCUS ON
## CAR T CELL THERAPY

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.

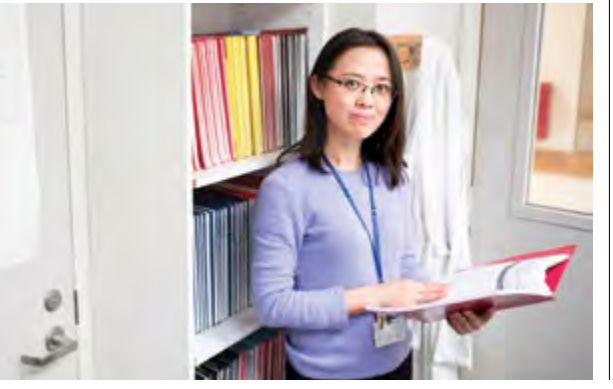
**It takes many people to bring CAR T cells, like the one shown in the photo at left, to life. Xiuyan Wang manufactures these cells for use in patients on MSK clinical trials.**

# 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.

continued ▸

## 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 ▶

> **"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. Then the bone marrow transplant was a secondary step so that I wouldn't grow more cancer cells."**
>
> –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.

> These are the practical conversations we're having with patients every day. 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."
>
> –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.

> "Our primary job is making sure that each person gets the very best care — whether that's CAR T cell therapy or another approach. 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."
>
> –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.

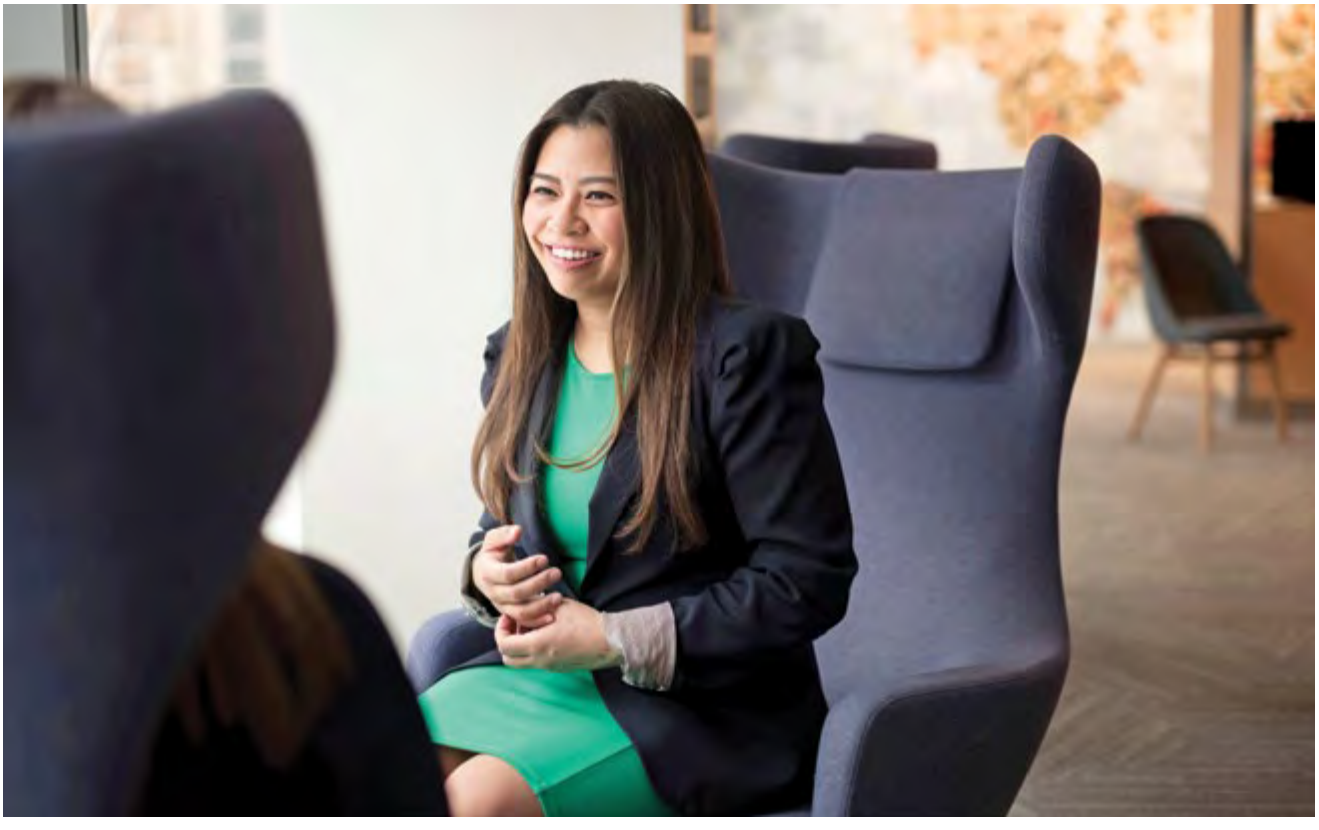
The RSAs "really are the backbone of the service," Ms. Bernal says. "They monitor the patients from the moment they walk through the door of MSK to the moment they are deemed cancer free."

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.

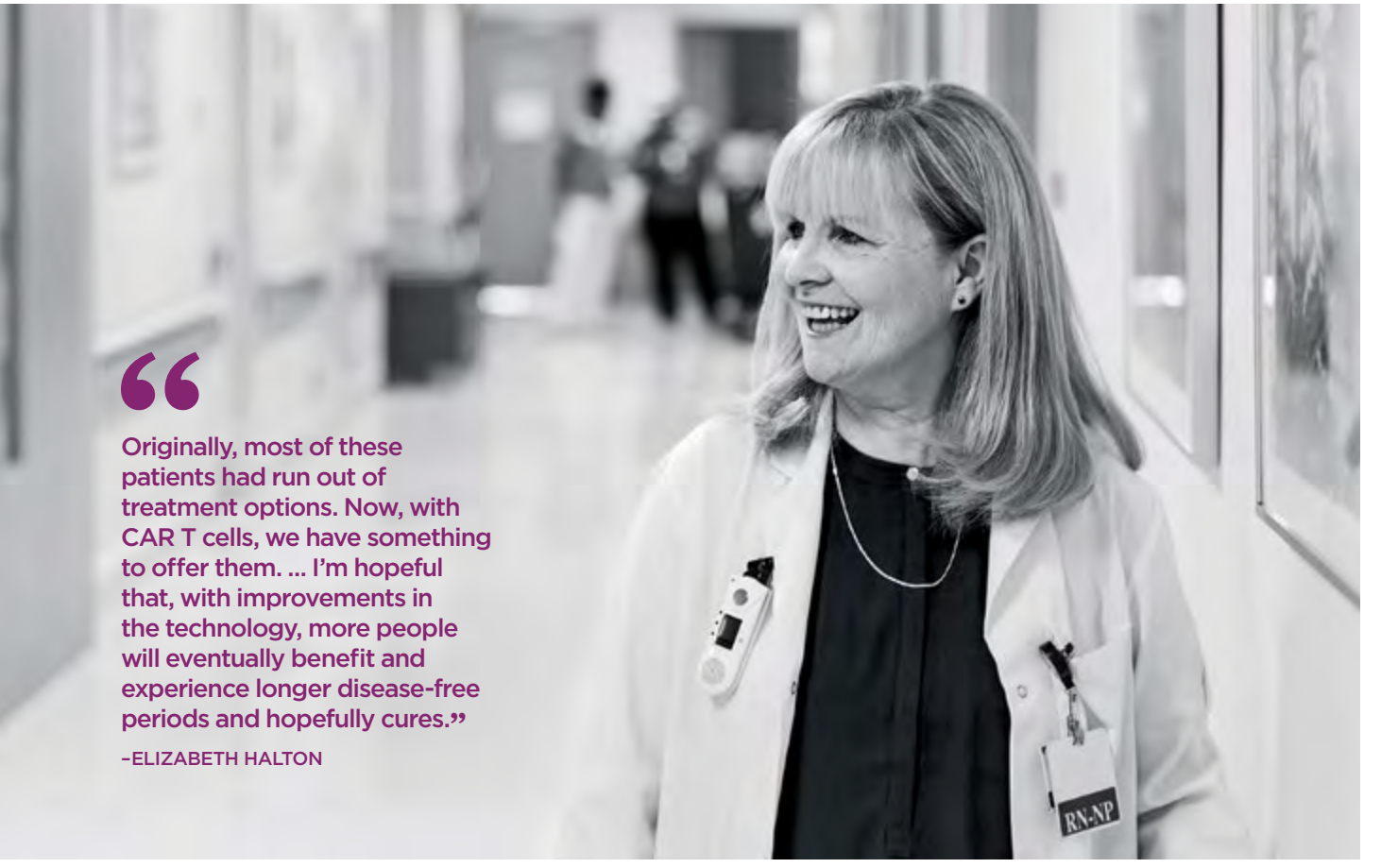
"It was an exciting but also an intimidating time," Ms. Halton says. "We did not know what to expect after infusing the CAR T cells."

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.




> Originally, most of these patients had run out of treatment options. Now, with CAR T cells, we have something to offer them. … I'm hopeful that, with improvements in the technology, more people will eventually benefit and experience longer disease-free periods and hopefully cures."
>
> –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.

# FOCUS ON
# THE CANCER GENOME

Thanks to the unwavering focus of Memorial Sloan Kettering researchers, the human genome continues to disclose vital secrets about the origins of cancer. These details are changing how cancer is treated, for patients both today and in the future.

**One main focus of precision oncology is to quickly translate discoveries made in the lab into treatment approaches that can benefit people with cancer.**

# In 2017, MSK investigators made major discoveries about the kinds of mutations that lead to runaway cell growth, including important insights into DNA repair, and the genetic factors that determine the effectiveness of treatments.

Timothy Chan studies how the immune system recognizes and responds to cancer-specific mutations.

INTERVIEW WITH

## **TIMOTHY** CHAN

*Director, Immunogenomics and Precision Oncology Platform*

**For some people with cancer, checkpoint inhibitors have been a game changer. These immunotherapy drugs work by taking the brakes off the immune system, enabling it to attack cancer. They have been shown to shrink even very advanced cancers to undetectable levels. For most people, though, these drugs have been disappointing. Researchers are trying to figure out why.**

**One of those studying this issue is MSK physician-scientist Timothy Chan. In December 2017, Dr. Chan and colleagues published in *Science* the largest-ever genetic analysis of people being treated with checkpoint inhibitors. They found that certain genes people are born with may play a critical role.**

**Q: How was this study different from others that have looked at responses to immunotherapy?**

**A:** It was large, including more than 1,500 people with many different types of cancer. This suggests that what we found applies broadly. And we looked not only at genetic changes inside the tumor tissue but also at certain genes that make up people's normal DNA. Specifically, we looked at human leukocyte antigen (HLA) genes, which are critical for regulating the immune system.

The HLA system is used to match recipients and donors for stem cell and bone marrow transplants. HLA genes guide immune cells called T cells to recognize what is the body's own and what is not. For transplants, we want the donor's HLA system to be similar enough to the recipient's that donated T cells will not attack the recipient's tissues. In the case of cancer, we want to boost the T cells' ability to destroy tumor cells. HLA proteins determine what T cells can see.

**Q: What gave you the idea to look at HLA genes and immunotherapy response?**

**A:** We have known for a while that HLA genes play a role in response to infections. Certain HLA profiles are associated with better outcomes in people with HIV, hepatitis B, and malaria. The human body is constantly under assault from pathogens, and HLAs are how we recognize and eliminate them.

We found that people who had more variation in their HLA genes responded much better to immunotherapy compared with those who had less. No one had ever looked at HLA genes in people undergoing immunotherapy, so this was a new finding.

> “We found that people who had more variation in their HLA genes responded much better to immunotherapy compared with those who had less. No one had ever looked at HLA genes in people undergoing immunotherapy, so this was a new finding.”
>
> –TIMOTHY CHAN

**Q: Did this result surprise you?**

**A:** Not completely. Several years ago our group at MSK and investigators elsewhere began looking at the effects of the tumor genome on immunotherapy response. We found that tumors with a greater number of mutations were more recognizable to the immune system.

Our latest findings represent the other side of the same coin: Just as tumors with a greater number of genetic changes are more recognizable to immune cells, having more-diverse HLA genes means that the immune system has a greater ability to recognize what doesn't belong inside the body. Both are important for maximizing the ability of the immune system to see and destroy cancer cells.

**Q: Will this finding change how people with cancer are treated?**

**A:** I think it will have a strong effect very soon. There is a rush to develop genetic tests to measure how many mutations are present in tumors as a way to predict response to immunotherapy. Our group was responsible for starting this revolution. Now we have shown that the other side of the equation — a patient's normal inherited DNA — is critical as well.

We now know that people with less diversity in their HLA genes as well as a low number of mutations in their tumors are much less likely to respond to checkpoint inhibitor drugs, especially when those drugs are given alone. So we may want to treat them with a combination of different immunotherapy drugs, or try other treatments instead.

**Q: What are the next steps for this research?**

**A:** Our findings will need to be validated in prospective studies, although because we included such a large and diverse number of people, we think we've set the bar pretty high.

We can't do anything about the HLA genes that people are born with. But we think that learning more about immune system recognition can help with the development of new cancer treatments. ■

Luis Diaz is looking for better ways to diagnose cancer at its very earliest stage, while it is still relatively easy to treat.

INTERVIEW WITH

## **LUIS** DIAZ

*Head of the Division of Solid Tumor Oncology*

**In May 2017, the US Food and Drug Administration approved the immunotherapy drug pembrolizumab (Keytruda®) for cancers that share a certain genetic abnormality. This marked the first approval for a cancer drug that attacks tumors no matter where they develop. Up to this point, drugs have been approved to treat cancers based on where they grow in the body.**

**Luis Diaz led the pivotal clinical trial that resulted in this approval while he was at Johns Hopkins University School of Medicine. He joined MSK as Head of the Division of Solid Tumor Oncology in the Department of Medicine in April 2017, prior to the approval.**

**Q: How did you discover that immunotherapy drugs may work better for cancers with a high number of mutations?**

**A:** Pembrolizumab is a checkpoint inhibitor, which helps the immune system fight cancer. From the early clinical trials in 2012, it was clear that these drugs worked very well for certain cancers. What became obvious was that the tumors that often responded well to these drugs, including melanoma and lung cancer, tended to have a lot of genetic mutations.

We noticed that with other types of cancer, including colon cancer, which doesn't have a lot of mutations, the drugs were rarely effective. Then one of my colleagues at Johns Hopkins told me about a person with colon cancer who was taking another checkpoint inhibitor drug, nivolumab [Opdivo®], and had responded very well. We looked more closely at the tumor and found that it had a high number of mutations. We immediately suspected that the increase was the reason this person had responded to the drug.

continued ▸

> MMR mutations are relatively rare, though that small proportion translates to tens of thousands of people with cancer in the United States every year and half a million worldwide. Our findings suggest that all people with advanced cancer should have their tumors screened for MMR deficiencies."
>
> –LUIS DIAZ

**Q: We normally think of mutations in cancer as a bad thing. In this case, why is it better to have more of them?**

**A:** Gene mutations can lead to the production of foreign substances called neoantigens. Neoantigens are an alien presence in the body that flags the tumor as something that doesn't belong. This draws an immune response. The more mutations you have, the more your chances increase that the immune system spots the tumor because there is a much greater possibility that it manufactures a neoantigen.

**Q: Why do some tumors have more mutations than others?**

**A:** Melanoma and lung cancer often have a lot of mutations because they are caused by exposure to environmental hazards — specifically UV light and tobacco smoke. The person whose colon cancer had so many mutations had a genetic defect called DNA mismatch repair [MMR] deficiency. MMR-deficient cells have lots of mutations — 1,700 on average compared with 70 in a typical cancer cell. That's because the mismatch repair pathway is a major way that cells fix DNA mistakes that happen during replication, which cells do each time they divide.

**Q: How did the pembrolizumab study come about?**

**A:** Based on the discovery with nivolumab, we began a study looking at whether pembrolizumab, which is similar, would work in people whose tumors had MMR deficiencies. We included people with a dozen different types of cancer.

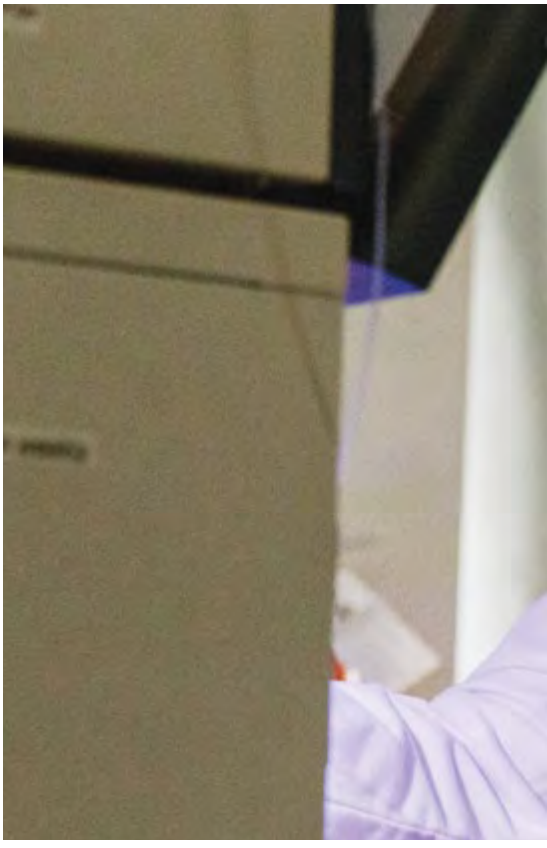
In 2015, we reported that MMR-deficient tumors were more likely to respond to pembrolizumab than those without the deficiency, regardless of where the tumor was located. The FDA approval was based on the data from that study.

**Q: How could this new approval change the way cancer is treated?**

**A:** MMR mutations are relatively rare, though that small proportion translates to tens of thousands of people with cancer in the United States every year and half a million worldwide. Our findings suggest that all people with advanced cancer should have their tumors screened for MMR deficiencies.

**Q: What are your plans in your new role at MSK?**

**A:** I'm involved in leading MSK's new Precision Interception and Prevention initiative. It's focused not only on catching cancer very early but also on eventually preventing it from developing in the first place. MSK is bringing together experts in many different areas to build this program. What we are doing is so far ahead of what any other cancer center is doing. ■



INTERVIEW WITH

## **ALEX** KENTSIS

*Cancer biologist and pediatric oncologist*

**In May 2017, a study led by MSK cancer biologist and pediatric oncologist Alex Kentsis found that many childhood cancers have a surprising cause. A gene called *PGBD5* becomes abnormally activated and snips out DNA segments, flipping them or moving them to a different location in the genome. The shuffling can drastically alter normal gene function and trigger cancer.**

**This discovery helps solve a baffling puzzle: why some children with no inherited gene defects develop tumors at a young age — especially ones with complicated genomic rearrangements. The finding also provides insight into what causes many cancers that affect children and young adults. Further research led by Dr. Kentsis suggests a strategy for turning this genomic havoc against itself.**


> We looked at human rhabdoid tumors, which are aggressive solid tumors that can affect children and young adults, and found evidence of DNA rearrangements associated with high activity of a gene called *PGBD5*. That really piqued our interest."
>
> –ALEX KENTSIS

In his lab, Alex Kentsis is studying the role of certain proteins in difficult-to-treat childhood cancers.

**Q: What about children's cancers made you look into this potential cause?**

**A:** Cancer is primarily a disease of aging. Over time, genetic mutations pile up, due to either copying mistakes as cells replace themselves or ongoing exposure to environmental factors. We were puzzled by why tumors develop in younger people, who presumably haven't had enough time for large numbers of random mutations to accumulate. We looked at human rhabdoid tumors, which are aggressive solid tumors that can affect children and young adults, and found evidence of DNA rearrangements associated with high activity of a gene called *PGBD5*. That really piqued our interest.

**Q: What is unusual about overactive *PGBD5* compared with most genetic mutations?**

**A:** It's a case where the overactive gene itself is causing mutations in other genes. Recently, my colleagues and I found that the protein made by *PGBD5* can act as a transposase, meaning that it can rearrange DNA segments known as transposons — so-called jumping genes. This phenomenon was first uncovered in the 1940s and '50s by Barbara McClintock in Nobel Prize–winning work using corn. These types of DNA rearrangements explain how corn can produce many colors of kernels on a single ear — the transposons alter the expression of pigment-controlling genes. But we didn't suspect that transposons can also function in human diseases like cancer.

**Q: What are the implications of the finding?**

**A:** This is a major advance in understanding pediatric cancers in particular and human cancers in general. It's an unexpected mechanism that raises the possibility that genome rearrangements can operate in human tissues. It also explains a longstanding conundrum about how pediatric tumors develop and provides a new understanding of human cancers that result from this process. And it underscores yet again that the human genome has unexpected features that have major functions in biology that we're just starting to appreciate.

**Q: How could this insight lead to better therapies?**

**A:** When *PGBD5* scrambles other genes, it creates breaks in the DNA that must continuously be fixed in order for the cell to survive. The cells become especially dependent on DNA repair and signaling pathways that sustain it. In November 2017, we published results showing that blocking DNA damage signaling causes tumor cells to become so overwhelmed by DNA damage that they self-destruct.

There are many drugs that interfere with DNA damage signaling already in clinical trials. One of them — olaparib [Lynparza®], a PARP inhibitor — was recently approved by the US Food and Drug Administration to treat specific subtypes of breast cancer with error-prone DNA repair. [See page 24 for more.] Understanding how *PGBD5* works has immediate therapeutic implications for a wide range of cancers. We hope to start testing these treatments soon. ■

INTERVIEW WITH

## **MARK** ROBSON

*Chief, Breast Medicine Service*

**In the summer of 2017, MSK medical oncologist and clinical geneticist Mark Robson reported results from the first multicenter phase III clinical trial of the drug olaparib (Lynparza®) for breast cancer that has spread to other parts of the body. Based on that work, the US Food and Drug Administration approved the drug in January 2018 for people with breast cancer who have inherited mutations in the *BRCA1* or *BRCA2* genes and who have been previously treated with chemotherapy. The BRCA genes have been linked to an increased risk of breast and ovarian cancers for more than two decades. Olaparib was the first drug in the class called PARP inhibitors to be approved for breast cancer.**

### Q: What are PARP inhibitors and how do they work?

**A:** PARP inhibitors block poly ADP-ribose polymerases, or PARPs for short. They are enzymes that help repair breaks in DNA. If DNA cannot be repaired, cells — whether normal or cancerous — cannot divide and will die. An emerging strategy in cancer therapy has been to block the repair role of PARPs. Normal cells can overcome having this method of repair blocked, but cancer cells from people with inherited *BRCA1* or *BRCA2* mutations cannot.

### Q: Besides breast cancer, what other cancers can be treated with PARP inhibitors?

**A:** Olaparib was previously approved for treating certain types of ovarian cancer. There are two other PARP inhibitors approved for these ovarian cancers as well.

Cancers that respond to PARP inhibitors are associated with mutations in the genes *BRCA1* and *BRCA2*. BRCA mutations prevent cells from repairing the damage caused by these drugs.

Besides their association with breast and ovarian cancers, BRCA mutations have been linked to many cases of advanced prostate cancer, as well as pancreatic cancer, in recent studies. Clinical trials currently under way at MSK and other centers are looking at expanding PARP drugs to these other cancers associated with BRCA.

### Q: Based on your findings, who should get BRCA testing?

**A:** Now that olaparib is an approved therapy, I would recommend that anyone with advanced breast cancer who might benefit from this treatment get the BRCA test. It can help guide their treatment and may allow them to avoid getting chemotherapy for longer.

Mark Robson, with medical resident Daniel Klufas, helps people incorporate findings about their genetic risks for cancer into their treatment plan. For people who haven't yet been diagnosed but are at an increased risk, the goal is to prevent cancer's development or limit its impact if it occurs.

People with earlier-stage breast cancer as well as other forms of cancer that have been associated with BRCA mutations may also want to consider getting tested, if their personal or family history suggests they might be carrying a mutation. That is best determined through consultation with a genetic counselor. Knowing that people have a mutation can help them plan ways to reduce their risk for developing another cancer. It also might tell them if there is a clinical trial available that might help them.

And because these are inherited genes, close relatives of people who are known to have BRCA mutations should strongly consider talking to a genetic counselor and getting tested.

Some have suggested that because BRCA mutations are more common in people of Ashkenazi Jewish descent, this whole group should be tested. There is certainly the potential to benefit, since many people with mutations don't have a family history that would prompt them to get tested. But there are also possible risks if people aren't prepared to learn that they have a mutation.

**Q: You have been studying BRCA for a long time. Is there anything that's surprised you about recent developments?**

**A:** It's an incredibly exciting and interesting time to be involved in this field. The ways that we are using genetic information now are how we always dreamed we would be able to. So I would not say that I'm surprised, even though I couldn't have predicted exactly what we'd be doing today. It's important to note that we have reached the place we're at in this field through investments in fundamental research. It's been a privilege to help turn promise into reality. ■

> "It's an incredibly exciting and interesting time to be involved in this field. The ways that we are using genetic information now are how we always dreamed we would be able to."
>
> –MARK ROBSON

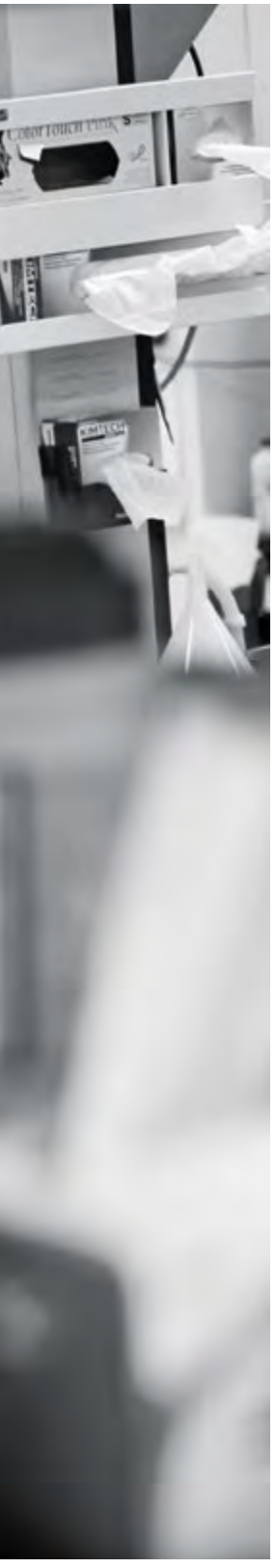
FOCUS ON

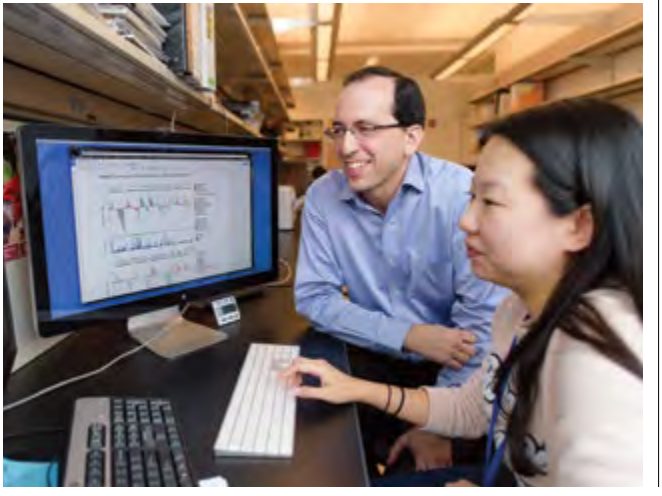
# MSK-IMPACT

Knowing more about the changes that drive tumors helps open the door for precision oncology, in which a person is matched with a treatment that targets the specific weaknesses in the cancer. MSK's genetic-sequencing test, which provides those details, marked two major advances in 2017.

Genetic counselors like Meg Sheehan meet with patients and families to explain the inherited risks for cancer that are passed down through generations.

# A SWEEPING IMPACT



## GUIDING TREATMENT WITH DATA

Not all genetic mutations cause cancer. But some do, and thanks to rapid advances in technology, scientists have amassed a wealth of information about which genetic mistakes are most likely to lead to the disease. The most pressing challenge has been testing people for cancer-causing mutations — and handling the data produced as a result.

MSK-IMPACT™, a genetic-sequencing test, is MSK's answer to this issue. Doctors can use it to probe a tumor for mutations and other genetic changes in 468 genes that are seen in both common and rare cancers.

Currently, all MSK patients with advanced solid tumors have their cancer tested by MSK-IMPACT, which has been in use as a clinical test approved by the New York State Department of Health since 2014. The test hit two major milestones in 2017: authorization from the US Food and Drug Administration as a tumor-profiling test, the first test of its kind to receive this designation; and the publication of data from the first 10,000 people whose tumors were sequenced.

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> **“These landmark achievements are the result of a major collaborative effort. In addition to guiding treatment choices, this test is producing valuable insights about how cancer grows and resists treatment.”**
>
> –MICHAEL BERGER

*Far left*: Marc Ladanyi (*right*), with molecular geneticist Liying Zhang (*left*) and pathologist Diana Mandelker, played a key role in the authorization of MSK-IMPACT. *Left, top*: The Biomek FXp machine uses unique bar-code sequences to tag patients' DNA, which will be sequenced using molecular testing like MSK-IMPACT. *Left, bottom*: Michael Berger, with computational biologist Helen Won, helped lead the development of MSK-IMPACT.

"These landmark achievements are the result of a major collaborative effort," says geneticist Michael Berger, who led the development of the test and is an Associate Director of the Marie-Josée and Henry R. Kravis Center for Molecular Oncology (CMO). "In addition to guiding treatment choices, this test is producing valuable insights about how cancer grows and resists treatment."

"MSK-IMPACT has allowed us to establish an entirely new paradigm for cancer care," says Marc Ladanyi, Chief of the Molecular Diagnostics Service. Dr. Ladanyi's team, including molecular pathologist Maria Arcila, was responsible for the clinical validation of the test and now oversees its performance as well as the analysis and interpretation of the test results. "In this new paradigm, it is critical not only to identify the exact type of cancer someone has and how far it has spread but also to determine the mutations that drive cancer cells to divide," Dr. Ladanyi adds.

MSK-IMPACT makes it possible for precision oncology to take place. Also called personalized medicine, this approach is based on the idea that the genetic alterations that drive cancer cells to grow can be targeted with specific drugs. The test has also allowed investigators to undertake basket studies. While traditional clinical trials focus on a particular cancer type, basket studies concentrate on a specific mutation found in the tumor, regardless of where the cancer originated in the body.

This type of testing is already changing how people are treated. In May 2017, MSK investigators published the aforementioned study in *Nature Medicine*, showing that nearly 37 percent of the first 10,000 people who had their tumors sequenced using the MSK-IMPACT test had at least one actionable mutation, which means drugs were available that precisely targeted the mutation. According to the study, about 11 percent of the people with actionable mutations participated in clinical trials involving molecularly targeted therapies as a direct result of MSK-IMPACT. Still others received immunotherapy based on their results.

"The breadth and depth of MSK-IMPACT has allowed us to detect important genomic alterations that would have been missed by other approaches," says David Solit, Director of the CMO, which financially supports the bulk of MSK-IMPACT testing.

## LOOKING FOR CANCER DRIVERS

Although MSK-IMPACT was developed largely to aid in diagnosis and to guide treatment, investigators knew from the beginning that the information they were collecting could be instrumental for research. Everyone who has had a tumor sequenced by MSK-IMPACT — more than 24,000 people to date — has had their genetic data linked to clinical records showing how they fared after treatment.

"This is a huge data set," Dr. Berger says. "It's extremely valuable to labs that are studying specific genes and biological pathways that are important in cancer. They can focus their research on the most frequently observed mutations, rather than having to guess which mutations may be the most important."

Beyond using those priceless data in MSK's own labs, it's equally important to share them with other organizations to move cancer research forward as quickly as possible. One of these efforts is AACR Project GENIE, initiated by the American Association for Cancer Research and spearheaded by Charles Sawyers, Chair of MSK's Human Oncology and Pathogenesis Program. This multicenter effort strips patient-identifying information from the records, then pools the information for analysis, allowing researchers across the nation to study the data. The resource enables them to discover new links between cancer-related genetic mutations and patient outcomes.

In January 2017, Project GENIE announced the release of its first batch of data: genomic-sequencing information on tumors from nearly 19,000 people with cancer, linked to information about their clinical care. These data, now up to 38,000 people, will help researchers figure out which mutations are drivers (changes that actually induce cells to grow out of control) and which are passengers. Knowing the difference is crucial to developing effective cancer drugs.

"Many of the mutations linked to cancer are rare, making it difficult for one institution to collect enough data to make statistically significant connections between a particular mutation and its role in causing cancer," Dr. Sawyers says. "There is a great value in joining together and pooling the insights that we're gaining from sequencing patient tumors."

*Above*: Maria Arcila, Director of the Diagnostic Molecular Pathology Laboratory, helps oversee the use of MSK-IMPACT. *Right*: Charles Sawyers, with research fellow Elizabeth Adams, is part of an international collaboration among research institutions that shares data from genetic sequencing.

> It was a tremendous effort to develop MSK-IMPACT, orchestrated by many people with diverse backgrounds.”
>
> –AHMET ZEHIR

Ahmet Zehir has participated in a number of studies relating to MSK-IMPACT and how it’s being used.

## FAR-REACHING VALIDATION

Before MSK-IMPACT, next-generation sequencing technology had been used mainly in the context of research studies. The pathologists, technologists, and bioinformaticians on the development team worked painstakingly to create and enhance methods for collecting and analyzing clinical samples, which present a much greater challenge. Moving such a complex research test into the diagnostic laboratory setting was a major advance.

“It was a tremendous effort to develop MSK-IMPACT, orchestrated by many people with diverse backgrounds,” says Ahmet Zehir, Director of Clinical Bioinformatics.

The FDA recognized this innovation when it authorized MSK-IMPACT as a tumor-profiling test in November 2017. A benefit of this designation, which is given to some medical devices and laboratory-developed tests, is to set up the test as a model and establish standards for the development and validation of similar tests in the future.

This validation could lead to broader insurance coverage for genomic-sequencing panels in cancer — a huge issue if these tests are to be widely accessible.

“People making reimbursement decisions for Medicare and private insurance companies are realizing that this kind of sequencing is a bargain because patients can receive all the information they need to get the right treatment from a single test,” says David Klimstra, Chair of the Department of Pathology. “We’re optimistic that as the positive impact of genetic sequencing becomes more apparent, we’ll be able to use the test to benefit more people.”

continued ▸

> There is a great value in joining together and pooling the insights that we’re gaining from sequencing patient tumors.”
>
> –CHARLES SAWYERS

## BRANCHING OUT TO THE FAMILY TREE

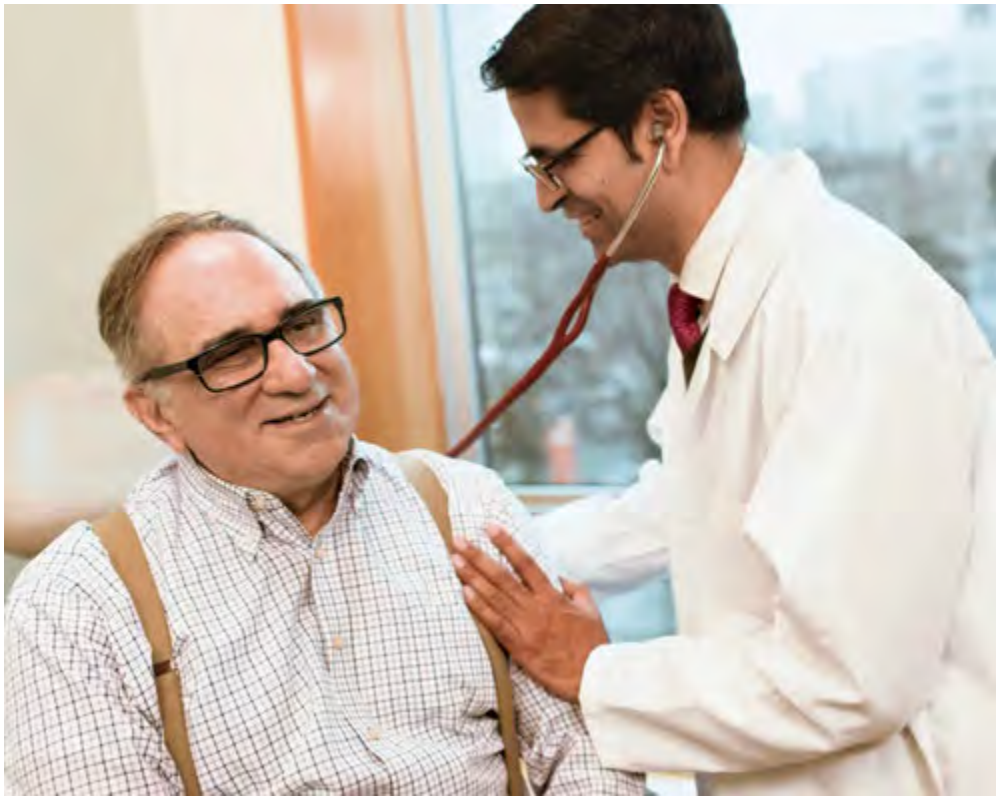
While the MSK-IMPACT test was established primarily to screen for mutations in tumor cells, it also offers the opportunity to better understand the contribution of inherited cancer-related genes among people with cancer and their families. For Mitchell Katz, 64, findings from MSK-IMPACT helped researchers understand why he responded so well to a new immunotherapy drug and, more importantly, may have saved the lives of several of his close family members.

Mr. Katz was first diagnosed with urothelial cancer in one of his kidneys in 2011 and had MSK-IMPACT testing in 2015. Although his family history did not suggest it, his test results showed he had a condition called Lynch syndrome. Also known as hereditary nonpolyposis colorectal cancer, Lynch syndrome is associated with a genetic predisposition to a number of different cancer types. It's most commonly linked to colon and rectal cancers, but it's also known to increase the risk of developing uterine, urothelial, and ovarian cancers, as well as other gastrointestinal cancers, such as tumors in the stomach, small intestine, and pancreas.

His doctors made this diagnosis because, in addition to flagging cancer-causing mutations in tumors, MSK-IMPACT provides extensive information about a patient's normal DNA. Clinical geneticists use this information to uncover which genetic changes were inherited by a person at birth and increase the risk of developing cancer and which developed over time within the cancer cell. Cancer-causing genes that are inherited are likely to be shared by brothers, sisters, and children, as well as parents.

MSK's specialists are uniquely experienced in interpreting these clues. People who harbor these genetic alterations can undergo genetic counseling and learn about what these findings mean. Their family members are also offered the opportunity to undergo genetic testing and counseling.

> "Once I knew, it was important to me that my family have testing too, just in case they had the same condition."
>
> –MITCHELL KATZ



After Mr. Katz learned he had Lynch syndrome in 2015, he met with MSK genetic counselor Meg Sheehan, who explained the risks to him and recommended that other family members get tested. "I was very surprised to find out I had this mutation because I didn't have a strong family history of cancer," he says. "Once I knew, it was important to me that my family have testing too, just in case they had the same condition."

Ultimately, his daughters, Stacy, 34, and Shana, 29, were found to carry the same mutation, as well as his older brother, Elliot, 66. All four of them, including Mr. Katz, who is still at risk of developing additional cancers, began undergoing regular colonoscopy screenings to check for the presence of colorectal cancer, an action they never would have known to take otherwise.

In February 2018, Elliot Katz was found to have an early-stage colorectal cancer, thanks to a colonoscopy. In April 2018, MSK surgeon José Guillem performed surgery to remove the tumor and a portion of his colon.

Mitchell Katz was already enrolled in a clinical trial for the immunotherapy drug atezolizumab (Tecentriq®) when he found out that his urothelial cancer had an excess number of mutations due to his underlying Lynch syndrome. It turned out that people with mutations in Lynch syndrome–associated genes were among those in the trial whose cancers responded best to the immunotherapy. Mr. Katz continues to see MSK medical oncologist Gopa Iyer for his treatment and has had no evidence of disease in the nearly four years since he started receiving the drug.

*Top*: Mitchell Katz and his doctor Gopa Iyer. *Above*: Mr. Katz (*right*) and his brother, Elliot, were both found to have Lynch syndrome.

## FAMILY MATTERS

For a long time, experts thought that only 5 to 10 percent of cancers were triggered in part by a hereditary component. But as a result of MSK-IMPACT, they're realizing that the inherited risk may be substantially higher for some people, particularly those with advanced cancer. They're also finding that inherited factors may play a role in a much greater variety of cancer types.

"At the time a person is diagnosed with advanced cancer, we have a vital opportunity to conduct comprehensive genetic testing," says Kenneth Offit, Chief of the Clinical Genetics Service and head of the Robert and Kate Niehaus Center for Inherited Cancer Genomics. The Niehaus Center, working closely with molecular pathologists Diana Mandelker and Liying Zhang, aims to use hereditary genomic data to develop new approaches for cancer prevention, early detection, and treatment for families with these inherited risks.

"By learning about the presence of inherited mutations, we can set the stage for providing genetic counseling to families. That in turn can lead to better screening and prevention," says Dr. Offit. "No other institution is doing tests that compare tumor and normal tissues and family notification to the same degree as MSK."

A study published in September 2017 in the *Journal of the American Medical Association* (*JAMA*) and led by Dr. Offit's team found that 17.5 percent of those with advanced cancer had inherited cancer-causing mutations, and half of those people would not have been screened for those mutations based on their personal or family history alone.

Like Mr. Katz, the other people in the *JAMA* study who were found to have inherited mutations in cancer-causing genes were invited to participate in counseling, along with their families. Family members then had the opportunity to undergo genetic testing as well.

Going forward, MSK hopes to expand tumor sequencing to even more people. "This new technology has enabled our doctors to extend the promise of precision medicine to many people, including those with common or rare tumor types," Dr. Klimstra says. ■

> **"By learning about the presence of inherited mutations, we can set the stage for providing genetic counseling to families. That in turn can lead to better screening and prevention. No other institution is doing tests that compare tumor and normal tissues and family notification to the same degree as MSK."**
>
> –KENNETH OFFIT

*Top*: In addition to consulting with adult patients and their families, Meg Sheehan also works with families of children who have cancer. *Above*: Kenneth Offit (*left*) and genetic counselor Yelena Kemel have found that inherited cancer mutations are more common than expected in people who have advanced cancer.

# FOCUS ON **CLINICAL TRIALS**

Clinical trials are the engine of new cancer treatments. Without them — and without all the people who participate in them, despite having no guarantee of success — progress in understanding and treating cancer would grind to a halt. Memorial Sloan Kettering's clinical trials program is among the largest in the world, with investigators from all disciplines and departments studying potential cures for hundreds of cancer types.

**At any given time, MSK offers hundreds of clinical trials for a variety of cancers, from the most common to the most rare.**

# THE CURE CONVERSATION

In 2017, clinical trials at MSK resulted in a number of firsts: the first cancer therapy developed simultaneously in children and adults; the first drug to rehabilitate cancer cells rather than kill them; the first treatment for a rare and deadly blood disorder. The year also saw progress for a treatment that helps children survive a nerve tissue cancer that spreads to the brain, a disease that used to be a death sentence.

**"When it comes to advancing cancer care, clinical research is the rocket fuel for better treatments, more accurate diagnoses, and ultimately cures."**

**–JOSÉ BASELGA**

*Clockwise from left*: David Hyman, Lauren Kaplanis, Alexander Drilon, Kim Kramer, Nai-Kong Cheung, and Eytan Stein.

## **NAI-KONG** CHEUNG

Pediatric oncologist;
Head, Neuroblastoma Program

**DRUG:** omburtamab

**TARGET:** neuroblastoma, a rare nerve-tissue cancer that often spreads to the brain and is most common in young children

Dr. Cheung created and tested omburtamab in clinical trials. When linked to a radioactive element and injected into the spinal fluid, it delivers precision liquid radiation to strike cancer cells dead. In 2017, the US Food and Drug Administration granted the drug a Breakthrough Therapy Designation for neuroblastoma that has spread to the brain. The designation is given when early clinical data indicate a drug demonstrates substantial improvement over existing therapies.

## **ALEXANDER** DRILON

Medical oncologist;
Clinical Director, Early Drug Development Service

**DRUG:** larotrectinib

**TARGET:** TRK fusions

Larotrectinib is a targeted cancer therapy that inhibits a protein called TRK fusion that fuels growth in multiple cancer types. This drug was developed simultaneously in children and adults and resulted in dramatic cancer shrinkage for some patients, regardless of age or cancer type. Dr. Drilon led MSK's phase II adult/adolescent clinical trial of larotrectinib as part of a multicenter study. In 2017, the drug's manufacturer, Loxo Oncology, submitted a new drug application to the FDA.

## **DAVID** HYMAN

Medical oncologist;
Chief, Early Drug Development Service

**DRUG:** vemurafenib (Zelboraf®)

**TARGET:** malignant histiocytosis, a rare blood disorder also known as Erdheim-Chester disease

Vemurafenib is the first targeted therapy that was approved based on a basket trial, a type of clinical trial pioneered at MSK by Dr. Hyman, MSK Physician-in-Chief José Baselga, and others that focuses on the genetic mutations fueling disease instead of where in the body tumors develop. The FDA approved it for treating melanoma in 2011. In 2017, vemurafenib became the first drug approved by the FDA to treat malignant histiocytosis.

## **LAUREN** KAPLANIS

Clinical research nurse

**SERVICE:** Early Drug Development

Ms. Kaplanis has been a nurse at MSK for more than seven years. She has participated in multiple clinical trials, including the study of larotrectinib with Drs. Drilon and Hyman. She specializes in caring for MSK's child and young adult patients.

## **KIM** KRAMER

Pediatric oncologist

**DRUG:** omburtamab

**TARGET:** neuroblastoma, a rare nerve-tissue cancer that often spreads to the brain and is most common in young children

Dr. Kramer headed the clinical trial involving 105 children that led the FDA to give omburtamab a Breakthrough Therapy Designation in 2017. MSK treats more people with neuroblastoma than any other institution in the world. Dr. Kramer is also researching new treatments to eliminate microscopic tumor cells in the central nervous system.

## **EYTAN** STEIN

Hematologic oncologist

**DRUG:** enasidenib (Idhifa®)

**TARGET:** acute myeloid leukemia (AML)

Enasidenib is the first drug to be approved that rehabilitates cancer cells rather than killing them. The drug reverses a stalled state of development for the cells, allowing them to mature normally. Dr. Stein led MSK's phase I/II clinical trials of the drug. MSK President and CEO Craig Thompson and physician-scientists Ross Levine and Omar Abdel-Wahab conducted much of the preclinical research upon which the therapy is based. In 2017, the FDA approved the drug for treating AML that has stopped responding to other therapies.

The researchers who spearheaded these advances sat down to talk about their efforts, what keeps them going when treatments don't go as planned, and what they appreciate about doing this work at MSK.

**NAI-KONG** CHEUNG

I bet you often get asked, "Why did you go into oncology?" But I have a different question: What keeps you in oncology? How do you sustain yourself in a field that we know is sometimes depressing?

**ALEXANDER** DRILON

Well, to me, things actually seem less depressing than they were before. We're finding new targets for treatment and developing new medicines. We're seeing palpable differences in how much longer people survive and an increase in their quality of life.

That keeps me going. We've seen Lazarus responses where patients whose tumors have a specific mutation come in horribly sick and turn around very quickly if you give them the right targeted therapy for their cancer. You can really make a huge difference in how they feel.

**EYTAN** STEIN

My experience is a little bit like Alex's. I worked as a research fellow with enasidenib. The first patient I gave the drug to went into a complete remission and the cancer disappeared. The depressing part came afterward, when many of the patients we gave the drug to started relapsing. What kept me going was figuring out how to prevent that relapse and to understand what combinations we needed to use to get those people in remission.

**DAVID** HYMAN

We were running a study of vemurafenib that targeted a specific cancer mutation, but I had no way to identify the people with that mutation. Then MSK's Information Systems group set up a way that once a person was identified through genetic testing, I would get a message.

So I got an email the first day that system went live, and I opened up the email really excited. But the pathology report said the patient had this condition called Erdheim-Chester disease. I was immediately disappointed because I didn't even know what that was. I Googled it, and even after that I wasn't sure it was a cancer.

It turned out that the company funding the trial was willing to treat the patient, so we went on to treat her and 30 others with the same disease. The drug is now approved in these patients — the first drug approved for people with this condition, ever. I'm a medical oncologist for gynecologic cancers. But all of a sudden my entire clinic was full of these patients with Erdheim-Chester disease and not ovarian cancer. There were days I would go from one room to another to another to treat people with this incredibly rare disease, which most doctors probably never see a single case of. That was the embodiment of "something is definitely working here." It was such an exciting experience.

**KIM** KRAMER

I'm really moved by the strides we've made in treating neuroblastoma. It used to be a death sentence. But now we have kids who have survived for decades, grown into adults, and gone on to have their own kids. And the FDA giving a Breakthrough Therapy Designation to omburtamab gives us even more cause for hope. This fall will be the 20th anniversary of our first celebration for survivors of neuroblastoma. It's been a real privilege to see these kids who had previously been given fatal diagnoses grow up and visit us to celebrate.

continued ▸

## THE CHALLENGES OF FAILURE

**NAI-KONG** CHEUNG

But what about when we don't get results for patients? What if we hit a roadblock? I always admire the nurses who are at the bedside taking care of the sickest patients. It's really hard for me to imagine how nurses can keep going.

**LAUREN** KAPLANIS

Thank you. I appreciate the acknowledgement. As an oncology certified nurse, I'm at MSK because the work is as rewarding as it is challenging. When you're involved in a clinical trial, you become such a part of each patient's life, from the day you first screen them to seeing them weekly to the time when they are clinically responding and getting back to their normal everyday lives — traveling, family, hobbies. The weight of the sadness that you see is overcome by the good that you see, and by how patients are really grateful for the time that you spend with them and the relationships that you form over time. It's really incredible.

**ALEXANDER** DRILON

With these therapies we're developing, sometimes it's actually more heartbreaking when you have something that can work really well and you know a person has done so great for a prolonged period of time. But then suddenly the cancer learns how to outsmart the pill. And you realize that you don't have anything left for that person. It's back to square one.

**EYTAN** STEIN

I'm really moved by the altruism of some patients when clinical trials don't turn out as we hope. I've had patients say to me, "Can't I just stay on the drug — even though it's not working — a little bit longer because maybe you'll learn something more from me being on this drug?" That kind of trust, that they're willing not only to help research but also to help other human beings, is really dramatic and very impactful.

**ALEXANDER** DRILON

I think that's an important point. I've also had patients have a really good response to therapy who tell me, "Doc, thank you so much. I wouldn't be here today if you didn't have this therapy on this trial." But we make it a point to tell them, "No. Thank you, because without your experience and without your contribution, we wouldn't have been able to establish this data and get this drug approved for other patients." I think it's important to feed that back to them, that they're part of this process.

## NEW TREATMENTS FOR CHILDREN AND YOUNG PEOPLE

**NAI-KONG** CHEUNG

I think pediatric oncology faces a lot of challenges. First, in young patients it's often difficult to give anything that is really toxic. They may have to live with the consequences for a long time.

The second thing is that there are very few pediatric patients. So that means the pharmaceutical industry doesn't pay as much attention. They're not going to make as much money developing drugs for pediatric patients. That's the way it is. Numbers count. This is the problem those of us in pediatric oncology have faced for decades. How do you get anything done, make a drug, prove that it works, and after all that have someone make it? Because a therapy can be great and help children on clinical trials at MSK, but it cannot be used anywhere else. That's why it's so important when treatments like omburtamab reach important milestones in approval from the Food and Drug Administration, so they can hopefully help more kids.

**KIM** KRAMER

There are some organizations that are trying to make drug accessibility equal for adults, young adults, and children. There's the RACE for Children Act [Research to Accelerate Cures and Equity] that was just passed earlier in 2018, which will mandate that drugs in development are accessible for pediatric patients as well. So hopefully the increased awareness at that level will improve things.

**ALEXANDER** DRILON

We're trying to address that issue in the development of therapies that target cancer-fueling gene mutations regardless of where tumors occur in the body. That's the idea with this new drug that David, Lauren, and I have worked on called larotrectinib, a TRK inhibitor. It's for cancers that have a particular gene change called a TRK fusion. It was recognized that a really important group of people with this gene change was adolescents. So we ran a phase II trial. Early in the development of the program, the cutoff was lowered for the adult trial to age 12 to make it an adult and adolescent trial. We're doing this with more clinical trials now.

continued ▶

## MSK PEDIATRICS

**MORE THAN 100**
years of expert pediatric hematology-oncology care

**90%**
of hematology-oncology treatments are performed on an outpatient basis

**MORE THAN 150**
patients in treatment each day

**MORE THAN 99%**
survival rate at MSK for patients with retinoblastoma

**MORE THAN 100**
clinical trials available

**TEAM OF MORE THAN 400**
doctors, nurses, and other specialists

**TWO UNIQUE**
antibody treatments and cellular therapies developed at MSK and patented for national trials

MORE THAN
850
NEW PATIENTS ANNUALLY

**DAVID** HYMAN

What it really comes down to is not protecting kids from research but protecting them through research. That's not a line I invented, but I think it's true.

I think what is a unique opportunity at MSK is that you have this enormous program that's treating as many kids, if not more, than anybody else. And it's embedded within this hospital that has a lot of adult research. A big opportunity, like Alex said, is bringing down the age limit on our studies. There's really no scientific reason that we've chosen 18. That gives the kids that are treated here access to studies that are just not available in pediatric hospitals.

**EYTAN** STEIN

With the CAR T cell program everyone's been very excited about, that program was pioneered in children and then moved to adults. That was primarily because the tumor that was being targeted is something that's very common in kids with acute lymphoblastic leukemia. I think there's a recognition that including kids doesn't hamper your trial; it helps your trial.

**LAUREN** KAPLANIS

Right. You always look at the patient as a whole, whether they're 18 or 81. Of course there is a uniqueness with the pediatric population because in general their understanding and expectation is different. And then there is the family too, so you have an additional aspect of care that you're providing to the family along with the patient. One of the great things about younger patients is their resilience, which is really cool.

**NAI-KONG** CHEUNG

I agree. They may be hurting one day with all the treatment, then the next day they act like they forgot what just happened. It's amazing how kids can bounce back like that.

## WHAT SETS MSK APART

**DAVID** HYMAN

When I started working here, I realized that everyone at MSK, no matter what role they play, knows they're at an institution dedicated to treating people with cancer. They could work at any other hospital. But from answering the telephone to pushing a stretcher or infusing a medicine, they know they're going to be working exclusively with people suffering from cancer. The doctors, nurses, and pharmacists show a dedication to patients I've never seen anywhere else.

**KIM** KRAMER

When it comes to developing great new therapies, there really is a multidisciplinary team effort. My department, pediatric oncology, is just one part of this. It's the nuclear medicine team, the medical physics team, the pharmacology team, the radiation safety officers, and all the other departments that buy into putting forth the time and effort to make something succeed. The dedication and loyalty and effort and diligence and experience are phenomenal here.

**ALEXANDER** DRILON

I agree. Another layer is that there's so much openness to new ways of thinking at MSK, even beyond having the best scientists. It's really a culture. This includes some of the innovations we've talked about, like dropping the age limit on some clinical trials and focusing on rare cancers. It's also partnering with pharmaceutical companies to pay for travel and lodging for people with rare cancers to come here from places like Brazil and China. That openness to new ways of doing research is a beautiful thing.

**LAUREN** KAPLANIS

I feel incredibly fortunate to work with talented doctors from around the world. But I can bounce off my opinions or my suggestions, and they're open to hear that too. Everyone has that caring and compassion, which is unique. You can't find that everywhere. I know from working on clinical trials with pediatric patients that it's important to the family that what they tell a nurse carries weight with everyone on the team, including the doctors.

“When I started working here, I realized that everyone at MSK, no matter what role they play, knows they're at an institution dedicated to treating people with cancer. ... The doctors, nurses, and pharmacists show a dedication to patients I've never seen anywhere else.”

–DAVID HYMAN


## PHASES OF CLINICAL TRIALS

**Clinical trials are grouped into phases depending on the purpose of the research. Each phase builds on the last.**

**PHASE I** TRIALS — Phase I trials focus on the safety of the treatment and finding the appropriate dose.

**PHASE II** TRIALS — Phase II trials determine if the treatment is effective.

**PHASE III** TRIALS — Phase III trials compare the treatment to the standard of care and are often the final stage before a drug is submitted to the FDA for approval, though sometimes trials enter phase IV if questions remain about their best use.

This framework has become more flexible in recent years. With the advent of targeted therapies, the individual characteristics of a tumor can help determine if a person is likely to benefit from a particular treatment, even before enrolling in a clinical trial. Research has shown that tumor profiling leads to significantly better outcomes for people in clinical trials, even as early as phase I. Another departure from the past is that treatments are being approved by the FDA without going through all of the stages.

**EYTAN** STEIN

Building on what you're saying, I think that in phase I drug development, everyone has a voice. If it's the nurse or the research study assistant, all ideas are taken seriously to contribute to the benefit of that specific patient and the benefit of the study as a whole.

**DAVID** HYMAN

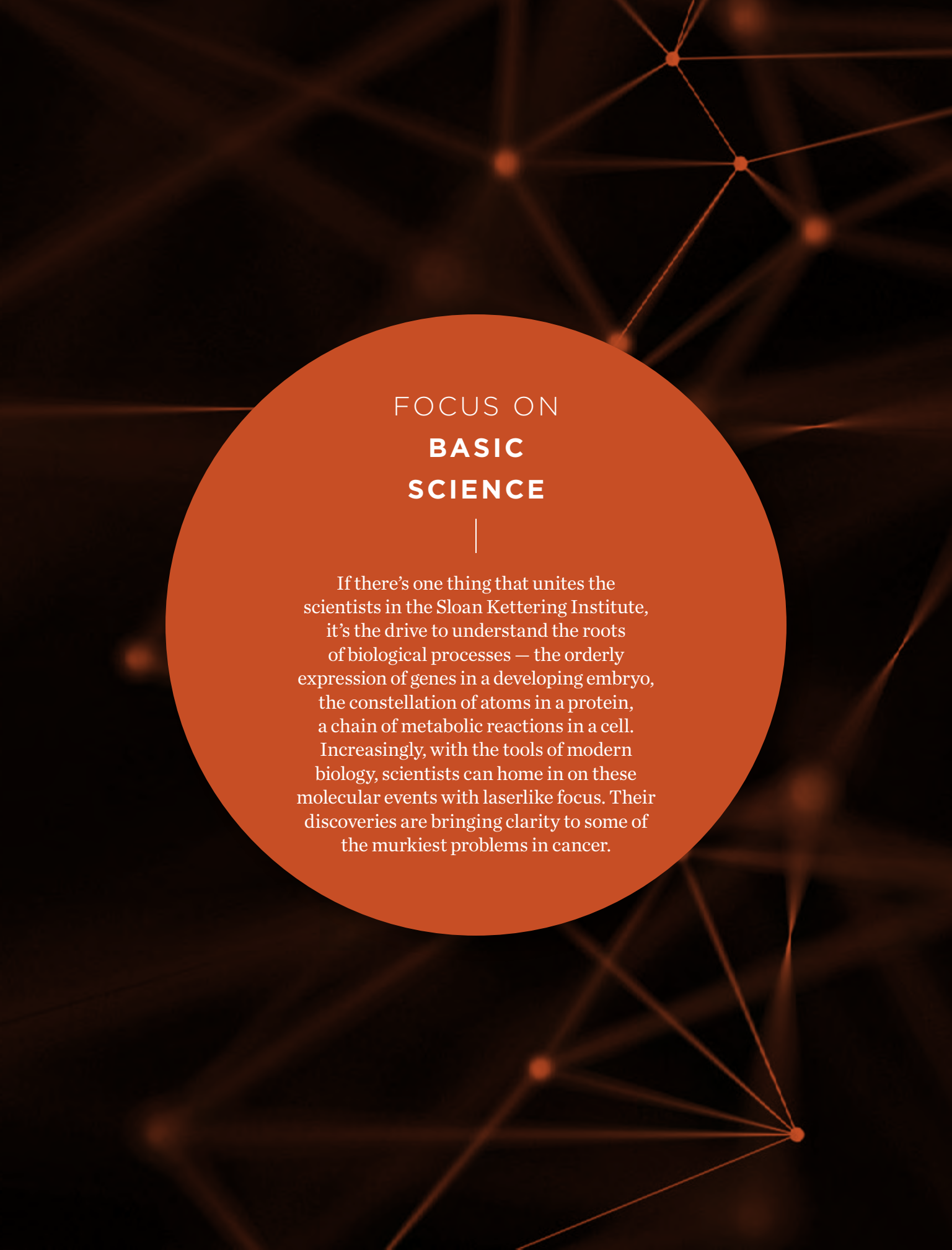
That same commitment to improving cancer care goes to the very top of the institution. It's not just about wait times and how many patients you see in a clinic. It's not just a business. It's about creating an environment that allows us to advance the field. When I go to other incredible institutions — great, wonderful institutions — they cannot believe the environment and the systems MSK has put in place to enable the type of work that we just take for granted here.

**ALEXANDER** DRILON

I agree with that. I think there's sort of an "if you build it, they will come" kind of theme here.

**NAI-KONG** CHEUNG

This brings us full circle to the question we began with, about why we stay in oncology. For me, I know that I need to meet a standard. It's almost as if you're trying to improve on your own self. In fact, you try to surpass yourself. You want to be a better doctor. And as you get better, the institution gets better. And that is the goal. ■



# FOCUS ON **BASIC SCIENCE**

If there's one thing that unites the scientists in the Sloan Kettering Institute, it's the drive to understand the roots of biological processes — the orderly expression of genes in a developing embryo, the constellation of atoms in a protein, a chain of metabolic reactions in a cell. Increasingly, with the tools of modern biology, scientists can home in on these molecular events with laserlike focus. Their discoveries are bringing clarity to some of the murkiest problems in cancer.

**Scientists are finding new ways to model disease in the lab, with the goal of determining the most effective treatments.**

# SEARCHING WIDE, DIVING DEEP

The genome-editing tool CRISPR has had a sizable effect on science and medicine in recent years. With these powerful molecular scissors, scientists can snip out specific pieces of DNA or make changes at precise genetic addresses. MSK researchers used CRISPR in several inventive ways this year to push cancer science forward.

*Left*: Ted Kastenhuber, a member of Scott Lowe's lab in the Sloan Kettering Institute, removes frozen cancer cells from liquid nitrogen. *Above*: Mr. Kastenhuber grows cancer cells in vitro. The cells are from mouse tumors that the team generated in the lab. Growing cancer cells outside the body could make it easier to test drug sensitivity more quickly and efficiently compared with studying the results in patients.

# NATURE'S SWISS ARMY KNIFE: THE MANY USES OF CRISPR

## UNRAVELING THE CAUSE OF A DEADLY CANCER

The rare liver cancer fibrolamellar hepatocellular carcinoma (FL-HCC) strikes fewer than 1,000 individuals a year worldwide, mostly children and young adults. There are few effective treatments besides surgery. FL-HCC is usually diagnosed late, so it is often fatal.

Because FL-HCC is so uncommon, it's hard for researchers to learn more about it, or even to conduct clinical trials of potential medicines. And without knowing more about the disease's underlying biology, they can't come up with solutions to stop it.

But what if the disease could be recreated in the lab? Could scientists use a synthetic model to test new FL-HCC drugs?

A team led by cancer biologist Scott Lowe, Chair of the Cancer Biology and Genetics Program in the Sloan Kettering Institute, decided to try just that. They used CRISPR to engineer mice with the same mutation that affects people with the disease.

It worked beautifully. "We showed that if you can reproduce that genetic event in mice, they will develop a cancer that looks very much like human FL-HCC," Dr. Lowe says. "This demonstrates that the mutant gene causes FL-HCC."

The research came about through a collaboration between Dr. Lowe's lab at MSK and Sanford Simon's lab at The Rockefeller University. Several years ago, Dr. Simon and colleagues discovered that nearly all people with FL-HCC share the same mutation in their tumors.

It was a big advance — one made even more remarkable by the fact that Dr. Simon's own daughter, Elana, suffered from FL-HCC and was centrally involved in the research effort. But still, it was only a correlation.

To find out for sure whether this mutation was responsible for driving the disease, Dr. Lowe's team, including Edward Kastenhuber, a student at the Gerstner Sloan Kettering Graduate School of Biomedical Sciences, used CRISPR to snip out the portion of the chromosome that is lost in people with FL-HCC. The remaining bits of chromosome then combined, fusing the two genes that are normally separated.

Scott Lowe creates genetically engineered mouse models to understand key cancer drivers.

> "Models give us the freedom to fail and to explore a wide variety of approaches. This way, we can accelerate the discovery of treatments that are more likely to be effective before exposing people to experimental medicines."
>
> –EDWARD KASTENHUBER

## CRISPR: A BACTERIAL CUT-AND-PASTE SYSTEM

CRISPR stands for

| C | R | I | S | P | R |
|---|---|---|---|---|---|
| Clustered | Regularly | Interspaced | Short | Palindromic | Repeats |

**These short sequences of repetitive DNA are found in bacteria and other microorganisms. Microbes use these sequences as a type of immune system against viruses.**

Key to the whole operation are stretches of DNA in the CRISPR sequences that match the genetic sequence of viral DNA. When these sequences are transcribed into RNA, they bind to viral DNA and direct an enzyme — for example, one called Cas9 — to snip the DNA at the match site. This disarms the invader. Bacteria retain a record of past viral infections, much like our own immune system does, stitched into their DNA.

In 2012, scientists at the University of California, Berkeley, and elsewhere realized they could turn this bacterial cut-and-paste system into a powerful tool for genetic engineering. Researchers can give the Cas9 enzyme a synthetic RNA as a guide, one that matches a gene or DNA sequence of interest. They can then use the CRISPR-Cas9 system to make very precise cuts and other alterations in the DNA of cells.

The team plans to use the model to test a variety of drugs to see if they can slow or stop the cancer's growth. FL-HCC could be a good target for drugs called kinase inhibitors, but scientists won't know for sure until they test them.

"Models give us the freedom to fail and to explore a wide variety of approaches," Mr. Kastenhuber says. "This way, we can accelerate the discovery of treatments that are more likely to be effective before exposing people to experimental medicines." The findings were published in the *Proceedings of the National Academy of Science*s in November 2017.

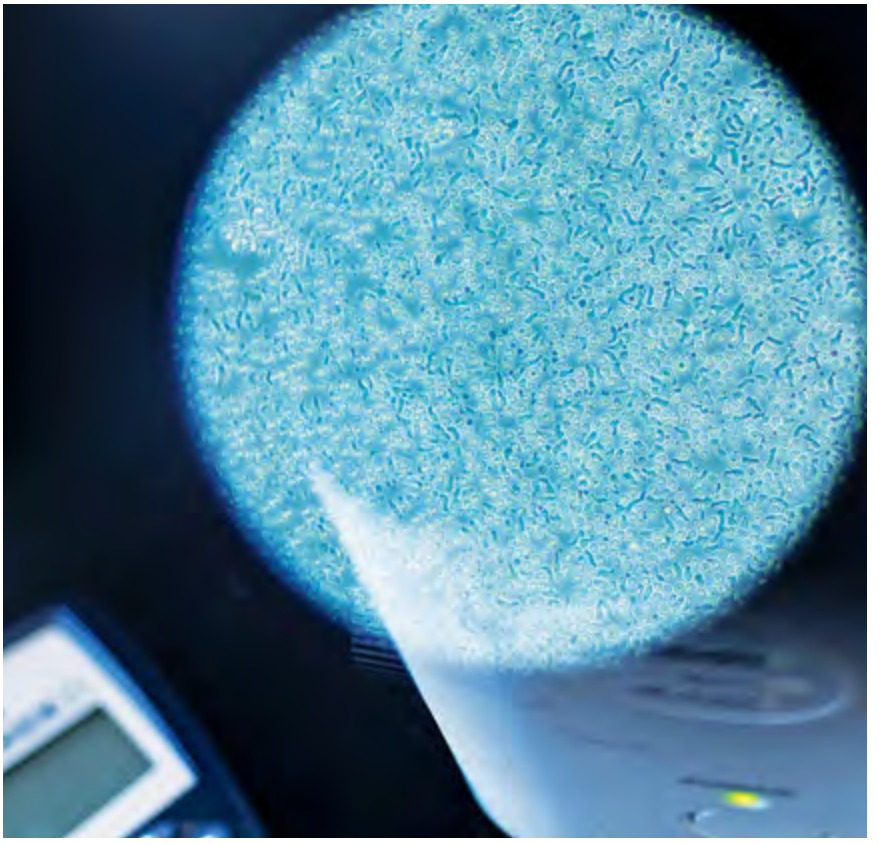
## BUILDING A BETTER CAR

Chimeric antigen receptor (CAR) T cells are a powerful tool to treat certain blood cancers. (Read more about CAR T therapy on page 8.) But the way they are made is somewhat inefficient. The current process involves removing immune cells from patients and using modified viruses to deliver the CAR gene into those cells. But this method inserts the gene randomly at multiple spots in the genome. This scattershot approach isn't as efficient as it could be, and could actually cause problems by disrupting the function of important genes.

This past year, researchers in SKI used CRISPR to build a better CAR T model.

continued ▸

*Below*: Activated T cells, shown under a microscope, are prepared and ready for gene editing. *Bottom*: Justin Eyquem (*left*) and Jorge Mansilla-Soto are postdoctoral fellows in Michel Sadelain's lab in the Sloan Kettering Institute.



Postdoctoral fellows Justin Eyquem and Jorge Mansilla-Soto, working in the lab of Michel Sadelain, showed that if they used CRISPR to place the CAR at a very specific genome location called the TRAC locus, the cells were not only more homogeneous, they were also more effective. The approach paves the way for more reliable CAR therapies and even off-the-shelf versions that would not need to be made from a person's own cells. They published their findings in the journal *Nature* in February 2017.

"The method we developed will likely transform a costly and variable T cell–manufacturing process into a more uniform, universal, and safer one," Dr. Eyquem says.

Also remarkable is the speed at which they were able to accomplish this feat. "We started to work on this project less than three years ago, and we expect to bring it to the clinic by early 2019," Dr. Eyquem says.

### KNOW THY GENOME

As precise and powerful as CRISPR can be, it's only as good as one's knowledge of the genome being cut. CRISPR can aim for multiple targets. But if it does, then instead of making precise snips in the exact spot in the genome you're aiming for, you might slice it too much.

In May 2017, researchers at SKI presented a way to solve this problem. The team — which included postdoctoral fellows Joana Vidigal and Yuri Pritykin, graduate student Alexendar Perez, and SKI faculty members Christina Leslie and Andrea Ventura — built computer software to help scientists design more-effective guide RNAs.

CRISPR uses guide RNAs to find specific regions of the genome, where it then makes a cut. The new software, called GuideScan, allows researchers to identify guide RNAs that have one or only a few possible matches in the genome, reducing the potential for too many cuts. GuideScan is freely accessible to researchers everywhere, to help enable even more skillful use of the CRISPR technology.

"Pretty much anything you can imagine, you can do," Dr. Vidigal says. "And now you can do it precisely." ■

## PLUGGING A HOLE IN METASTASIS

### STOPPING CANCER'S SPREAD

Cancer metastasis — which occurs when cells break off from a tumor, spread through the bloodstream or lymph vessels, and take root in another part of the body — causes the overwhelming majority of cancer-related deaths. In fact, it's widely estimated that 90 percent of cancer deaths are due to metastatic disease rather than the original tumor.

Many primary tumors can be wiped out with surgery, chemotherapy, and other treatments. Once cancer migrates, however, it becomes much harder to stop. This is especially true when it spreads to vital organs, such as the lungs, liver, or brain.

One of the most challenging types of metastatic cancer attacks the fluid and tissues that surround the brain and spine. If people develop this condition, called leptomeningial metastasis (LM), they usually die within weeks or months.

MSK cancer biologist Joan Massagué, Director of SKI and Executive Director of the Alan and Sandra Gerry Metastasis and Tumor Ecosystems Center, has been studying the intricacies of cancer metastasis for nearly two decades. Much of Dr. Massagué's current work is focused on latent metastasis, which happens when cancerous cells left behind after treatment form new cancers years or even decades later.

Joan Massagué (*center*), with medical oncologist Karuna Ganesh (*right*) and research associate Harihar Basnet, has made groundbreaking discoveries about the genes that influence how tumors interact with their environment.

> "It's difficult for cancer cells to seed new tumors in other parts of the body. To get through all the barriers that are waiting for them when they leave the mother ship, the ones that survive have to be tougher than the average cancer cell."
>
> –JOAN MASSAGUÉ

"It's difficult for cancer cells to seed new tumors in other parts of the body," he says. "To get through all the barriers that are waiting for them when they leave the mother ship, the ones that survive have to be tougher than the average cancer cell. This explains why these cells tend to be more aggressive and harder to treat."

In March 2017, Dr. Massagué and physician-scientist Adrienne Boire published a paper in the journal *Cell* on LM. To figure out how certain cancer cells grow in spinal fluid, the researchers implanted several cell lines of breast and lung cancer in mice and monitored them to see which ones resulted in LM.

To their surprise, they discovered that all of the cell lines that colonized the spinal fluid had the same well-known protein in common. After they understood how that protein worked, Drs. Massagué and Boire looked for a way to block its function. The solution was just as surprising as the initial discovery: A compound targeting the protein — originally developed to treat asthma but ultimately ineffective against that disease — suppressed LM and slowed its progression in mice. Now the researchers are investigating the possibility of using the compound to treat people with LM.

"In the past, LM was part of the fatal end stage of cancer," Dr. Boire says. By that point, people had so many other complications that not many efforts were focused on LM. But "now that patients are living longer and we're able to treat other sites of metastasis, this is becoming a clinical problem that we need to learn how to address." ■

> "In the past, LM was part of the fatal end stage of cancer. [But] now that patients are living longer and we're able to treat other sites of metastasis, this is becoming a clinical problem that we need to learn how to address."
>
> –ADRIENNE BOIRE

Adrienne Boire (*right*), with senior research technician Majdi Alghader, was inspired to study leptomeningial metastasis by a patient of hers who had the condition.

# TOR DE FORCE: CRYO-EM TECHNOLOGY

## BRINGING A KEY PROTEIN INTO FOCUS

Scientists call it the master growth regulator: a protein complex in cells that senses when they have enough nutrients and cues them to grow and divide.

When this complex, called mTOR, is triggered, cells begin making copies of key ingredients, such as membranes, DNA, and organelles. They use these extra materials when they split into daughter cells.

For years, scientists have sought to target abnormally active mTOR with drugs as a way to treat cancer. Two such drugs are approved by the US Food and Drug Administration for the treatment of some types of kidney and breast cancer.

But overall, mTOR-targeted drugs have been disappointing. That may be because mTOR is a large and complicated piece of cellular equipment. There are many interacting parts, and it may be hard to take down the whole thing with a single shot. Without a clear map of the protein's structure, it's impossible to know how it works — or how to stop it.

In December 2017, a team of scientists led by Nikola Pavletich, Chair of the Structural Biology Program, and Haijuan Yang, a senior research scientist in his lab, assembled an impressively detailed view of mTOR — the first ever — including what it looks like in action. To do so, they used an innovative technology called cryo-electron microscopy (cryo-EM), a kind of satellite imagery for the cell.

With this technique, scientists shoot beams of electrons at a purified sample of molecules that is flash frozen in chilled liquid ethane. The electrons bounce off the molecules in the sample, creating an image. Thousands of individual pictures are taken, and then a scientist uses sophisticated algorithms and high-powered computers to assemble the


Nikola Pavletich (*left*), with lab member Buren Li, a student at the Gerstner Sloan Kettering Graduate School of Biomedical Sciences, studies biological molecules at an atomic level, including the proteins that control cell growth and proliferation.

pictures into a crisp, three-dimensional image. MSK installed a cryo-electron microscope, the Titan Krios, in 2017. One of its first uses was to help scientists tackle the structure of mTOR.

"Once you solve a protein's structure — in essence, creating a three-dimensional map showing where all its atoms are — you gain a much deeper understanding of how the protein works and how its function could be manipulated with drugs," Dr. Pavletich says.

Previously, such detailed atom-by-atom pictures could only be produced with X-ray crystallography, a painstaking and time-consuming method that involves first making a crystal out of a protein and then X-raying it. But not all proteins will form crystals. That's especially true of large proteins and protein complexes with multiple moving parts, like mTOR. Cryo-EM eliminates the crystallization step, which makes determining structures much easier and faster.

The mTOR protein is actually part of a larger assembly of several interlocking protein pieces that operate together. The whole complex is called mTORC1.

The structure newly obtained by cryo-EM shows how all the pieces fit together, including how mTOR is turned on. What once would have taken years to complete took just a few months.

"Before cryo-EM, people could model bits of this protein and bits of that protein," Dr. Yang says. "Now we can put it all together." ■

> **"Before cryo-EM, people could model bits of this protein and bits of that protein. Now we can put it all together."**
>
> –HAIJUAN YANG

*Below*: Buren Li with Haijuan Yang and the cryo-electron microscope that arrived at MSK in 2017. *Bottom*: Structural biologist Stephen Long (*right*), with lab manager Jason Cruz, also utilizes cryo-EM technology.

# FOCUS ON **PATIENT CARE**

Every advance at MSK is intended to achieve a singular goal: improving our patients' well-being. In 2017, teams across the organization optimized surgeries, minimized unnecessary treatment, built new spaces for recovery, and made facilities feel a little bit more like home.

**Lyndell Kegerise (*right*) was among the first to stay in MSK's 75th Street Patient Residence, an apartment-style facility for people recovering from bone marrow transplants.**

# JUST LIKE HOME

A CONVERSATION WITH

## **LYNDELL** KEGERISE
*MSK patient*

## **WESLEY** KEGERISE
*Lyndell's husband*

Life at the Jersey Shore was good for Lyndell Kegerise. The former real estate professional was diagnosed with non-Hodgkin lymphoma in 2005, but under the care of MSK oncologist Paul Hamlin, her disease went into remission and stayed there for eight years. But in 2014, when she was 66, her disease relapsed, and then relapsed again in 2015. When chemotherapy and immunotherapy couldn't keep her in remission for longer than a year, Mrs. Kegerise and her husband, Wesley, learned that her best option was a stem cell transplant with hematologic oncologist Craig Sauter.

*Left*: Wesley and Lyndell Kegerise at the 75th Street Patient Residence. *Above*: Mr. Kegerise and Noel Neylon. *Right*: Mrs. Kegerise's doctor Craig Sauter.

**LYNDELL** KEGERISE

In January 2017, Dr. Hamlin said that we were running out of options. That hit me hard. He said that I would be a great candidate for a stem cell transplant and he'd like me to meet Dr. Sauter, who would perform it.

**CRAIG** SAUTER

Lyndell had high-risk disease, so that dictated the transplant. When patients approach 70, we have a little more pause, but she didn't have any major medical problems.

**WESLEY** KEGERISE

Our MSK team found a donor through the Be the Match program — this 25-year-old fellow who was a wonderful match. We're extremely grateful to him.

**LYNDELL** KEGERISE

I was afraid he was going to back out after I initially didn't achieve remission. I hope I get to meet this man one day because he stuck in there with me. He was ready when I was ready.

### A NEW PLACE TO HEAL

*Mr. and Mrs. Kegerise had looked into staying at a New York City hotel while she recovered from her transplant, until a nurse at MSK Basking Ridge gave them another idea: MSK's brand-new 75th Street Patient Residence, an apartment-style facility for bone marrow transplant patients and their caregivers that opened in 2017. The studio, one-, and two-bedroom units are outfitted with full kitchens, bathrooms, laundry, cable TV, and Wi-Fi. For some patients, their stay may be covered by insurance.*

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**LYNDELL** KEGERISE

Eric, one of my chemo nurses at MSK Basking Ridge, said, "You know, the new facility might be open by the time of your transplant." The next time I was back, he said, "Lyndell, it opened!" So I pursued it.

**CRAIG** SAUTER

I thought it was great because she lives in New Jersey. She didn't need inpatient care, but we like to have our patients close by for follow-ups. It's a good resource for patients who need to be here frequently.

**WESLEY** KEGERISE

We said, "This is great — take our reservation now!" When your loved one is going into a long hospital stay, what is the caregiver going to do? How are you going to go back and forth? All of these thoughts were going through my head. But MSK was sensitive to the needs of the caregiver as well as the patient. At a hotel, the room isn't sanitized. They don't understand your medical needs. But here the staff is trained to understand the needs of the patient.

> "The people at MSK work so well integrating with all the departments that the patient doesn't have to worry about anything except getting better."
>
> –WESLEY KEGERISE

"We try to provide a warm and casual environment," says Noel Neylon, seen here in one of the residence's apartments. "Our patients have enough hardships to deal with. They shouldn't have to worry about having any problems at their home away from home."

**LYNDELL** KEGERISE

They thought of things we didn't even think about. Our air was filtered. Our water was filtered.

**WESLEY** KEGERISE

This is the remarkable thing about MSK. The 75th Street Patient Residence team was so easy and wonderful to work with. I had to move our reservation about six times because we didn't exactly know when Lyndell would be OK for the transplant, and nothing was a problem for them. Your room is ready when you're ready. The people at MSK work so well integrating with all the departments that the patient doesn't have to worry about anything except getting better.

**LYNDELL** KEGERISE

Everything was coordinated for us. We just had to show up. And it was wonderful being on the east side near the hospital, so we didn't have to go across town.

## LIFE AFTER TRANSPLANT

*Mrs. Kegerise had her transplant and stayed in Memorial Hospital to recover for 30 days. Mr. Kegerise stayed at the residence. Then Mrs. Kegerise joined him at the residence a few blocks away, where they stayed for 40 more days.*

**LYNDELL** KEGERISE

Even when you get out of the hospital, you're still going to see the transplant team every other day. The whole coordinating team at the 75th Street Patient Residence made it easy for us. They would call in the evening and say, "Your van will be here at 8 AM" to go to the hospital. If for some reason it was late, they would call a driver.

**WESLEY** KEGERISE

At the residence, you have your own little apartment. If Lyndell wanted to take a nap, she could go in the bedroom and I could be in the living room watching TV. That's a real benefit. And the staff couldn't be more accommodating. Lyndell loves Bigelow mint tea, and they even got it for her. The session assistant, Ritsuko, and door attendant, Terry, would call us and say, "Do you need a ride in tomorrow at a certain time?" Noel, the superintendent who changed the filters, was so nice.

**LYNDELL** KEGERISE

He became like our family.

**NOEL** NEYLON (*MAINTENANCE SUPERVISOR*)

I know the people who stay with us, like the Kegerises, need support from our entire staff. Doing everything I can to create a warm, friendly environment for patients and their families to come home to is very important to me. I am proud to have been at MSK for more than 23 years, and I hope that we can continue to make a difference in our guests' experiences by treating them like family.

The couple on their wedding day in 1968 (*left*), and Lyndell Kegerise in treatment at MSK (*right*).

## A COMMON BOND

**LYNDELL** KEGERISE

At the residence, you are with people who are going through the same thing as you. We met a gentleman who worked on 9/11 and got blood cancer. We befriended a family from Saudi Arabia, and the son took Wesley under his wing. He cooked for him. The night before we left, they said, "Come down to our apartment and spend some time with us." At the end of the evening, the father, who was also a transplant patient, gave me his prayer beads.

**WESLEY** KEGERISE

Most days I would go with her to her appointments and have lunch with her. Some days I would go to the art museum or the Museum of Natural History. A couple days I would hit golf balls at Chelsea Piers. I could go back for lunch, see her in the afternoon, and walk home in the evening. It was so convenient.

**LYNDELL** KEGERISE

I encouraged him to get out. I said, "I'm taken care of — it's you I'm worried about! Go do something fun."

**WESLEY** KEGERISE

Our daughters came in from Delaware and Atlanta. They could stay with me at the residence while Lyndell was in the hospital. That was another beautiful thing: People could visit.

**LYNDELL** KEGERISE

That was very nice. Our Saudi Arabian family was able to join us for pizza in the common area.

*In October 2017, Mrs. Kegerise was cleared to return home.*

**LYNDELL** KEGERISE

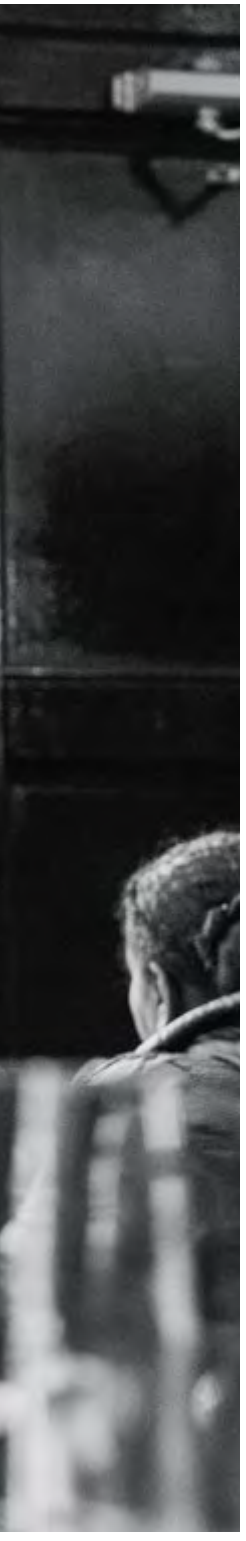
I was nervous leaving, but it was very coordinated. I had a little setback at Christmas — I got an infection so I was back in the hospital — but I'm doing great. I feel great. I have energy, and I'm getting stronger. Every December, I would have scans done, and the cancer was always back. This was the first time in three years I didn't hear the word "cancer" at Christmas. It was unbelievable.

*The couple will celebrate their 50th wedding anniversary in September.*

**LYNDELL** KEGERISE

We want all the special people in our lives over the past 50 years to come celebrate with us. We are so blessed. Every day is a gift. ■

# SEEING PROSTATE CANCER IN A NEW LIGHT



New York City dentist Gregory Page came to MSK for a less-invasive approach to prostate cancer treatment. After undergoing light-activated therapy with Jonathan Coleman, Dr. Page was able to resume his normal activities within days, including lunch at the Renaissance Harlem, near his office.

> **“The whole ambience they created was just outstanding. I always felt that if I ever had a diagnosis of cancer, I would not walk but run to MSK. And that’s exactly what I did.”**
>
> –GREGORY PAGE

## DOCTOR BECOMES PATIENT

As a dentist, Gregory Page knew the importance of staying on top of his health. He had prostate-specific antigen (PSA) tests, which measure for a protein in the blood that is elevated in men with prostate cancer, as part of his regular routine. When his PSA came back abnormally high in 2007, he made sure to see his doctor each year to more closely monitor his level.

In April 2017, his doctor saw that Dr. Page’s PSA had risen high enough to warrant a biopsy. The test came back positive for cancer. The news was understandably difficult for Dr. Page to take in — even more so because it came on top of what had been a challenging year so far. His godmother, best friend, and brother had all recently died.

“It was not a good year for me,” recalls the 68-year-old from New York City. “I said, ‘God, you’re giving me a lot to handle here.’ ”

Dr. Page was already under the care of a urologist, but hearing he had cancer made him reconsider where he wanted to go for treatment. He remembered the times he had escorted one of his good friends, a lung cancer survivor, to MSK’s Rockefeller Outpatient Pavilion.

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"The whole ambience they created was just outstanding," he says. "I always felt that if I ever had a diagnosis of cancer, I would not walk but run to MSK. And that's exactly what I did."

Before calling MSK's Patient Access Service, which schedules first appointments for people coming to MSK, Dr. Page researched urologists online. When he saw a YouTube video of MSK urologic surgeon Jonathan Coleman, he knew he had found the doctor he wanted to see.

Dr. Page recalls, "Dr. Coleman discussed the various treatments for prostate cancer, and he also used the word 'cure,' " which is possible for many men with prostate cancer. "That's a good word to hear when you have cancer," he adds.

Another point in the video that really resonated with Dr. Page was when Dr. Coleman said that the procedures he does have minimal side effects.

"I had friends who had their prostates taken out, and it took them years to recover," Dr. Page says. "One of my friends had incontinence problems for a year. I have another friend who had to have a pump put in. I didn't want all of that."

## FINDING A LESS-INVASIVE OPTION

In June, Dr. Page and his fiancée, Cynthia, met Dr. Coleman and his nurse, Connie Estes. Dr. Coleman remembers how impressed he was with Dr. Page's knowledge of his circumstance.

"He had definitely done his homework," Dr. Coleman says. "He was extremely intelligent and well informed. He was thoughtful, inquisitive, and concerned about his cancer while also being concerned about treating it too aggressively."

Ms. Estes was equally taken by the couple. "They are both the nicest people, and every interaction we had was a delight," she says. "It was obvious that they had researched prostate cancer and treatment."

She told the duo that Dr. Coleman was doing promising research with vascular-targeted photodynamic therapy, a form of prostate cancer treatment that uses a light-activated drug to zap prostate tumors with minimal side effects.

Dr. Coleman has been offering vascular-targeted photodynamic therapy since 2010. The procedure requires only light sedation — the same type used for a colonoscopy. Once sedated, the patient receives a medicine called padeliporfin (Tookad®) through an IV. Then the doctor places a thin laser fiber into the prostate gland, which activates the drug so it can kill the cancer. Patients can go home the same day.

"There's a need for new technology to better destroy cancerous tissue without harming the surrounding tissue, and that's where this type of therapy comes into play," Dr. Coleman says.

Right now, vascular-targeted photodynamic therapy is performed only through clinical trials, and it's not an option for every man with prostate cancer. However, efforts are under way to make it more widely available.

At their next meeting, Dr. Coleman told Dr. Page that he was recruiting men for a trial that would bring vascular-targeted photodynamic therapy closer to US Food and Drug Administration approval. He had 30 out of the 50 men he would need. Dr. Page knew this was his opportunity.

"I looked at my fiancée, I looked at Dr. Coleman, and I said, 'Could I be number 31?' " he recalls. "He said yes, and I hugged him like he was my long-lost brother. I knew I was getting world-class treatment."

*Above*: Jonathan Coleman is hoping the drug becomes a mainstream option for men with this type of cancer. *Right*: Narrow optical fibers activate Tookad to destroy prostate cancer.


Connie Estes helped prepare Gregory Page for his treatment with Jonathan Coleman.

### THE BIG DAY — AND A QUICK RECOVERY

Dr. Page had his procedure in October 2017 at Memorial Hospital. He went home the same day. He had to stay in shaded light conditions for the first two days he was home because Tookad is activated by light, but his fiancée helped him pass the time.

“When the 48 hours were up, I got up, put on my clothes, and went to a baseball game. And I felt fine,” he remembers.

After the procedure, the only side effect Dr. Page experienced was some minor soreness. And unlike other major forms of prostate cancer treatment, he hasn’t had any serious issues with incontinence or erectile dysfunction. At his three-month postsurgery checkup in January, Dr. Coleman didn’t find any cancer. Ms. Estes relayed the good news to Dr. Page.

“I remember I was so excited to make that call,” she recalls. “As an office practice nurse, you really get to know patients and their families. When the biopsy came back benign, it was great news. It makes my day when I am able to call a patient with news like this.”

Now, nearly a year postsurgery, Dr. Page is doing great. He’s busy at work and helping plan Cynthia and his wedding. He says this year is shaping up to be much better than the last.

“As a healthcare provider, it’s important for me to spread the word about positive things that can enhance and prolong people’s lives,” he says. “I feel very fortunate that I was at the right place, at the right time, with the right doctor and staff. How many people can say they had a complete turnaround in nine months?” ■

Lisa DeAngelis (*right*) is searching for ways to improve outcomes for people with brain tumors and neurologic complications of cancer. Viviane Tabar studies the use of stem cells to model cancer and to repair brain tissue after injury. Dr. Tabar also leads the Multidisciplinary Pituitary and Skull Base Tumor Center at MSK.

INTERVIEW WITH

**VIVIANE** TABAR
*Chair of the Department of Neurosurgery*

**LISA** DEANGELIS
*Chair of the Department of Neurology*

There are few diseases as feared — or as challenging to treat — as cancers of the brain. But there are very few doctors in the field of neuro-oncology with the expertise, experience, and compassion of Lisa DeAngelis and Viviane Tabar. Both have spent nearly all of their distinguished careers at MSK. Dr. DeAngelis has been Chair of the Department of Neurology since 1997; Dr. Tabar was named Chair of the Department of Neurosurgery in 2017.

In addition to treating patients, both doctors also conduct groundbreaking research. They sat down to talk about their approach to treating people with neurologic cancers, what makes MSK special, and much more.

## THE UNIQUE CHALLENGES OF BRAIN CANCERS

**LISA** DEANGELIS

People have very different ideas about what makes life meaningful. It's important that we know what that means to all of our patients, so we can not only treat their disease but also help guide them through difficult decisions and honor their wishes and their values, especially if they reach a point at which they may not be able to articulate that. So you need to know that early on.

**VIVIANE** TABAR

I agree. I think it's absolutely crucial to understand what patients really want and to tailor our treatment to their expectations. I remember early in my career someone who had a large, benign tumor, and we were very proud to have removed it completely. But the patient was not really satisfied because she turned out to be a wine connoisseur and she lost her ability to smell. That impacted her quality of life far more than we had anticipated.

Obviously, some people deal with much more challenging neurological and psychological problems related to a brain tumor diagnosis than that. That kind of experience is why I often tell my trainees that your first ten years as a surgeon are focused on developing your skills and becoming a good surgeon. But what's more challenging afterward is developing good judgment.

**LISA** DEANGELIS

It's also really important to understand that treating the family is an integral part of treating the patient. It's the family who bears the consequences if the person's personality and identity are changed dramatically by their illness. In some ways, the family struggles more than the patient. I've often said to people, "This is going to be harder on you than it's going to be on your spouse," or father, or whoever the patient is. I think that's something that we in the neurology world confront much more frequently than other doctors.

**VIVIANE** TABAR

Yes, that's very insightful. The families do take on a large burden that sometimes leaves me in awe of their generosity. Brain cancers are probably some of the most challenging diseases to deal with.

**LISA** DEANGELIS

You sometimes ask yourself, "How do these people even get out of bed in the morning and face the day?"

> "I think it's absolutely critical to understand what patients really want and to tailor our treatment to their expectations."
>
> –VIVIANE TABAR

## NEW DEVELOPMENTS IN THE FIELD

**LISA** DEANGELIS

Having taken care of people with glioblastoma and malignant brain tumors for more than 30 years, I really have seen a noticeable improvement in the quality of life for people who live with these diseases. One reason is newer drugs, such as temozolomide [Temodar®], which is much less toxic than prior chemotherapies and better tolerated. Also, the addition of bevacizumab [Avastin®] has helped patients avoid corticosteroids for brain edema or swelling and the attendant side effects. That's been very gratifying and enabled patients and families to make the best use of whatever time they have left.

The other thing that's changed is that there are people who are living many years with this illness. That's not something that we saw — or saw very rarely — in the '80s and '90s. It's important to understand that the proportion of these people is very small. And the fact that we haven't substantially prolonged life for more patients is the most important problem that we struggle with. But those people who live for six or seven years after treatment often do extraordinarily well. They are able to work and enjoy life. That's a dramatic change.

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> "It's also really important to understand that treating the family is an integral part of treating the patient. It's the family who bears the consequences if the person's personality and identity are changed dramatically by their illness."
>
> –LISA DEANGELIS


**VIVIANE** TABAR

In the neurosurgery department, we've evolved over the last ten years to put a greater focus on offering surgery while maximizing function. That's in part because of technologies that I expect will continue to evolve and allow us to offer people more options. Take, for example, patients who suffer from brain metastases, when cancer spreads from another part of the body. Traditionally they were told that their life expectancy was a year or less, and I would admit that they perhaps received less attention from surgeons in the past. But today, we often focus our discussion on what surgery can do to improve quality of life. If a patient suffers from a weak leg or a weak arm, we are more likely to offer them surgery if we think that it can help them overcome that deficit, even if we cannot impact life expectancy.

> "In the neurosurgery department, we've evolved over the last ten years to put a greater focus on offering surgery while maximizing function."
>
> –VIVIANE TABAR

## THE IMPORTANCE OF TREATMENT

**LISA** DEANGELIS

We've seen in both of our disciplines, whether with primary or metastatic tumors, that there can be recovery of function. Particularly with primary tumors, I think there was a lot of therapeutic nihilism associated not only with the fact that these are difficult cancers to treat but also with the long-held belief that people could not recover neurologically. If they were left severely compromised from a functional point of view, what was the point?

But in fact we have learned that with multiple means of treatment — surgery, radiation, chemotherapy — patients with very considerable deficits can make substantial recoveries and have a very meaningful return of function. That's been a paradigm shift and is very encouraging therapeutically.

**VIVIANE** TABAR

Improving function also allows some people to be eligible for more-aggressive treatments, for clinical trials or new drugs. I think that's where strides are going to be made. Gains at the individual level and for a subset of patients are going to move the field forward.

## WHAT SETS MSK APART

**LISA** DEANGELIS

MSK is about the people. It's about the team. We have a fantastic multidisciplinary, collaborative team — people with deep expertise in their respective fields, such as neurosurgery, radiation oncology, neural pathology and neural imaging, and so on.

We work incredibly well together, which doesn't mean that we always agree with each other. In fact, some of the most valuable exchanges are when we don't agree. Somebody will bring another consideration to the table that makes you think about a problem or see a patient from a different perspective, and you realize that perhaps you haven't considered every aspect of things.

I'm absolutely convinced that this is all to the benefit of the patient. There is no question in my mind that what we bring to the table collectively far exceeds the sum of the individual parts.

**VIVIANE** TABAR

I agree. The depth of expertise and dedication of my colleagues at MSK is really what keeps me and my patients afloat. There's great comfort in being able to discuss a challenging case with the group. To listen to the input of people with deep experience as well as younger people who have a different perspective — people who have one foot in the lab and one foot in the clinic, or those who are willing to challenge the norm.

It's also very inspiring to be surrounded by not only clinical and scientific excellence but also people with genuine dedication to the patient. It's no secret to all of us that this is a challenging job, particularly caring for people with brain tumors. We lose a lot of patients. It would be terrifying if you didn't have your colleagues next door.

When we are facing a difficult surgery or a difficult outcome from surgery, it's very reassuring to us and to the patient to be able to reach out to our neuro-oncologists, who sort of pick up the person where he or she landed and move them to the next phase. That provides not only support to each other but also support to the patient, giving a different perspective and usually a positive outlook on what's to come.

**LISA** DEANGELIS

Our nurses and nurse practitioners are a critical component of this. They're very much a part of our team. We are so fortunate to have an incredible nursing workforce here, including the floor nurses and the advanced practice nurses. Nurses are our front line to patients — we jointly share that focus on addressing patient and family needs.

**VIVIANE** TABAR

Yes. It's the norm for me if I get a thank-you note from a patient that also refers to my nurse.

**LISA** DEANGELIS

Absolutely.

**VIVIANE** TABAR

They are an invaluable component of what we do. And I think the patients definitely appreciate it. Our nurses contribute to patients' well-being throughout their hospital stay and afterward.

The patients definitely appreciate the team effort among doctors too. It's not uncommon for us to say to patients, "Well, let me discuss this with my colleagues and we'll get back to you." I enjoy when the patient is a little incredulous that you get back to them the following day with an opinion from several experts that would have taken maybe a few months to get individual appointments with. That model works extremely well between our two departments.

**LISA** DEANGELIS

Our global team approach is so different from other institutions that it does sometimes take patients and families a little bit of time to acclimate to it. But I think they rapidly come to appreciate the benefit of it. ■

> "There is no question in my mind that what we bring to the table collectively far exceeds the sum of the individual parts."
>
> –LISA DEANGELIS

INTERVIEW WITH

**LEE** ERICKSON
*Deputy Physician-in-Chief for Clinical Operations*

**CHRISTIAN** OTTO
*Director of Teleoncology*

Telemedicine uses electronic communications such as video conferencing and secure email to provide care without an in-person visit. Here, Lee Erickson, Deputy Physician-in-Chief for Clinical Operations, speaks with Christian Otto, Director of Teleoncology, about this burgeoning field at MSK. They both joined MSK in early 2017.

## A BOLD NEW TAKE ON CARE

**LEE** ERICKSON

Implementing telemedicine is about a bigger paradigm shift. We want to move the majority of cancer care out of the healthcare setting entirely. Instead of making you come to us, we'll come to you. If we can turn this whole model inside out, it'd be amazing.

**CHRISTIAN** OTTO

Telemedicine can have a significant impact on quality of life. When patients feel unwell and we're asking them to travel, that can be challenging. We're also seeing data showing survival benefits. For example, take a study done by [MSK epidemiologist] Ethan Basch that was presented at the American Society of Clinical Oncology annual meeting in June 2017.

**LEE** ERICKSON

It showed five months of additional survival just from having patients report their symptoms to their physician.

Lee Erickson (*right*) and Christian Otto are bringing new and existing technologies to MSK to allow patients to receive care virtually.

**CHRISTIAN** OTTO

And that's only one component of symptom monitoring at home. We haven't even added coaching, in which nurses educate patients on corrective behaviors, or the collection of biomedical data. What if we were able to identify an infection early by following our patients' temperatures, and then start antibiotics several days earlier?

**LEE** ERICKSON

I've read about gadgets being worked on that do simple lab tests through your smartphone. Prick your finger and instead of putting the blood into a glucose machine, it's a little insert that goes into your phone.

**CHRISTIAN** OTTO

These tools give a full picture of how the patient is doing. It's being present almost 24-7 versus an oncologist receiving a call when the patient is having a challenge.

## TELEMEDICINE IN ACTION

**LEE** ERICKSON

Patients at the Josie Robertson Surgery Center use a program within our patient portal to report how they're doing once they're home, and they seem very happy with it. Say we send you a message every day asking how your pain is, and on day three you text us and say, "Shouldn't I be feeling better by now?" We've actually accumulated enough data to show you a chart for pain that's normal, and you can compare yourself against it. Patients like it. They feel safer and more connected.

**CHRISTIAN** OTTO

I think there's a level of comfort in it. At MSK, we have implemented a falls prevention program that patients are asked if they'd like to participate in. It involves having a camera in the room that lets the nursing staff monitor the patient. You can place a virtual border around the patients who are at high risk for falls so that an alarm sounds if they try to get up unassisted.

**LEE** ERICKSON

Then the person watching the monitor can say to the patient through the system, "I'll come help you."

**CHRISTIAN** OTTO

In the first eight months of a pilot on the fourth floor of Memorial Hospital, patient falls decreased by 50 percent. It's solving a real issue that poses a danger to patients.

## MAKING APPOINTMENTS EASIER

**CHRISTIAN** OTTO

I think we will get to a place where the majority of preoperative assessments, symptom management, oncology follow-ups, postoperative wound checks, and discussion of results could be done via telemedicine. And on the other side, there are Uber-like services that go to the patient's home.

**LEE** ERICKSON

We had a patient who had his blood drawn at his kid's Little League game.

**CHRISTIAN** OTTO

We're not trying to do away with face-to-face interaction. We really want to supplement the times that we're not with a patient, and perhaps make some of their appointments easier by having them stay home.

## LOOKING AHEAD

**CHRISTIAN** OTTO

First, we're expanding telemedicine across our Manhattan sites. Then we're moving into the regional sites. We have a number of pilots in services like genetics and psychiatry. Our third prong is going to the patient's home.

**LEE** ERICKSON

I think of it like smartphones. In the beginning, they were this really expensive thing for people with disposable income. But we hit a tipping point, and it changed the culture. A similar thing needs to happen in healthcare. When we hit another tipping point, I think we're in for some major disruption.

**CHRISTIAN** OTTO

We've been able to begin pilots in Manhattan, the regional care network, and patients' homes. I think there's so much momentum because of the can-do attitude here.

**LEE** ERICKSON

The can-do attitude around this place is pretty amazing. ■

"We've been able to begin pilots in Manhattan, the regional care network, and patients' homes. I think there's so much momentum because of the can-do attitude here."

–CHRISTIAN OTTO

# DRIVING CANCER CARE

Going the extra mile for people affected by cancer is what Ansar Mohammed and Luther Nickelson do best. They are part of a team of 36 shuttle drivers who, on any given day, transport 750 patients, caregivers, and staff to MSK's facilities throughout Manhattan. They also deliver critical medicines, supplies, and patient samples.

Driving patients and families between appointments means they often share personal moments with their passengers. Some of those experiences, like enduring a challenging treatment session or receiving a life-changing diagnosis, are understandably tough. "I can't shy away from this part of my job," Mr. Mohammed says. "I make sure my passengers know I will take care of them. Their doctors and nurses will take care of them. We are all in this together."

But there are many positive moments too. "When I first started three years ago, I was driving a woman who started singing a song that came on the radio," Mr. Nickelson recalls. "She was singing with such passion, and when I looked in the mirror, I saw tears streaming down her face. She was happy. She had just gotten good news, and it was a healing song. That's what MSK is about — it's a healing place."

Both men are proud to be part of the more than 17,000 scientists, doctors, nurses, and support staff who make up the MSK community. Whether it's offering words of encouragement during a ride between appointments, making groundbreaking scientific discoveries, or providing unmatched patient care, the focus is clear, Mr. Mohammed says: "We all come to work each day to help." ■

> **"I make sure my passengers know I will take care of them. Their doctors and nurses will take care of them. We are all in this together."**
>
> **–ANSAR MOHAMMED**


*Left*: Ansar Mohammed (*left*) and Luther Nickelson in front of MSK's 53rd Street patient shuttle. *Above left*: Mr. Mohammed, Mr. Nickelson, and manager Paul Adamec. *Above right*: Mr. Mohammed in the driver's seat.

# STATISTICAL PROFILE

## PATIENT CARE

| | 13 | 14 | 15 | 16 | **17** |
|---|---|---|---|---|---|
| **Patient Admissions: Adults** | 20,773 | 20,640 | 21,064 | 21,708 | **21,953** |
| **Patient Admissions: Children** | 1,553 | 1,504 | 1,403 | 1,370 | **1,553** |
| **Total Admissions** | 22,326 | 22,144 | 22,467 | 23,078 | **23,506** |
| **Total Patient Days** | 144,345 | 146,855 | 151,827 | 160,072 | **161,661** |
| **Average Patient Stay (days)** | 6.5 | 6.6 | 6.8 | 6.9 | **6.9** |
| **Bed Occupancy Rate** [1] | 83.0% | 84.3% | 90.9% | 92.5% | **94.3%** |
| **Outpatient MD Visits: Manhattan** | 463,724 | 480,260 | 489,897 | 512,142 | **526,006** |
| **Outpatient MD Visits: Regional Network** | 108,198 | 113,699 | 136,506 | 153,451 | **196,232** |
| **Total Outpatient Visits** | 571,922 | 593,959 | 626,403 | 665,593 | **722,238** |
| **Screening Visits** | 12,826 | 10,282 | 22,403 | 23,497 | **31,683** |
| **Surgical Cases** | 20,465 | 20,420 | 21,368 | 23,066 | **25,330** |
| **New Radiation Oncology Patients Starting Treatment: Manhattan** | 4,031 | 4,268 | 4,408 | 4,831 | **5,283** |
| **New Radiation Oncology Patients Starting Treatment: Regional Network** | 2,653 | 2,714 | 3,017 | 3,399 | **4,510** |
| **Diagnostic and Interventional Radiology Procedures** | 416,360 | 435,501 | 466,848 | 498,372 | **543,322** |
| **Clinical Investigation Protocols** [2] | 735 | 776 | 879 | 1,072 | **1,133** |

(1) Based on adjusted bed count
(2) Excludes studies closed to accrual

| | 13 | 14 | 15 | 16 | **17** |
|---|---|---|---|---|---|
| **STAFF** | | | | | |
| **Sloan Kettering Institute Members** | 143 | 140 | 140 | 131 | **133** |
| **Hospital Attending Staff** | 935 | 995 | 1,033 | 1,091 | **1,148** |
| **Registered Nurses** | 2,221 | 2,373 | 2,605 | 2,864 | **3,721** |
| **Administrative and Support Staff** | 9,707 | 10,223 | 10,965 | 11,638 | **12,325** |
| **Total Staff** [1] | 12,975 | 13,699 | 14,711 | 15,697 | **17,301** |
| **Volunteers** | 1,004 | 902 | 967 | 943 | **1,019** |
| **EDUCATION** | | | | | |
| **Residents and Clinical Fellows: Positions** | 464 | 465 | 464 | 468 | **468** |
| **Residents and Clinical Fellows: Annual Total** | 1,691 | 1,674 | 1,723 | 1,734 | **1,749** |
| **Research Fellows** | 323 | 351 | 355 | 344 | **346** |
| **Research Scholars** | 133 | 110 | 98 | 92 | **120** |
| **Research Associates** | 91 | 95 | 110 | 112 | **115** |
| **Graduate Research Assistants** | 41 | 47 | 47 | 43 | **37** |
| **PhD Candidates** | 227 | 239 | 265 | 292 | **278** |
| **MD/PhD Candidates** | 19 | 18 | 20 | 26 | **24** |
| **Registrants in CME Programs** | 3,681 | 5,614 | 3,581 | 4,724 | **6,098** |
| **Medical Observers** | 630 | 579 | 574 | 563 | **511** |
| **Medical Students** | 392 | 505 | 548 | 569 | **577** |
| **Nursing Students** | 179 | 257 | 312 | 351 | **355** |
| **Social Work Students** | 7 | 7 | 4 | 8 | **7** |
| **Radiation Oncology Technology Students** | 15 | 15 | 15 | 12 | **12** |
| **Physical Therapy Students** | 2 | 6 | 5 | 5 | **6** |
| **Occupational Therapy Students** | 2 | 3 | 2 | 2 | **2** |
| **Laboratory Medicine Students** | 9 | 9 | 18 | 20 | **13** |

(1) In 2017, 26 staff members held appointments in both the institute and the hospital.

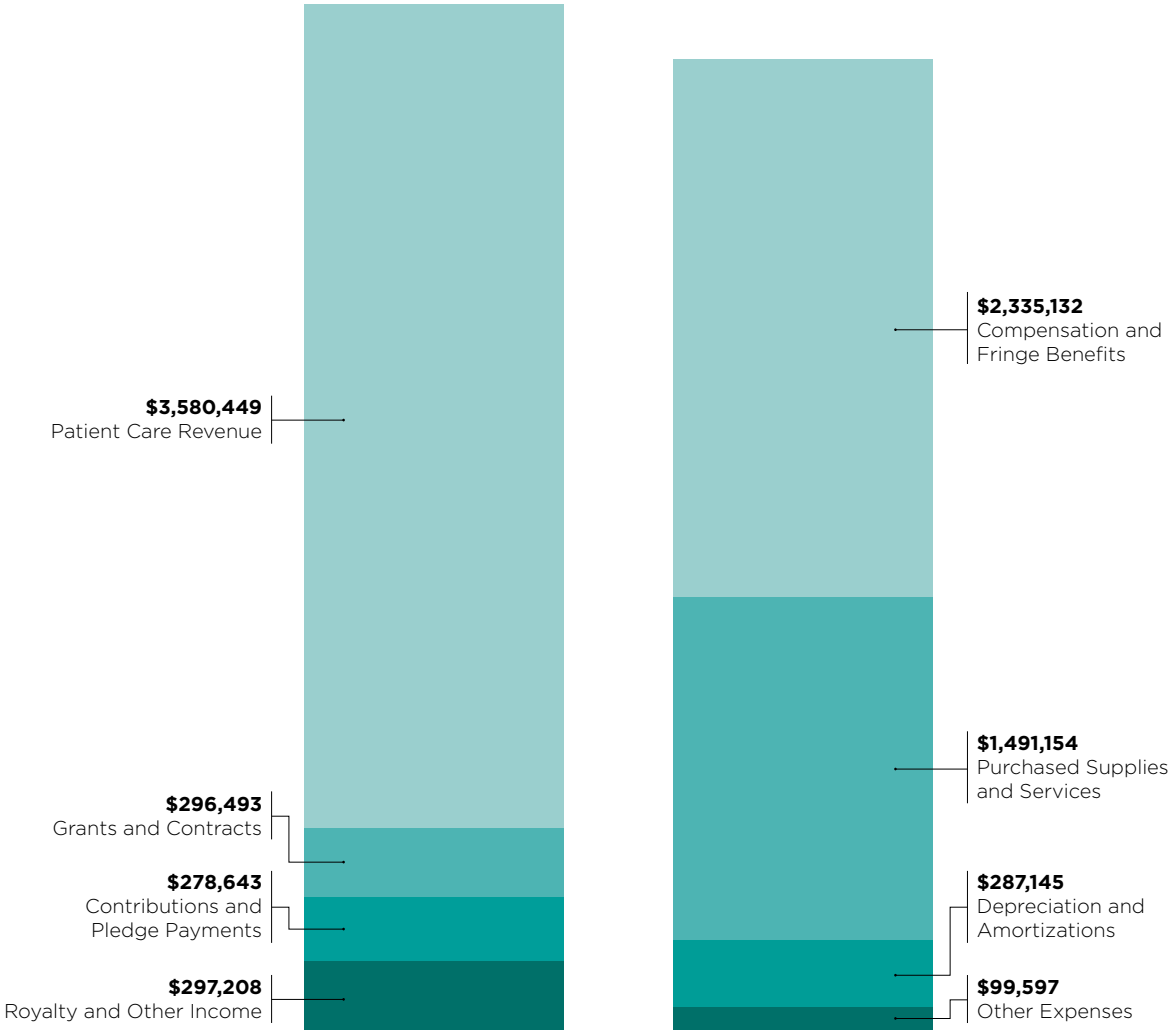
## FINANCIAL SUMMARY

### 2017 TOTAL OPERATING REVENUE
(in thousands)

**$4,452,793**

### 2017 TOTAL OPERATING EXPENSES
(in thousands)

**$4,213,028**



| | 13 | 14 | 15 | 16 | **17** |
|---|---|---|---|---|---|
| **OPERATING REVENUE** (in thousands) | | | | | |
| Patient Care Revenue | $2,367,731 | $2,560,457 | $2,809,813 | $3,094,461 | **$3,580,449** |
| Grants and Contracts | 202,061 | 229,562 | 234,402 | 257,893 | **296,493** |
| Contributions | 138,343 | 168,797 | 137,538 | 161,245 | **191,843** |
| Net Assets Released from Restrictions — Pledge Payments | 79,199 | 103,112 | 129,528 | 86,850 | **86,800** |
| Royalty and Other Income | 208,703 | 241,238 | 273,556 | 242,934 | **159,458** |
| Unrestricted Investment Return Allocated to Operations | 82,028 | 87,917 | 90,648 | 136,979 | **137,750** |
| Total Operating Revenue | $3,078,065 | $3,391,083 | $3,675,485 | $3,980,362 | **$4,452,793** |
| **OPERATING EXPENSES** | | | | | |
| Compensation and Fringe Benefits | $1,689,501 | $1,782,477 | $1,987,388 | $2,131,070 | **$2,335,132** |
| Purchased Supplies and Services | 924,691 | 1,062,603 | 1,172,467 | 1,311,764 | **1,491,154** |
| Provision for Bad Debts and Assessments | 19,969 | 35,859 | 64,194 | 35,003 | **54,254** |
| Depreciation and Amortizations | 210,373 | 217,342 | 232,866 | 263,964 | **287,145** |
| Interest Expense | 55,039 | 50,147 | 49,401 | 48,724 | **45,343** |
| Total Operating Expenses | $2,899,573 | $3,148,428 | $3,506,316 | $3,790,525 | **$4,213,028** |
| **INCOME FROM OPERATIONS** | $178,492 | $242,655 | $169,169 | $189,837 | **$239,765** |
| **PHILANTHROPIC REVENUE** | $380,500 | $376,533 | $276,747 | $317,270 | **$318,386** |
| **CAPITAL SPENDING** | $315,282 | $473,859 | $710,873 | $634,134 | **$737,965** |
| **BALANCE SHEET SUMMARY** | | | | | |
| Assets | $8,481,418 | $8,963,268 | $9,592,021 | $9,891,492 | **$10,636,012** |
| Liabilities | 3,337,444 | 3,596,860 | 4,058,058 | 4,160,515 | **4,530,909** |
| Net Assets | $5,143,974 | $5,366,408 | $5,533,963 | $5,730,977 | **$6,105,103** |

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# MEMORIAL SLOAN KETTERING DEVELOPMENT: THE MOMENTUM CONTINUES

MSK's fundraising operation maintained strong forward momentum during the course of 2017, building on the many achievements of the Campaign for Memorial Sloan Kettering. The Campaign, which officially concluded on December 31, 2016, compiled a record of historic success under the leadership of Co-Chairs Douglas A. Warner III and Louis V. Gerstner, Jr., along with MSK President and CEO Craig B. Thompson.

*Clockwise from top left*: Douglas A. Warner III, Louis V. Gerstner, Jr., Craig B. Thompson, and a Cycle for Survival event in Bethesda, Maryland.

New gifts and pledges to MSK for 2017 totaled $344.5 million, a 12.1 percent increase over the year before. Of that amount, $330.3 million were cash gifts.

Dedicated benefactors at all levels contributed to this impressive success. Of the many gifts received, the following stand out for the impact they are having on the institution:

- Alan and Sandra Gerry's commitment of $15 million to create the Alan and Sandra Gerry Metastasis and Tumor Ecosystems Center, which brings their total support for this vital area of research to $25 million
- a pledge of $12.5 million from Board member Stephen Friedman and his wife, Barbara, through their foundation to create the Friedman Family Foundation Functional Genomics Initiative
- the Olayan Group's commitment of $10 million to establish a precision pediatrics cancer medicine program
- a $10 million pledge from the Warren Alpert Foundation to create the Warren Alpert Center for Digital and Computational Pathology
- $7 million from the estate of Mamdouha S. Bobst, which brings the total received from Mrs. Bobst's estate to $29 million

As in past years, MSK also benefited significantly from the energy and dedication of thousands of volunteers who took part in athletic fundraisers. Cycle for Survival, which ranks as the fastest growing athletic fundraiser in the country, attracted 31,000 participants in 16 cities across the United States and internationally, in the process raising $35 million for rare cancer research. And in November, 875 runners participated in the TCS New York City Marathon as members of Fred's Team and raised more than $5.3 million to fund research at MSK.

Continuing at the helm of the MSK development team in 2017 were Anne M. McSweeney, Special Advisor to the President for Development, and Senior Vice President Richard K. Naum, who over a span of years built MSK's fundraising office into one of the best in the country. The operation is well positioned to support the continued growth in strength and stature of all three aspects of the institution's mission as MSK leads the way into a new era in cancer medicine. ■

# DONORS TO MEMORIAL SLOAN KETTERING

JANUARY 1, 2002–DECEMBER 31, 2017

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David H. Koch

**$100,000,000–$199,999,999**

The Estate of Geoffrey Beene
Mr. and Mrs. William H. Goodwin, Jr., and the Commonwealth Foundation for Cancer Research
Henry and Marie-Josée Kravis
The Starr Foundation
Mortimer B. Zuckerman

**$50,000,000–$99,999,999**

Stanley F. and Fiona Druckenmiller
The Leonard and Evelyn Lauder Foundation
Virginia and D. K. Ludwig Fund for Cancer Research
Robertson Foundation

**$25,000,000–$49,999,999**

The Atlantic Philanthropies
The Elmer and Mamdouha Bobst Foundation
The Breast Cancer Research Foundation
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Steven A. Greenberg Charitable Trust
The Sidney Kimmel Foundation
Parker Institute for Cancer Immunotherapy
Prostate Cancer Foundation
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Stand Up To Cancer
The Tow Foundation

**$20,000,000–$24,999,999**

Anonymous
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## SUPPORTING RESEARCH

The Society of Memorial Sloan Kettering's Special Projects grants fund innovative research at the Sloan Kettering Institute that is often too nascent to receive support from conventional sources. This year, the grants were awarded to five scientists conducting research in developmental biology, immunology, and computational biology.

Each spring, The Society also awards research grants that specifically focus on providing crucial funding to MSK's promising young investigators. In 2017, the grants were awarded to eight projects, including a study involving diet and obesity and their effect on breast cancer risk, a project exploring the mysteries of cancer metastasis, and a type of radiation therapy for advanced malignant pleural mesothelioma.

The Society's Associates Initiative focused on the effort to establish a new standard of care for pediatric cancer survivors. The number of children surviving cancer is increasing, but the treatments that help these children survive their cancer can have a lasting negative impact, leading to learning disabilities as well as social-emotional and behavioral difficulties. Some children, free of cancer, then face challenges with attention and concentration, processing speed, memory, and social isolation — leading to lowered overall quality of life.

MSK's researchers are seeking ways to identify specific groups of pediatric cancer patients at diagnosis that are at an increased risk for these issues and are implementing home-based computerized cognitive training programs immediately after finishing treatment to minimize ill effects.

The Society's Campaign focused on precision cancer prevention. Launched by Luis Diaz, Head of the Division of Solid Tumor Oncology, the Precision Interception and Prevention initiative is developing ways to tailor cancer prevention and early detection based on an individual's genetic, lifestyle, and environmental risk factors. The goal is to prevent cancer from ever occurring or to intercept it at its earliest stages, maximizing the chance of a cure.

The Society Prize is awarded at the annual MSK Academic Convocation to a researcher, doctor, or team leader who has made a positive and lasting impact in the fight against pediatric cancer. The 2017 recipient of this prize was James Downing, President and CEO of St. Jude Children's Research Hospital in Memphis. Among his many accomplishments, he has had a major influence on defining the genetics and genomics of pediatric cancers. Dr. Downing was instrumental in launching the Pediatric Cancer Genome Project, which has compared the complete genomes from the cancerous and normal cells of more than 800 young patients.

## SUPPORTING PATIENT CARE

Some of the most cherished traditions and events at MSK — including the festive holiday parties held throughout the year, complete with overflowing gift bags for patients — are sponsored by The Society. This year was no different, with more than 200 of our youngest patients and their families and friends at Pediatric Prom in May.

## SUPPORTING EDUCATION

Established in 2016 and first awarded in 2017, The Society Scholars Prize is intended to honor postdocs performing at the highest levels who are also managing additional familial obligations and adjusting to being new parents.

This merit-based prize is awarded annually to at least ten full-time postdoc researchers who complete a brief application and personal statement. They are reviewed by a selection panel made up of MSK faculty parents, with final approval from The Society president in consultation with its executive committee. The prize provides a cash award for up to four years and is open to postdocs at MSK who have a dependent child under four years of age. ■

> "The Society is a group of dedicated, caring women. It is absolutely necessary that we continue to support the incredible strides Memorial Sloan Kettering Cancer Center has made through its research and patient care initiatives."
>
> –JAMEE GREGORY

1. Society President Jamee Gregory and Madison Avenue Business Improvement District President Matthew Bauer at the 31st Miracle on Madison Avenue shopping event benefiting The Society of MSK on December 2.
2. Pediatric oncologist Farid Boulad, Medical Director of the Pediatric Day Hospital, with a young friend at Pedatric Prom.
3. *From left*: Physician-in-Chief José Baselga, Silvia Garriga, Board Chair Douglas Warner, former Society President Lavinia Branca Snyder, Roser Salavert, Sloan Kettering Institute Director Joan Massagué, Tullia Lindsten, and MSK President and CEO Craig Thompson at The Society's Spring Ball.
4. *From left*: Kristin Allen, Walter S. Tomenson III, Deborah DeCotis, Kirk Henckels, Jamee Gregory, Eugenie Niven Goodman, Mindy Webster, Benjamin Stokes, and Samuel Goldworm at The Society's Special Projects Dinner.

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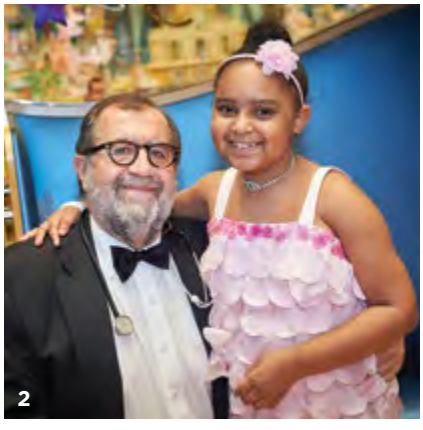
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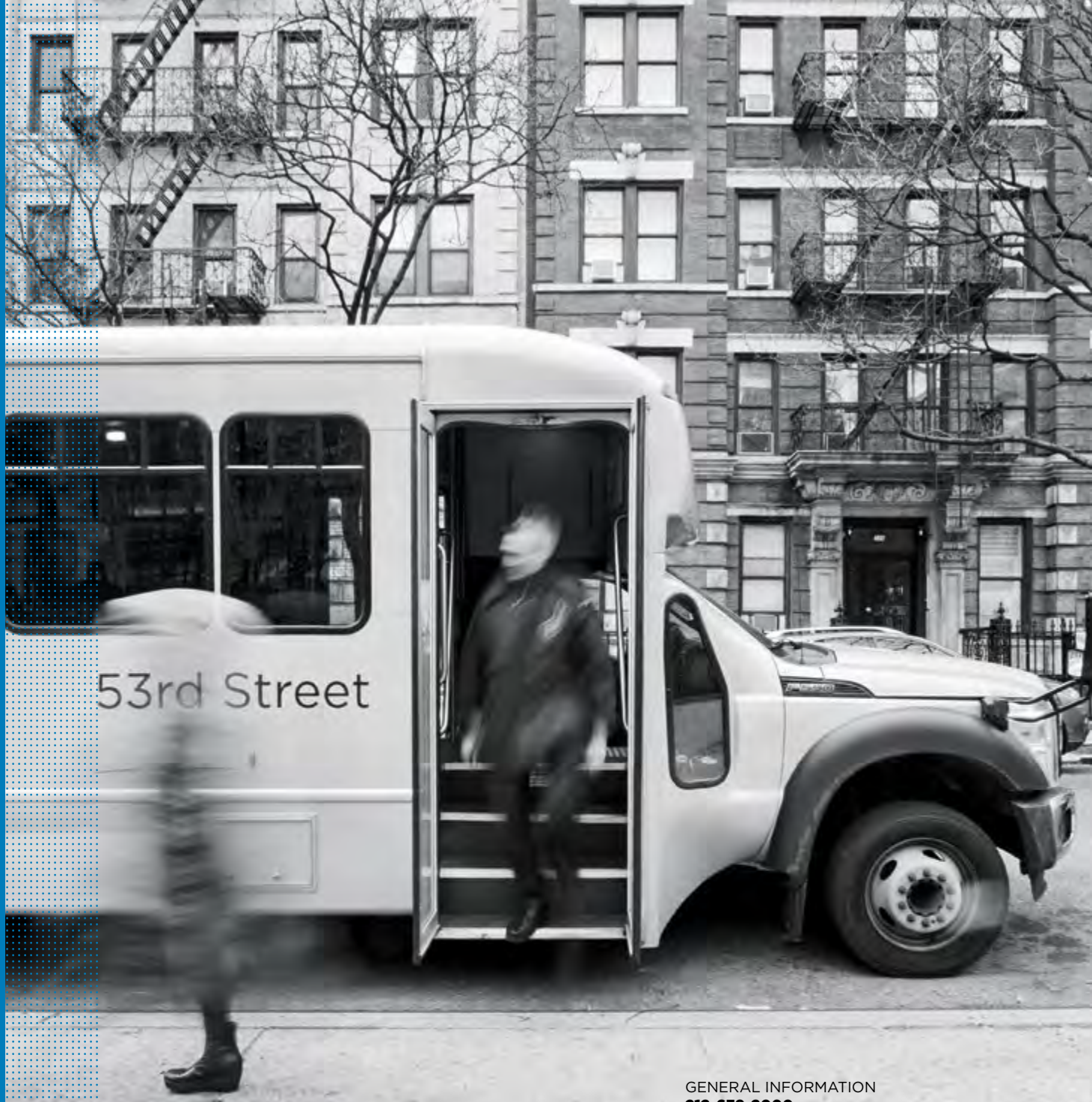


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