
WE'RE CHANGING HOW THE WORLD TREATS CANCER.



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CONTENTS

Message from the Chairman
and the President **03**

**WE'RE CHANGING HOW
THE WORLD TREATS CANCER BY
BUILDING
RELATIONSHIPS** **06**

**WE'RE CHANGING HOW
THE WORLD TREATS CANCER WITH
BOLD
ADVANCES** **16**

**PIONEER/PRIME MOVER:
JOHN GUNN**

**30 YEARS OF
CHANGING HOW
THE WORLD
TREATS CANCER** **42**

Statistical Profile **50**

Financial Summary **52**

Boards of Overseers and Managers **54**

Leadership **55**

Facilities Update **57**

The Campaign for
Memorial Sloan Kettering **58**

Donors to the Campaign for
Memorial Sloan Kettering **59**

The Society of Memorial
Sloan Kettering Cancer Center **72**

CHANGING HOW THE WORLD TREATS CANCER HAS A DOUBLE MEANING AND A RIPPLE EFFECT.

It denotes making groundbreaking discoveries and practice-changing treatment advances. It also suggests sharing that knowledge with as many people as possible.

At Memorial Sloan Kettering, we've created new ways to facilitate more discoveries, even more rapidly. We've also put in place creative new approaches to sharing — reaching within our own walls and beyond them to move what we know about cancer research, treatment, and care delivery into an ever-expanding universe of patients and fellow clinicians and scientists.

We aspire to touch the lives of as many patients as possible and to forge new collaborations with colleagues who will join with us in changing how the world treats cancer.

Message from the Chairman and the President



CRAIG THOMPSON

President and
Chief Executive Officer

DOUGLAS WARNER III

Chair, Boards of Overseers
and Managers

The theme of our Annual Report this year is *It's time we changed how the world treats cancer*. At MSK, we're making decisive progress toward this goal, transforming how research is done, how care is delivered, and how treatments are personalized to each individual's disease. In fact, changing how the world treats — and thinks about — cancer has been our mission for more than 130 years.

Today, scientific discovery in all its forms is constantly yielding new understanding of human biology. We now have the tools, technologies, and therapies to improve cancer prevention, diagnosis, and treatment. Much of this will come to life in the following pages.

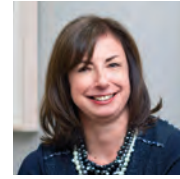
Among the innovative ways in which we're reshaping the conversation around cancer is through an array of new relationships and collaborations.

In 2014, the Hartford HealthCare Cancer Institute (HHCCI) became the first member of the MSK Cancer Alliance, an initiative designed to collaboratively guide community providers toward state-of-the-art cancer care. The concept emerged out of an awareness that community oncologists deliver the vast majority of cancer care in the United States, but that advances in treatment and research can take years to reach patients.

Among several distinctive aspects of the partnership is the establishment of an MSK Cancer Alliance clinical trials site, which will give physicians at HHCCI the opportunity to offer our pioneering clinical trials to their patients in Connecticut. (Read more about the MSK Cancer Alliance on page 9.)

Our basic-science, translational, and clinical-research enterprises excelled in 2014. New cross-disciplinary initiatives and collaborations both within MSK and beyond its walls contributed to advancing discovery.

The establishment of the Functional Genomics Initiative (FGI) is an effort to analyze the data produced by the Marie-Josée and Henry R. Kravis Center for Molecular Oncology (CMO). The CMO speeds the process by which genetic discoveries made through tumor analysis can be used to produce more-precise treatments for people with cancer. The FGI draws on the expertise of scientists and physicians in fields as diverse as stem cell science, molecular biology, and infectious disease to test new theories based on the genetic information flowing from the CMO. (For more on precision medicine, see "Cancer Genes Reveal Their Secrets" on page 10.)



KATHRYN MARTIN
Chief Operating Officer

A new genomic test developed by our researchers called MSK-IMPACT™ allows pathologists to screen more than 340 genes for cancer-causing mutations. In 2015, more than 10,000 MSK patients will have their cancer profiled using this test, which can detect gene mutations and other critical genetic aberrations in both rare and common cancers. The information gained will help physicians select personalized approaches to improve the effectiveness of each patient's treatment.

In addition, we have entered into a collaborative relationship with Quest Diagnostics, a major provider of clinical diagnostic testing services, so that more patients can benefit from MSK's clinical and research insights into genetic mutations associated with solid tumors. The aim is to use molecular laboratory testing to improve physicians' ability to treat patients with breast, prostate, colon, lung, and a variety of other solid tumor cancers by giving them a better understanding of the genomic underpinnings of their patients' illnesses. (Go to page 11 for more details on MSK-IMPACT and our partnership with Quest.)

As we gain a deeper understanding of the role of cellular differentiation and reprogramming in the pathogenesis of cancer, several members of our faculty have developed noteworthy new insights into how our bodies regulate the replacement or regeneration of damaged cells within individual organs. MSK's new Center for Epigenetics Research (CER) will facilitate this work. The CER fosters inquiry in the rapidly growing fields of cancer epigenetics and epigenomics by bringing together MSK scientists and clinicians with different areas of expertise, including basic science discovery, translational cancer research and drug development, and the transfer of new ideas into early-phase clinical trials.

Immunology and immunotherapy are especially dynamic areas at MSK. The year opened with great excitement about the efficacy of reengineering immune cells to treat an aggressive form of leukemia. MSK also played a lead role in the clinical trials that led to FDA approval of new drugs that make it easier for the body's immune system to recognize tumor cells as foreign. In addition, our investigators made important discoveries in areas as diverse as the role of regulatory T cells in controlling the immune system and approaches that might enable immunocompromised patients

to fight bacterial infections. (Find more details on immunotherapy in "T Cell Armies," starting on page 23, and in "Bacteria versus Bacteria," beginning on page 27.)

We are acutely aware of the imperative to develop new models of care delivery that reach more patients and to provide care closer to home that is exactly the same as patients would get if they were treated in Manhattan. In 2014, MSK West Harrison — a beautiful, 114,000-square-foot ambulatory care facility in Westchester County — joined our growing family of suburban locations. This facility, and others like it (including MSK Monmouth, set to open in 2016 to serve residents of the Jersey Shore and beyond) are designed to extend MSK's clinical expertise to local communities.

Today, the majority of people with cancer are able to receive treatment outside a hospital. Even having cancer surgery doesn't necessarily mean that a person has to spend a night in the hospital. Among our responses to this happy reality are two extraordinary new facilities that will allow us to offer the highest quality, state-of-the-art outpatient care to more people.

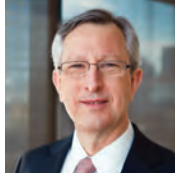
The first to open, in early 2016, will be the Josie Robertson Surgery Center (JRSC). This 16-story building will feature 12 operating rooms equipped to provide technologically sophisticated surgical care, including minimally invasive and traditional open surgeries, both of which can be performed safely and expeditiously on an outpatient basis. Great care has been put into the overall experience and comfort of both patients and caregivers — with private rooms, places to eat, and spaces to socialize, relax, and work — to create an environment specially designed for those who need to stay only a short time. (More details on the JRSC can be found in the Facilities Update on page 57.)

Then, in 2019, we expect to complete construction on the new complex we are developing jointly with The City University of New York/Hunter College on a site located between East 73rd and 74th Streets along the FDR Drive. The complex, for which we have now received all regulatory approvals, will play a critically important role in our outpatient cancer care delivery system.

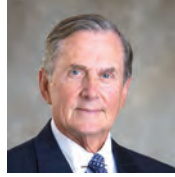
We underwent several important transitions this year, beginning with the retirement of John Gunn, our Chief Operating Officer. He guided MSK for more than



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



JOHN R. GUNN
Executive Vice President

30 years and served three successive presidents as an indispensable colleague and advisor. He has touched the lives of everyone in the MSK community: our staff, our patients and their families, and the city we serve. We owe him a tremendous debt of gratitude and wish him well in the next chapter of his life. (For more on his retirement, in his own words, read the interview “Pioneer/Prime Mover: 30 Years of Changing How the World Treats Cancer,” starting on page 43.)

As much as we will miss John, we have a worthy successor in Kathryn Martin. Formerly Executive Vice President and Chief Hospital Operating Officer, Kathryn joined MSK in 1999 as Senior Vice President and Hospital Administrator after serving in a variety of leadership roles at the New York Hospital before and after its merger with the Columbia Presbyterian Medical Center. Kathryn has been an extraordinary leader of Memorial Hospital, guiding its operations with skill, vision, and creativity, and we know she will continue to demonstrate her deep commitment to our institution.

We’re also delighted that Memorial Hospital Physician-in-Chief José Baselga was elected in 2014 to the Institute of Medicine (IOM). The IOM is a branch of the National Academies and was established to honor professional achievement in the health sciences. Membership is one of the highest honors in the fields of health and medicine. And, in another honor, Dr. Baselga was inaugurated President of the American Association for Cancer Research (AACR) at their annual meeting in April. The AACR is the world’s oldest and largest professional organization dedicated to advancing cancer research.

We are equally excited about the international recognition that Sloan Kettering Institute Director Joan Massagué received this year when he was awarded Spain’s highest scientific honor, the Spanish National

Research Award, in recognition of his contributions to biomedical research. In addition, MSK led the list of most impactful cancer research centers in a ranking published by the prestigious scientific journal *Nature*.

MSK’s 2014 financial results met our expectations. Our operating revenues increased by 9.1 percent compared with our expense growth of 8.4 percent. A portion of the growth resulted from the opening of two new clinical facilities. During February 2015, MSK completed its financing program for the planned major clinical capital expansion (74th Street complex) at very favorable long-term interest rates. (See page 52 for more on MSK’s financials.)

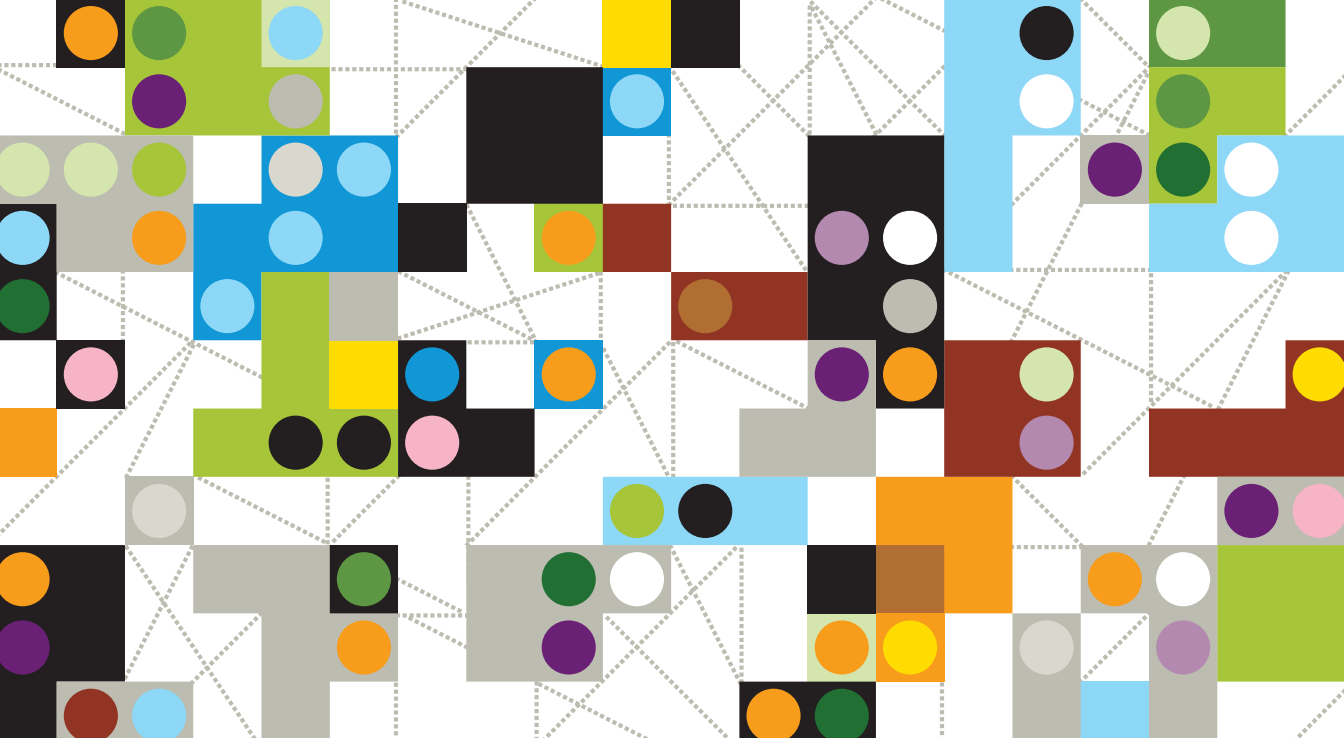
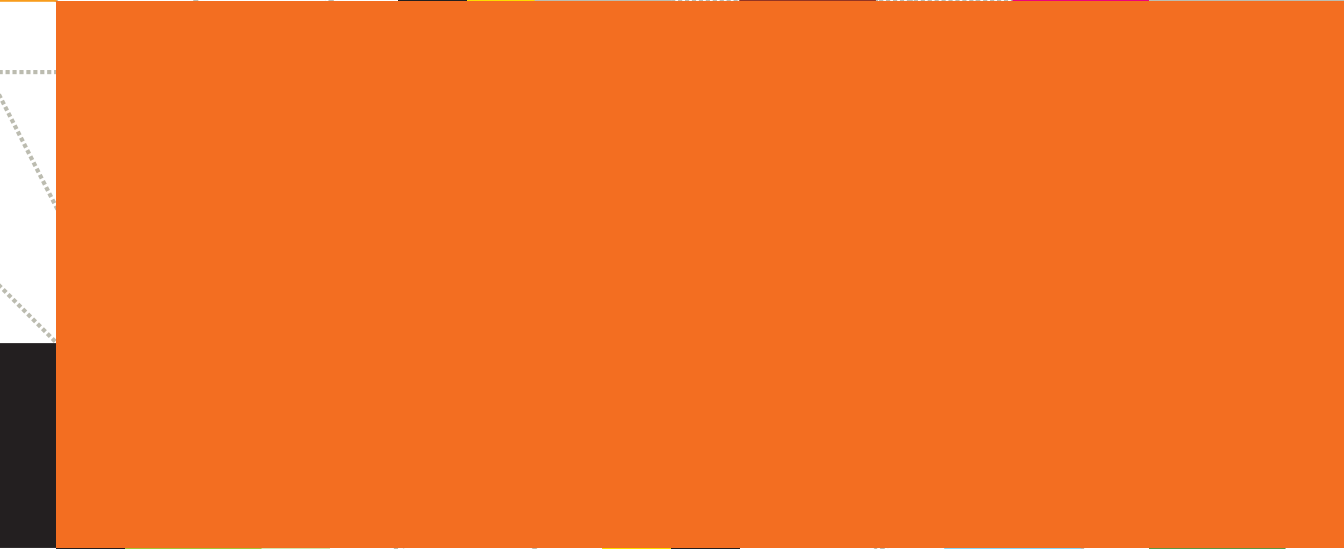
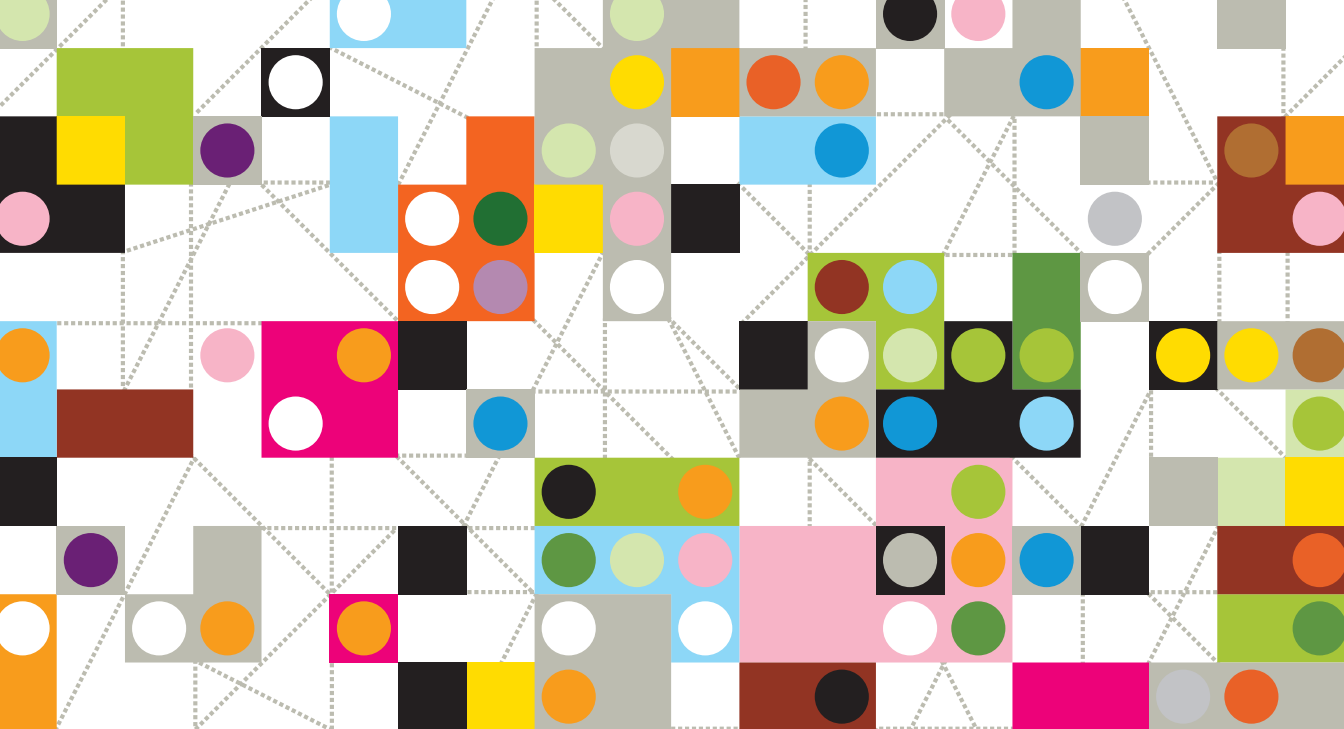
For the 25th consecutive year, MSK was named a top hospital for cancer by *U.S. News & World Report* in its annual listing of Best Hospitals; we led the list as number one, an acknowledgement of our incomparable community. The tireless and selfless contributions of our staff, regardless of their roles within the institution, continue to ensure the highest level of patient satisfaction, clinical and research excellence, and a culture that supports caring, creativity, and discovery.

“More Science. Less Fear.” It’s the core creative concept of our new advertising campaign, launched in September 2014. And it’s really what Memorial Sloan Kettering is all about: defusing the fear surrounding cancer by doing the best basic and clinical science, leading to improved treatments and better outcomes for people with cancer everywhere.

As we advance into the future, our goal is nothing less than to revolutionize the treatment and understanding of the disease. In this year’s Annual Report, you’ll read about some of what we’ve mentioned only briefly in this message and will learn more about the remarkable men and women who are working to change the way the world treats cancer.

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

Craig B. Thompson
President and Chief Executive Officer





WE'RE CHANGING HOW THE WORLD
TREATS CANCER BY

BUILDING RELATIONSHIPS

LAYING OUT THE WELCOME MAT

Today, the majority of people with cancer receive their care outside a hospital. Memorial Sloan Kettering recognized this need for more convenient care as early as the 1990s, when we began establishing a network of suburban locations to bring the comprehensive services and unparalleled expertise of our staff closer to where our patients live and work. Our seventh location, MSK Monmouth, will open in Middletown, New Jersey, in 2016.

While mere miles may separate patients from Manhattan, shortening the physical distance between them and their doctors can mean avoiding a potentially long and often

arduous commute. What it doesn't mean is being separated from the MSK community. Patients at our suburban locations know they're truly part of one family.

In 2014, **MSK West Harrison** — a 114,000-square-foot facility that's home to a staff of 140 cancer surgeons, oncologists, radiologists, and other healthcare professionals — became the newest member to join that family.

"MSK West Harrison enables us to further extend the reach of our extraordinary cancer care, bringing the skill of our staff to patients where they live and work — in a serene, beautiful, and patient-friendly environment," says Craig B. Thompson, MSK President and CEO. "And a key part of our mission is creating strong, long-lasting relationships with the community."

No detail was overlooked in this modern, comfortable space designed to cater to all our patients' needs. Amenities include valet parking, Wi-Fi, a grab-and-go fresh food counter, and a peaceful outdoor garden. And most importantly, MSK West Harrison provides care that is exactly the same as patients would receive if they were treated at any other MSK facility.

Specialized disease management teams offer diagnostic, treatment, and support services to people with breast, gynecologic, gastrointestinal, lung, urologic, and other cancers. MSK's world-class surgeons provide

A light-filled and expansive lobby welcomes patients and caregivers at MSK West Harrison.



pre- and postsurgical care, and patients receive the latest chemotherapy treatments and the most advanced radiation therapies. Other offerings include genetic and nutrition counseling and social-work support.

“West Harrison was designed to extend the culture of MSK from the Manhattan site out to Westchester and the surrounding communities, so that we can bring what we’ve been doing in Manhattan to the local area,” explains Chau Dang, Chief of the Medical Oncology Service at MSK West Harrison.

“When we began thinking about clinicians who might want to work in West Harrison, rather than thinking only about hiring new people who may not be familiar with the MSK culture, we came up with a new model,” adds Richard Barakat, Deputy Physician-in-Chief for MSK’s Regional Care Network and Cancer Alliance. “We have physicians and surgeons and even chiefs of services who have been at MSK — in some cases for many years — who live in the community and who now work at MSK West Harrison. This allows us to truly infuse the MSK multidisciplinary culture into this new facility.”

“Physicians practicing at MSK West Harrison are thought leaders in cancer treatment and research, and many of them developed the current treatment standards in their respective fields,” says José Baselga, MSK’s Physician-in-Chief and Chief Medical Officer.

A wide range of clinical trials are available at MSK West Harrison. These include early-stage studies of novel targeted anticancer drugs and the specialized on-site staff and dedicated lab space that make those trials possible, allowing patients to both receive new treatments and schedule their follow-up appointments at the facility.

“Clinical trials are critical for translating scientific discoveries into new treatments that improve patient care,” says Ephraim Casper, Medical Director of MSK’s Regional Care Network. “For many, clinical trials offer the most promising treatment options available. The opportunity to participate in our trials is one of the special benefits of treatment at MSK, and patients who live in Westchester County, the Hudson Valley, and southwestern Connecticut will have access to the latest clinical trials close to home.”

Adding to patient convenience is an innovative relationship with the multispecialty **Mount Kisco Medical Group (MKMG)**. People receiving treatment at MSK West Harrison can



make appointments with MKMG physicians for non-oncology care, including cardiology, gastroenterology, pulmonology, gynecology, infectious disease, and internal medicine services — all without leaving the building.

CHAU DANG, MD
Chief, West Harrison
Medical Oncology Service

AN ALLIANCE FUELS PROGRESS AGAINST CANCER

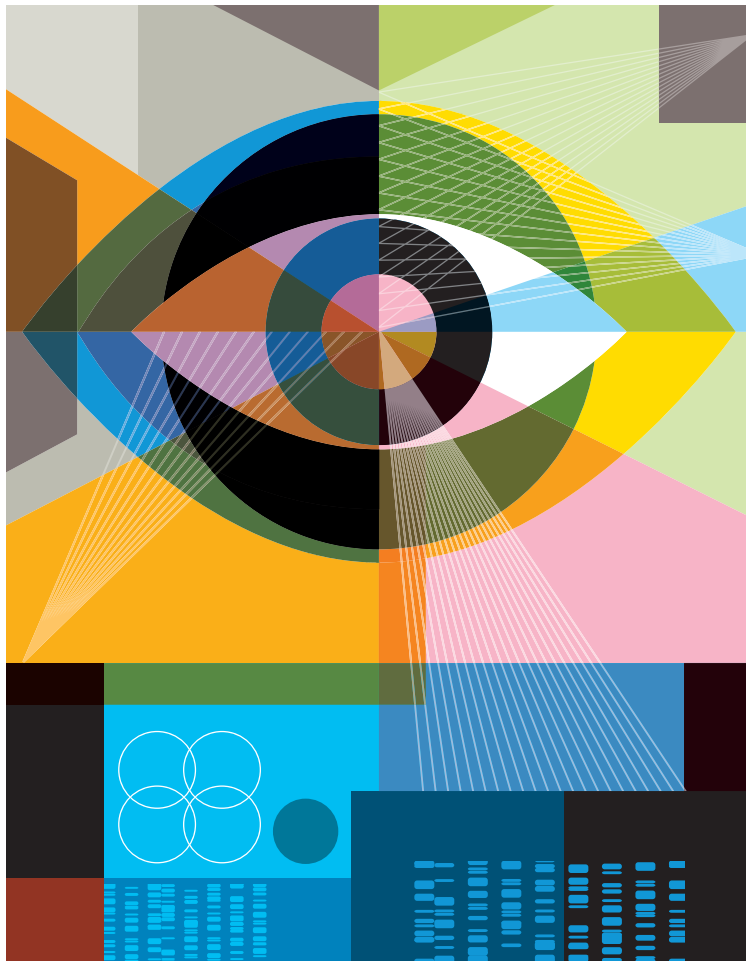
The **MSK Cancer Alliance** reaches beyond the walls of the institution in a different way, addressing the need to help ensure that the newest knowledge about cancer finds its way into the community. “Cancer advances can take years to be adopted in a community setting,” observes Dr. Baselga, who notes that ongoing relationships are needed to effectively close this gap.

A multihospital healthcare system in Connecticut, **Hartford HealthCare (HHC)**, is the pioneering member of the MSK Cancer Alliance, which is designed to rapidly move innovative, evidence-based cancer care into the community setting and to enable bidirectional learning. “We’re building the MSK Cancer Alliance — beginning with our relationship with HHC — in the belief that we have something to learn from one another,” Dr. Thompson says. “This is definitely a two-way street.”

Among the many distinctive aspects of the collaboration will be the establishment of the MSK Cancer Alliance clinical trials site, which will give physicians at the Hartford HealthCare Cancer Institute the opportunity to offer MSK clinical trials to their patients in Connecticut.

“At the end of the day, patients and their families are the motivation behind everything we do,” says Dr. Thompson, “and this means building relationships like the one we’ve built with Hartford to create real change in improving cancer care and extending that care to wider patient populations.” ■

CANCER GENES REVEAL THEIR SECRETS



In order to treat a cancer effectively, you need to know as much as you can about what you're treating. In recent years, it's become clear that certain gene mutations influence the efficacy of cancer drug therapies — and that a therapy that may be effective for one type of cancer may also be useful for other types that share the same mutations.

President Barack Obama's announcement in January 2015 of a precision medicine initiative addresses this issue of individual genetic variability and how its lessons can be applied to disease prevention and treatment across a wide range of conditions — with a near-term focus on oncology.

Oncology is an obvious choice for exploiting the promise of precision medicine. As we learn about each cancer's own tumor-specific genetic features, individualized approaches to diagnosis — and a resulting revolution in treatment — are already becoming a reality. At Memorial Sloan Kettering, we're moving further and further away from the paradigm of treating cancer as if it were one disease. Now, our goal is to treat individual cancers based on their specific mutational profile. But in order to successfully offer mutation-based therapies and strategies of targeted cancer prevention, we need to screen patients for the mutations of interest.

IT'S FOUNDATIONAL

Recently, MSK announced two new partnerships aimed at just that: giving our clinicians — and scientists everywhere — innovative cancer diagnostics. The first, with **Foundation Medicine**, brings together clinical, genomic, and computational expertise to advance patient care in hematologic (blood) cancers. The collaboration has focused on the co-development of a new Foundation Medicine molecular diagnostic product designed to match patients who have leukemia, lymphoma, or myeloma with the most-effective targeted therapies or clinical trials for their individual disease.

The new test — called FoundationOne™ Heme — analyzes blood samples from patients with these cancers and provides information about the hundreds of genes known to be associated with them. This genetic profile helps physicians make more-accurate prognoses and also guides clinical decision-making.

The profile may include data that can help decide whether taking an aggressive approach

with existing drugs is indicated or whether to enroll a patient in a clinical trial investigating a novel therapy.

Medical oncologist Ross Levine led the MSK research that contributed to the development of FoundationOne Heme along with physician-scientists Marcel van den Brink, Ahmet Dogan, and Scott Armstrong. The test now plays a central role in the clinical care of most patients with blood disorders at MSK and, it's expected, will be used in the care of patients throughout the United States.

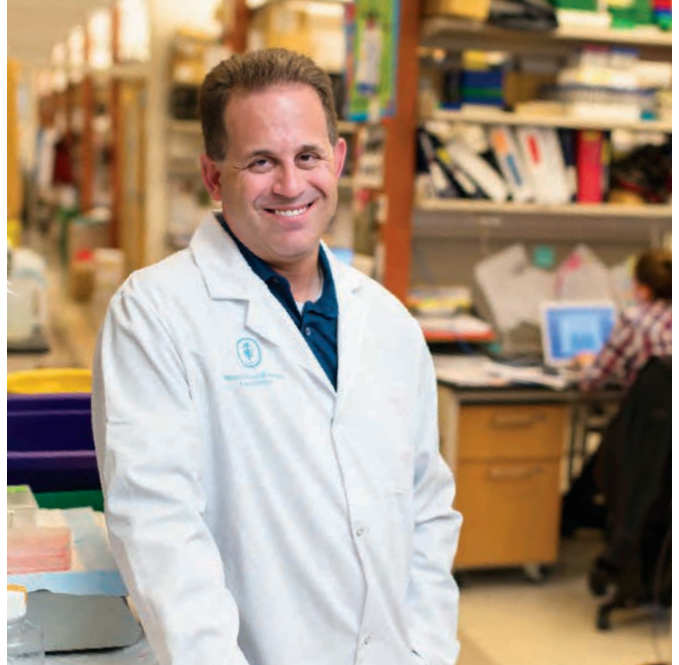
"Our hope is that the test will become available to all patients in the country with these malignancies," says Dr. Levine. "We are excited that we aren't just developing a tool for patients who are treated at MSK but also providing access to state-of-the-art genomics more broadly."

The test analyzes more than 400 cancer-related genes and, unlike most standard tests, looks for alterations in both DNA and RNA. (RNA, one of two types of nucleic acid made by cells, contains information that has been copied from DNA – the other type of nucleic acid. Cells make several different forms of RNA, each with a specific job.) In addition to improving treatment for patients, MSK will use information gleaned from the tests to advance research into blood cancers.

QUESTING FOR MORE- ACCURATE DIAGNOSES

MSK's second partnership is with **Quest Diagnostics**. The world's leading provider of diagnostic information services, Quest will use our clinical and research insights into gene mutations associated with solid tumors. The goal is to employ molecular laboratory testing to improve physicians' ability to treat patients with breast, prostate, colon, lung, and a variety of other solid tumors by giving them a better understanding of the genomic underpinnings of their patients' illnesses.

The collaboration's first phase involves MSK providing contextual information about individual mutations identified as part of Quest's OncoVantage™, a test that enables molecular characterization of solid tumors. MSK has amassed vast databases of gene mutations linked to various types of cancers and has developed pharmaceutical treatments based on the scientific literature, therapies given to our patients, and clinical trials conducted here by our physicians and scientists.



MSK has extensive experience in this area over the past decade and has developed a pioneering test – called MSK-IMPACT™ – that can reliably and accurately screen for mutations in more than 400 genes. Tumors from MSK patients studied thus far have had on average between two and ten potentially actionable mutations; in other words, genomic changes that cause and contribute to a cancer's growth and may respond to therapies targeting these underlying genomic alterations.

Physicians who order OncoVantage will benefit from the MSK data through a joint report designed to aid in the assessment of a patient's progress, as well as to guide treatment selection and monitor disease progression.

"With unprecedented access to MSK's knowledge of gene mutations in solid tumors and the therapies most effective in treating them, this relationship will empower clinicians to improve their patients' health by identifying the best therapies for them and by identifying specific patients who may benefit from participation in clinical trials," says Craig B. Thompson, MSK's President and CEO. "The needs of tomorrow's patients will also be addressed as, together with Quest, we deepen our knowledge base and its potential to help discover new therapies for people with cancer worldwide."

Over time, MSK and Quest will further study and extend the mutation database to generate improved diagnostics, in addition to collaborating in research and clinical trials.

ROSS LEVINE, MD
Laurence Joseph Dineen
Chair in Leukemia
Research



Left to right

KENNETH OFFIT, MD
Chief, Clinical Genetics
Service

MARK ROBSON, MD
Clinic Director, Clinical
Genetics Service

ENLISTING FAMILIES

One of the challenges of the practice of clinical cancer genetics today is the need to test dozens of cancer genes, some of which have recently been discovered and for which clinicians don't have adequate information to guide preventive or treatment strategies. A newly formed consortium including experts from MSK, Dana-Farber Cancer Institute, Mayo Clinic, the Abramson Cancer Center of the University of Pennsylvania, and genetics laboratories nationwide has established the Prospective Registry of Multi-Plex Testing, or PROMPT, to address this challenge. PROMPT is an online registry for individuals and families who have undergone testing for inherited cancer-causing genetic mutations.

The registry seeks to provide data that are vital to improving the understanding of the level of risk associated with testing for panels of cancer-associated genes as well as outcomes following the tests. PROMPT offers a novel way for individuals, families, investigators, and labs to work together to accumulate the data needed to guide clinical decisions for people who have been or who will be found to carry mutations of these less commonly altered genes. Creating a database where patient information is gathered allows research teams from across the United States to better define the cancer risks associated with newly discovered genes and to measure the effects of cancer prevention studies in the future.

“The registry is designed in a flexible way that allows participants to choose how much personal information they provide,” explains medical oncologist Mark Robson, Clinic Director of the Clinical Genetics Service at MSK. “By participating in the study, even anonymously, families and individuals will increase the knowledge base not only for themselves but also for future generations that may be at risk because of these same genetic mutations.”

PROMPT has received initial funding from the Robert and Kate Neihaus Initiative in Clinical Cancer Genetics, based at MSK; the Basser Research Center at the University of Pennsylvania; and the Breast Cancer Research Foundation.

“We believe that PROMPT will provide an exciting new global model for using online portals to empower individuals to participate in ongoing genomics research to better target prevention in families at risk for cancer and other diseases,” says Kenneth Offit, Chief of MSK's Clinical Genetics Service.

People can gain access to the PROMPT portal in several different ways: through crowdsourcing; on the project's website, www.promptstudy.org; and via direct referral from genetic counselors and participating commercial testing labs.

EXCEPTIONAL RESPONDERS PROVIDE CLUES

Profound and sustained responses are often seen in only a small minority of patients enrolled in early-stage clinical trials of novel cancer agents, and investigators have long posited that these responses have a genetic basis. But until recently it wasn't feasible to perform a comprehensive genomic analysis of such patients, who are known as exceptional responders.

Now, in collaboration with the **New York Genome Center** and 11 New York-based biomedical institutions, along with cancer researchers at Weill Cornell Medical College, MSK has launched the Exceptional Responder Initiative.

The initiative focuses on patients who have dramatic and durable responses to experimental cancer drugs in trials in which results are disappointing overall. “Statistically, these are negative studies. The drugs did not work for most patients,” explains physician-scientist David Solit, Director of the Marie-Josée and Henry R.



SETTING CANCER STRAIGHT

It's not much of a stretch to compare cancer to a badly behaved child. Quiet, well-mannered cells rarely call attention to themselves. But when they act up — like unruly three-year-olds — they can wreak havoc. Man has always searched for ways to control cancer by cutting it out or poisoning it. More recently, we've deployed the power of the immune system and targeted drugs to help destroy the disease. But is there yet another way — perhaps by setting cancer back on a more normal course?

THE EPIGENOMIC LIBRARIAN

Our bodies are a stew of cell types. Billions of nerve cells transmit electric impulses throughout the brain. White blood cells called macrophages gobble up debris and dead bacteria. And star-shaped osteocytes dwell in the bone, some growing to be several decades old. In spite of their different tasks, these cell types — and about 200 others — have a common origin and share the same DNA.

So how can a single genetic blueprint, known as the genome, create so much diversity?

For a long time, scientists thought the answer lay solely in the process of transcription, in which a segment of a cell's DNA is copied into a molecule called RNA.

Much has been learned about cancer through the study of factors that regulate transcription over the last 40 years. But it has only recently become apparent that the regulation of gene expression is more complex than scientists previously imagined. How a brain cell chooses to activate one set of genes while a skin cell selects a different set has remained unclear.

An important part of the equation is the epigenome, an intricate system of chemical labels superimposed on DNA. These molecular

Kravis Center for Molecular Oncology and leader of the initiative. “But for the responding patients, the experimental agent was the ‘correct’ therapy. By analyzing these patients using next-generation sequencing methods, we have been able to identify genetic signatures that explain their dramatic drug sensitivity.”

Researchers then seek to identify other patients whose tumors have a similar genetic profile to these exceptional responders. The expectation is that many of these patients will be similarly responsive to the same therapy that was so effective in the outlier patients. “This approach has enabled us to resurrect therapies whose development was prematurely halted because the treatment showed little benefit in most patients,” says Dr. Solit. “In many cases, the approach has also identified new drug targets or areas of research that we’re now pursuing in the laboratory.” ■

annotations tell the cell which of the more than 20,000 genes in the genome should be turned off or on at any given moment. Each cell type has its own epigenetic program that shapes and maintains its identity.

“If we think of the genome as a library with thousands of books, the epigenome is the library’s indexing system or librarian,” explains Memorial Sloan Kettering President and CEO Craig B. Thompson, whose laboratory investigates how metabolic changes affect the epigenome. “Cells organize their DNA into bits of information that they access and use on a need-to-know basis. The epigenome provides a system through which each cell can identify the pieces of information it needs to access in order to maintain its identity.”

A host of diseases — including almost all types of cancer — have been linked to epigenetic programming errors. “There is now tremendous excitement about the possibility of developing a new type of cancer drug that manipulates a cell’s epigenome,” says physician-scientist Scott Armstrong, who directs MSK’s collaborative Center for Epigenetics Research.

STRAIGHTEN UP AND FLY RIGHT

Epigenetic therapies offer an unconventional treatment strategy. Rather than eliminate cancer cells — which is what most currently available treatments do — they seek to set the cells on a path back to normal growth and development.

At MSK, several such therapies have begun to show promising results for some patients enrolled in early-stage clinical trials, mainly for blood cancers. In addition, MSK investigators are developing novel drugs that could make it possible to curb a variety of tumor types by undoing specific epigenetic changes within them. Investigator Minkui Luo is exploring this new field of cancer science with an eye to being able to create a new drug that will one day help patients.

“I trained as a pure chemist,” says Dr. Luo, “and I knew very little about cancer before I came here.” However, since joining MSK in 2008, his research has taken him deep into the largely unexplored territory of epigenetics and cancer.

Dr. Luo’s laboratory investigates a family of enzymes called protein methyltransferases (PMTs), which tune the expression of many genes by modifying histones, the proteins that package DNA. Histones form disk-shaped structures around which a cell’s DNA strands are wrapped.

Collaborating with physician-scientist Yariv Houvras at Weill Cornell Medical College, Dr. Luo set out to explore the function of SET8, a PMT that had been implicated in cancer in a number of independent studies.

By screening a library of small drug compounds, Dr. Luo’s team developed two that could inhibit the activity of SET8. Working in a zebrafish model of melanoma developed in Dr. Houvras’s lab, they found that these compounds had powerful anticancer effects.

SEEING INTO THE HEART OF THE MATTER

Zebrafish, striped freshwater fish, naturally succumb to some of the same diseases as humans, including melanoma. They make elegant cancer research tools for a number of reasons, one being that their melanoma tumors are as dark as ink. Using just the naked eye, researchers can see cancers develop or watch tumors shrink in response to a drug.

“We got very excited when we found the SET8 inhibitor could block one of the key pathways known to drive melanoma,” Dr. Luo says. “Meanwhile, other scientists reported SET8 might also be involved in

Left to right

MINKUI LUO, PhD
Lab Head

YARIV HOUVRAS, MD, PhD
Surgeon and Assistant
Professor of Cell and
Developmental Biology,
Weill Cornell Medical College



metastatic breast cancer, so we knew we were onto something.”

PMTs regulate genes by adorning certain sites of histones and other molecules with chemical labels called methyl groups. Because these marks are so tiny (they’re a cluster of one carbon and three hydrogen atoms), PMT activity used to be very difficult to study, Dr. Luo says. But his lab has developed a technology — essentially a way to amplify molecular anatomy — that enables them to monitor the biochemical reactions.

Using this and other chemistry methods, they are working to optimize the pharmacological properties of the SET8 inhibitors, with the goal to generate a drug that could be tested in patients.

“The next step is to test the drug in mouse models of melanoma and metastatic breast cancer,” Dr. Luo says. “We want to see in what kinds of tumors it might have the best chance to work, whether it causes side effects, and at what dose it’s effective.” The researchers will also continue to explore the biology of SET8 and whether it might be implicated in additional cancers. ■

Dr. Luo’s research has been funded by the Tri-Institutional Therapeutics Discovery Institute, the Starr Cancer Consortium, and the National Institutes of Health.



Left to right

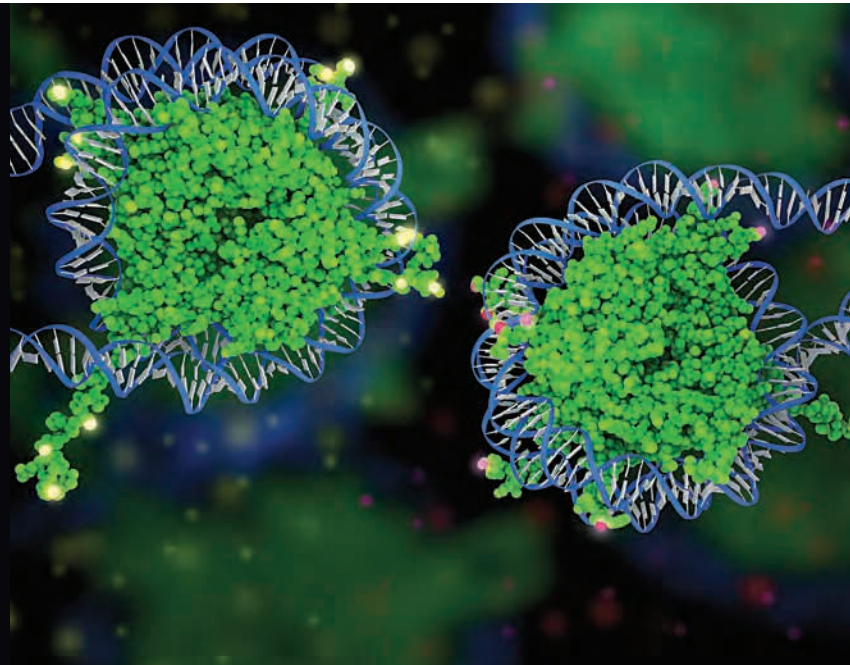
MICHAEL KUEHN
Research Fellow

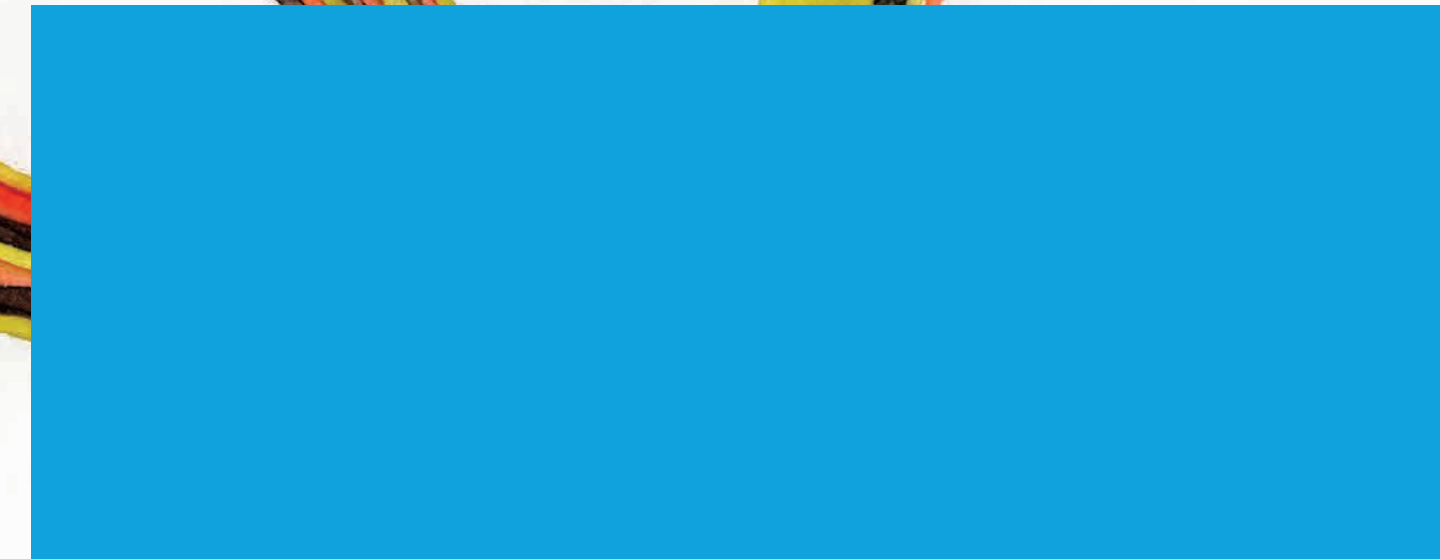
SCOTT ARMSTRONG,
MD, PhD
Director, Memorial
Sloan Kettering Center
for Epigenetics Research;
Grayer Family Chair

ABOUT THE ILLUSTRATION



Many cancers are fueled by chemical changes in histones, the proteins that serve as spools for DNA (histones are pictured in green with cancer-induced changes in red and purple). New drugs that reverse histone changes could convert cancer cells back to normal.





The background of the entire page is an abstract watercolor illustration. It features various organic shapes, including circles, ovals, and elongated forms, in a palette of bright colors: yellow, green, blue, orange, red, brown, and grey. Some shapes are layered or overlapping, creating a sense of depth and movement. The overall style is soft and artistic, reminiscent of traditional watercolor painting.

WE'RE CHANGING HOW THE WORLD
TREATS CANCER WITH

BOLD
ADVANCES



IN THE BEGINNING...

...is the embryo and the events that shape the earliest stage of life.

But the expression of the same genes — along with the cell divisions, specializations, and movements that sculpt us into complex multicellular organisms — can also be responsible for cancer. Developmental biologists at Memorial Sloan Kettering work to elucidate the normal behaviors of developing cells that can go awry in the disease and its progression — and the contributions of these researchers are vital to cancer science.

“By understanding how cell types are generated and tissues are formed normally, we can start to tease apart what happens when things are deregulated or aberrant in cancer,” explains Anna-Katerina Hadjantonakis, a member of the Sloan Kettering Institute’s Developmental Biology Program. Dr. Hadjantonakis conducts pioneering research in mice to understand how cells regulate their identity and organize themselves into tissues. For her work in developmental stem cell biology, the mouse is an ideal model. In simple terms, “what’s important in the mouse is likely also important in humans,” she says.

Dr. Hadjantonakis’s special interest is in embryonic stem cells and the critical events that guide early development in the mouse embryo. Her research has allowed her to learn how individual cells evolve their identities during embryonic development.

SEEING IS BELIEVING

Embryonic stem cells are unique, with features that make them especially attractive to scientists. They are pluripotent, meaning that they give rise to all the cells of the fetus and the adult organism; they can be “captured” and maintained indefinitely in culture; and they can be directed to differentiate, or evolve, into various cell types.

Dr. Hadjantonakis’s laboratory currently addresses two interrelated questions: How do pluripotent cells arise and how do they differentiate in the embryo?

A significant distinction of Dr. Hadjantonakis’s research team is their ability to visualize cells individually within a living tissue and to monitor the activities of those cells. One of the key techniques she and her colleagues use is sophisticated live-imaging microscopy, a technology that allows them to observe and track the journey of a single cell in the developing mouse embryo. “We can actually see where the cells are in the embryo, where they travel, what genes they express, and what they do if certain genes are turned on or turned off,” she says.

The technology, developed in Dr. Hadjantonakis’s lab, is the first to allow scientists to visualize individual pluripotent stem cells in live embryos, as opposed to studying them in culture or looking at whole populations of cells in an animal. The cells are labeled with genes that control the expression of what are called fluorescent protein “reporters” that light up in different colors, allowing those cells to be seen and tracked. In whatever process they’re investigating, Dr. Hadjantonakis and her colleagues can then observe the cells involved over a period of time.

In a recent paper in the journal *Cell Reports*, Dr. Hadjantonakis and her colleagues showed that as cells decide to become pluripotent or differentiated, they rarely — if ever — change their state. This is an important observation, she says, “because pluripotent cells exhibit diversity in stem cell cultures, which seemed to suggest their level of ‘stem-ness’ can change.”

So, she says, “the million-dollar question was whether these fluctuations exist between different developmental states in vivo [in the body].” The answer they’ve uncovered is no. The pluripotent cells studied in mouse embryos in Dr. Hadjantonakis’s lab “never changed their minds — once they decided they were pluripotent, they stayed that way,” she says. In another recent paper in the journal *Developmental Cell*, her group identified a critical factor promoting a cell’s identity away from pluripotency to an alternative differentiated state.

ILLUMINATING CANCER METASTASIS

In a third recently published paper, in *Nature Cell Biology*, Dr. Hadjantonakis’s lab looked at a process called gastrulation, an early phase of embryonic development in which pluripotent cells are organized into a three-layered structure known as the gastrula. These three layers, called the ectoderm, mesoderm, and endoderm, are the founding tissues of our bodies.

Again, Dr. Hadjantonakis and her group achieved something that no one else has previously been able to accomplish. “We live-imaged cell identity decisions and morphogenesis [the formation and differentiation of tissues and organs],” she says. “In this instance, we visualized the formation of the endoderm, which is the progenitor of the respiratory and digestive tracts, and associated organs including the liver, pancreas, and thyroid. We found a critical factor that’s involved in instructing cells to become the endoderm.”

What the researchers also discovered is a cell behavior that may be co-opted in cancer metastasis. “We uncovered a cellular and molecular program, or mechanism, for the insertion of cells into an epithelium [the cellular covering of internal and external body surfaces]. We hypothesize that some aspects of this process may be involved in cancer when it spreads from a primary tumor, invading and colonizing distant organs of the body,” Dr. Hadjantonakis says.

“In essence, what we’re doing is deconstructing cancer to its basic building blocks: We need to understand the ‘forward engineering’ in order to unravel what happens in reverse,” she concludes. “There’s great promise in using knowledge gained from the study of developmental biology to help patients with cancer. But to continue developing new, safe, and effective treatments means to continue elucidating the basic defects in the disease. For that, one needs to understand the entire continuum of cell behavior and development — and learning everything we can about when and how cells first become different is paramount. This is what my colleagues and I devote our professional lives to revealing.” ■

ANNA-KATERINA HADJANTONAKIS, PhD
Developmental Biologist



Above: Dr. Hadjantonakis at her microscope. Top right: An early structure of a developing mouse embryo called a blastocyst, imaged by confocal 3-D microscopy. The colored areas represent cell layers called the epiblast (pink) and the primitive endoderm (blue). The white and blue images show the different fluorescent protein "reporters" that light up and allow cells in the embryo to be visualized and tracked over time. Bottom right: Dr. Hadjantonakis works in her laboratory with graduate student Minjun Kang (center) and postdoctoral research fellow Sophie Balmer.

“What we’re doing is deconstructing cancer to its basic building blocks. We need to understand the ‘forward engineering’ in order to unravel what happens in reverse.”

– ANNA-KATERINA HADJANTONAKIS



T CELL ARMIES

The Cancer Killers Within

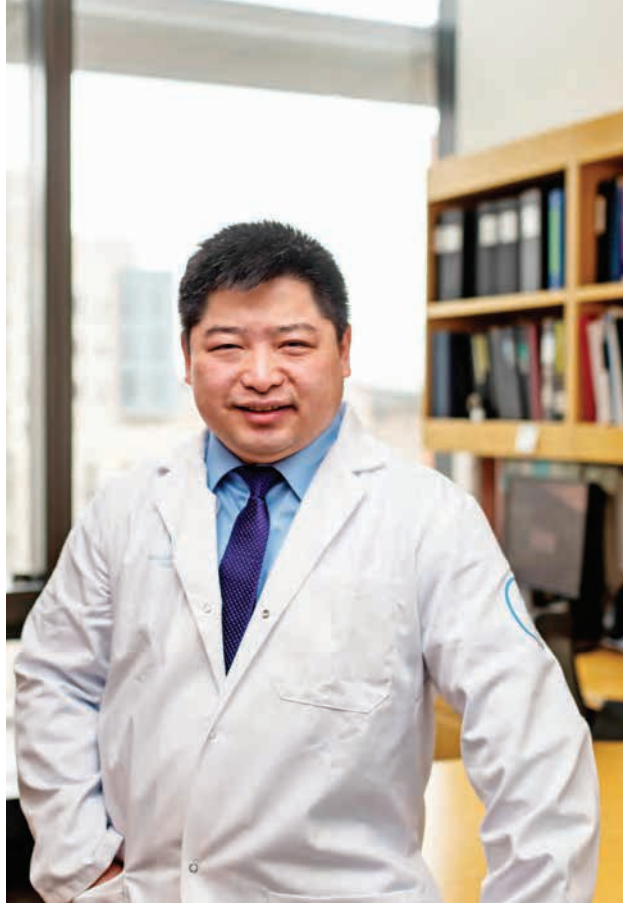
Your T cells are the foot soldiers of your immune system, searching out and destroying invaders they recognize as foreign. Ceaselessly patrolling the body, they're on the lookout for cellular abnormalities and infections. When they find an intruder, they kill it. They even have the ability to recognize and destroy cancer — although in order to do so with maximum efficiency, they need what you might call close air support.

Left to right

TIMOTHY CHAN, MD, PhD
Frederick Adler Chair;
Director, Translational
Oncology Division

JEDD WOLCHOK, MD, PhD
Chief, Melanoma and
Immunotherapeutics Service;
Lloyd J. Old Chair for
Clinical Investigation

ALEXANDRA SNYDER CHAREN, MD
Medical Oncologist



Drs. Chan, Wolchok, and Snyder Charen combine research with active clinical practices.

This support takes the form of the burgeoning field of cancer immunotherapy, which is centered on the idea that a person's own immune system can be manipulated to fight cancer. Breakthroughs are coming with astonishing rapidity. One of these is ipilimumab (Yervoy™), a drug that's produced practice-changing results for a number of people with melanoma and works by boosting the body's natural immune defense against tumors. For certain patients, it shrinks their tumors and significantly prolongs their lives. Memorial Sloan Kettering physicians and scientists played a major role in the development of this therapy.

THE BATTLE WAGES ON

Unfortunately, immunotherapy doesn't help everyone. In fact, in the case of ipilimumab, about 80 percent of people with melanoma get little or no benefit. And thus far, doctors haven't had a way of predicting which patients are more or less likely to respond to the drug.

MSK scientists now understand more about how ipilimumab works and why it's able to control melanoma in certain people but not in others. In a report published in 2014 in the *New England Journal of Medicine*, the researchers showed that the cancer cells of patients who responded to the drug carried a high number of gene

mutations — and that some of these mutations were what enabled the immune system to “see” and attack the tumor.

“For the first time, it might be feasible to develop a reliable diagnostic test to help guide treatment decisions by predicting who will respond,” says physician-scientist Timothy Chan, who co-led the study with MSK melanoma expert and immunologist Jedd Wolchok. The finding could also inform new research that may lead to more-powerful immunotherapies for melanoma and other cancers.

HERE COMES AIR SUPPORT: ACTIVATING A T CELL RESPONSE

Ipilimumab works by blocking a protein called CTLA-4. Under normal circumstances, CTLA-4 keeps the tumor-fighting activity of the immune system's T cells in check. But in the presence of ipilimumab, T cells are unleashed and cancer's ability to evade immune system attack is stripped away. It can now go to work at full force, recognizing and destroying cancer cells.

Recent studies have shown that about one in five patients with metastatic melanoma who are treated with the drug live for more than three years after starting treatment. Before the drug became available, median life expectancy for the disease was seven to eight months.



T CELL, T CELL, WHAT DO YOU SEE?

To gain insight into why some people respond to ipilimumab and others don't, the researchers collected tumor samples from 64 melanoma patients who had been treated with ipilimumab or tremelimumab, an experimental drug that works in a similar way. About half the tumors came from people who benefited from the treatment and half from people who didn't.

What investigators discovered was a series of genetic mutations in some of the patients that caused their cancer cells to produce short stretches of protein molecules — called tumor antigens — that make cancerous cells visible to the immune system.

“We found that tumors that had responded to the drug had a higher mutational burden, or overall number of DNA changes,” explains medical oncologist Alexandra Snyder Charen, the study's first author. “But the correlation isn't perfect. Not all patients with a high mutational burden in their tumors responded.”

“This made us ask, ‘What is the immune system seeing?’” adds Dr. Wolchok, who played a major role in the development of ipilimumab. “What is it about the mutational landscape of a tumor that helps the immune system recognize and attack it?”

Using sophisticated computational tools, the investigators explored their data and found that the drug-responsive tumors shared a certain type of mutation that makes cancer cells express a new subset of tumor antigens — substances that T cells can detect

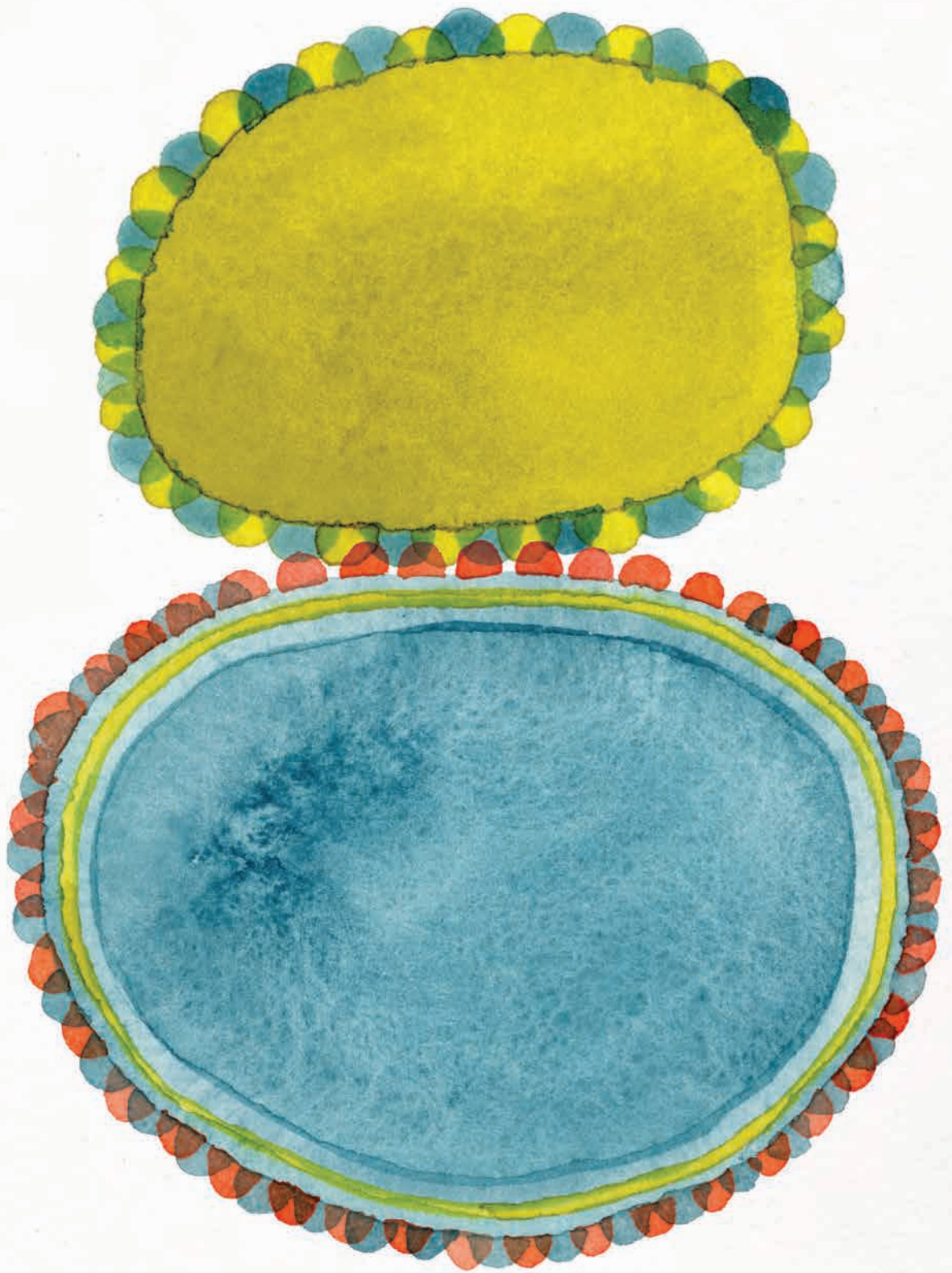
as foreign to the body. Researchers believe the mutations in these patients' tumors cause them to express the new antigens, which the immune system then reacts to — and ipilimumab works by enhancing that reactivity.

WHAT'S NEXT?

The study findings could translate into a diagnostic test to detect the mutations in melanoma tumors, the results of which could assist doctors and patients in making more-informed treatment decisions. The MSK team also plans to investigate whether specific tumor mutations influence the effectiveness of other immunotherapy drugs.

“By mapping the mutations that make different types of tumors sensitive to different drugs, we may ultimately be able to offer more patients successful immunotherapy,” Dr. Chan says. “If we know a patient won't respond to ipilimumab, we may be able to identify other drugs that are more likely to be effective against that person's tumor.” ■

This research was supported by Ludwig Cancer Research and grants from the Frederick Adler Fund, the National Institutes of Health, Swim Across America, the Ludwig Trust, Melanoma Research Alliance, Stand Up to Cancer-Cancer Research Institute Immunotherapy Dream Team, Hazen-Polsky Foundation, and the Starr Cancer Consortium. Stand Up to Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research.



BACTERIA VERSUS BACTERIA

*A new approach pits one
bacteria against another
to fight infection.*

Bacteria are the most abundant organisms on Earth and are among the earliest forms of life to have appeared on our planet. One might say that they're our oldest relatives. Many of us know them only as germs — unpleasant, invisible creatures that can invade our bodies and make us sick. But bacteria are complex and fascinating, coexisting with us all the time and helping us do an array of useful things like make vitamins, break down garbage, and even maintain our atmosphere.

Yes, it's true: Bacteria do have the power to infect, even to kill. However, Memorial Sloan Kettering researchers have revealed that, when pitted against one another, they may also have the power to heal.

A GROWING THREAT

Infection with the bacterial pathogen *Clostridium difficile*, or *C. diff*, is a serious and increasing problem. The Centers for Disease Control calls *C. diff* “an immediate public health threat that requires urgent and aggressive attention.”

C. diff infections mostly occur in people who have had recent medical care and antibiotics, often including those who are or have recently been hospitalized. *C. diff* releases toxins that damage the lining of the large intestine, leading to abdominal pain, diarrhea, and sometimes more serious conditions that can take weeks or months to resolve and can — in rare circumstances — lead to death.

Now research from MSK is providing support for a novel preventive strategy that uses a bacterial species naturally found in healthy gastrointestinal tracts to prevent *C. diff* infections.

“It’s been well established that the loss of normal bacteria in the intestines can lead to infection with *C. diff*,” says Eric Pamer, Head of the Division of General Medicine, Chief of MSK’s Infectious Diseases Service, and the senior author of a 2014 study published in *Nature* on the topic. “Now that we know which bacterial species has a protective effect, we can begin to look for ways to develop a clinical treatment.”

RESTORING THE BALANCE

For several decades, experts have known that antibiotics can destroy the beneficial bacteria in our guts and allow *C. diff* to flourish. Yet people with *C. diff* infections are usually treated with more antibiotics. The treatment can result in high recurrence rates and persistent colitis, a chronic inflammation of the colon — for which very prolonged antibiotic courses are prescribed.

It would certainly be preferable to treat the infection in a more effective way. But until recently it was unclear which bacterial species provide protection against *C. diff*. Then, clinical studies showed that fecal transplants — in which feces from a healthy donor is introduced into the colon of someone with chronic *C. diff* — can eradicate the infection.

Because it’s impossible to determine all the components and infectious agents in a fecal transplant, doctors have been reluctant to offer the treatment to patients who are immunocompromised. This is especially true of patients undergoing bone marrow transplants (BMTs) or receiving chemotherapy for leukemia or lymphoma.

“The goal of our study was to identify specific bacterial species present in the normal intestinal tract that can be used to prevent or treat *C. diff* infections,” Dr. Pamer says.

C. SCINDENS TAKES ON C. DIFF

Charlie Buffie, a graduate student in Dr. Pamer’s laboratory, worked with MSK computational biologists Joao Xavier, Vanni Bucci, and Richard Stein to analyze the DNA sequences of intestinal bacteria obtained from antibiotic-treated lab mice. In doing so, they were able to identify bacterial species that inhibit *C. diff* infection.

In samples from patients undergoing BMTs, they also used computational tools to establish correlations between specific microbes found in the intestines and how susceptible those patients were to *C. diff* infection.

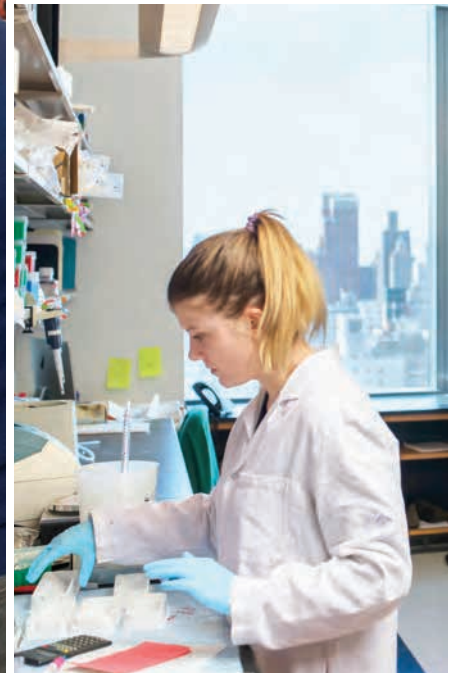
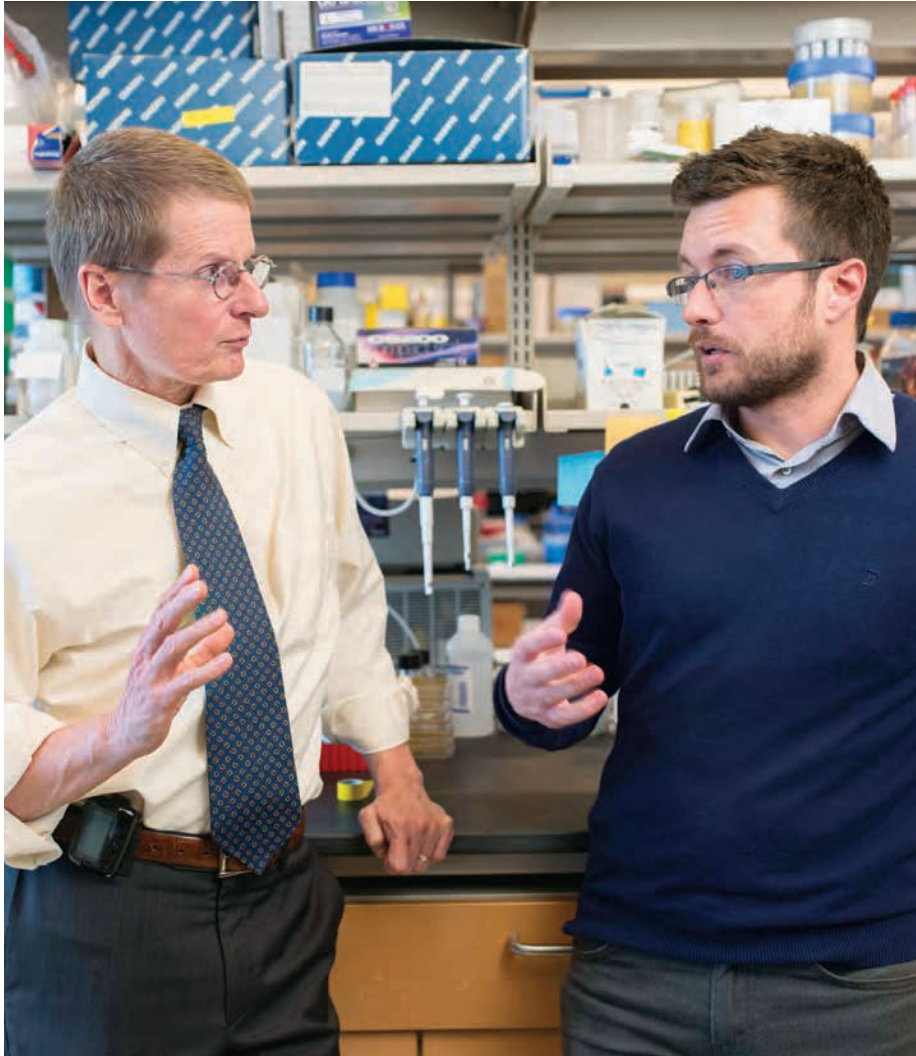
The research team identified a strain found in both mice and humans called *Clostridium scindens* that confers resistance to *C. diff*. When the team gave *C. scindens* to susceptible mice prior to infection with *C. diff*, they found it led to lower levels of the harmful bacterium, which in turn led to a decrease in toxin production and a reduction in colitis.

Before clinical trials in humans can begin, additional research in mice is needed. “One thing we still need to work out is the optimal bacteria companions for *C. scindens*,” Dr. Pamer says. “Our study demonstrates that it’s more effective against *C. diff* if it’s accompanied by three other species. That’s not surprising, because bacteria often work together to support each other in a complex environment like the human intestine.” ■

This research was funded by the National Institutes of Health and the Tow Foundation.

“Now that we know which bacterial species has a protective effect, we can begin to look for ways to develop a clinical treatment.”

– ERIC PAMER



ERIC PAMER, MD
Head, Division of General Medicine;
Chief, Infectious Diseases Service;
Enid A. Haupt Chair in
Clinical Investigation

JOAO XAVIER, PhD
Computational Biologist

Research technician Rebecca Carter works
in the laboratory of Eric Pamer.



FROM BETSY TO DOROTHY

20 Tons of Precision-Based Medicine

Scientists get very attached to the tools of their trade. Each object becomes like an old friend — like a car that has seen you through good times and bad. Despite some rust and dings, your affection for it remains undiminished.

“At MSK, we’ve developed more than 30 promising new PET agents. And some are now being used worldwide to translate new drugs into clinical practice.”

– JASON LEWIS

Below left and bottom right

JASON LEWIS, PhD
Chief, Radiochemistry and
Imaging Sciences Service;
Emily Tow Jackson Chair in Oncology

Below right

WOLFGANG WEBER, MD
Head, Molecular Imaging and
Therapy Service



This may in part explain Betsy — or certainly her name. “She” was Memorial Sloan Kettering’s first cyclotron, a particle accelerator used to produce radioactive molecules for medical imaging. MSK was the first hospital in the nation to have this nuclear medicine equipment. Installed in 1967, “she served us faithfully for almost 40 years,” recalls Hedvig Hricak, Chair of MSK’s Department of Radiology. “When old Betsy was finally decommissioned, she was partially held together with duct tape and Krazy Glue!”

You can’t say she wasn’t beloved, but it was finally time to move on. So in 2014, MSK took a leap into the future with the launch of a new cyclotron. This 44,000-pound instrument and the production facility built around it are changing the way our patients are diagnosed and treated by allowing doctors to examine and target tumors with increased precision.

“With the new cyclotron, we’re able to fully capitalize on our strength in radiochemistry, nuclear medicine, and molecular imaging to monitor and study cancers in unparalleled detail,” Dr. Hricak says. “It’s advancing the medicine of the 21st century — for patients we are treating today and those we’ll treat in the future.”

A NEW NAME, A NEW FACILITY

The latest cyclotron also has an affectionate moniker: Dorothy, in honor of her namesake, who was swept out of Kansas and into Oz by a tornado.

MSK President and CEO Craig B. Thompson welcomed her at a ceremony in May 2014. He marveled at the tour de force of engineering and logistics required “to actually drop a 20-ton [cyclotron] through the middle of the hospital one weekend” in November and successfully install it in the basement while keeping the hospital fully operational.

“This is truly a cutting-edge facility and one of the largest of its kind in the world,” says radiochemist Jason Lewis, who runs the cyclotron facility and also directs MSK’s Center for Molecular Imaging and Nanotechnology.

“The cyclotron is part of a wide-ranging effort to build the best cancer center in the world in precision-based medicine,” adds Physician-in-Chief and Chief Medical Officer José Baselga. “We have tremendous insights in biology. We have the capacity to produce the best therapies. And now, with this new facility, we’ll have the ability to interrogate tumors and really know what’s going on in individual people’s cancers.”

COUNTING ATOMS

MSK’s cyclotron is now producing the radioactive molecules used in PET imaging. This type of imaging makes it possible to watch biological processes play out in tumors and normal tissues using radioactively labeled imaging agents. “The PET scanner is our molecular microscope,” explains physician-scientist Wolfgang Weber, who heads the Molecular Imaging and Therapy Service. “It allows us to localize molecules in a patient’s body and measure their concentrations with amazing sensitivity. The PET scanner is literally counting individual atoms.”

The technique has multiple uses: It can assess whether a patient will benefit from a drug, monitor a drug’s effectiveness, or study its mechanism of action in a clinical trial. Still other types of PET scans are used to diagnose and stage cancers by measuring tumors’ glucose uptake. PET is also a vital tool for lab studies into the basic biology of cancer.

Radioactive isotopes — the components of PET agents that make molecules visible in the body — are produced in a cyclotron by hitting a nonradioactive molecule with a charged particle flying at extremely high speed, accelerated in a powerful magnetic field.

Hospital cyclotrons produce almost no radioactive waste, and patients who undergo PET imaging are exposed to very low doses of radiation.

DRUG MANUFACTURE

There’s yet another reason Memorial Hospital needed a new cyclotron: Our researchers are creating new medical technologies that require radioactive drugs to be produced and delivered to patients very quickly.

Dr. Lewis points to the manufacture of the isotope carbon-11 as an example. “Carbon-11 can be used to produce hundreds of highly selective PET agents, including some of the best markers available for monitoring prostate cancer and some types of glioma brain tumors,” he says.

But using the isotope poses a challenge due to its short half-life, which is the time it takes for a freshly made batch of the isotope to decay until half of it is gone. Carbon-11’s half-life is all of about 20 minutes.

So while a patient waits in a scanner, Dr. Lewis and his team make the isotope, take it off the cyclotron, couple it with a tracer or drug molecule, sterilize the product, and perform nine or ten different tests to ensure optimal quality and safety. The compound is then propelled to the imaging suite via one of seven pneumatic tubes that connect the cyclotron facility with clinical areas in the hospital. For carbon-11 and a number of other isotopes, the entire process needs to be accomplished within minutes.

“At MSK we’ve developed more than 30 promising new PET agents,” Dr. Lewis notes. “And some are now being used worldwide to translate new drugs into clinical practice.” ■



LIFE AFTER CANCER

Surviving and Thriving

“When a patient completes cancer therapy, that shouldn’t be the end of the story,” says Kevin Oeffinger, Director of Memorial Sloan Kettering’s Adult Long-Term Follow-Up Program and the inaugural Director of our new Cancer Survivorship Center.

At MSK, we’ve long understood that the experience of cancer doesn’t end when treatment does. In 2003, we established the Survivorship Initiative — the first of its kind in the country — to coordinate comprehensive services for survivors of adult-onset cancers. And in 2014, the initiative came of age with the creation of this new center.

The goal of survivorship research and patient care is to allow people who've had cancer — even multiple times — to live long lives and retain good quality of life through expert surveillance, timely health-preserving interventions, and research into the causes of the long-lasting side effects of treatment.

As the preeminent leader in cancer survivorship, MSK created the Cancer Survivorship Center to bring together already existing initiatives and programs and provide an infrastructure to support cancer survivorship studies. Under the leadership of Dr. Oeffinger and his colleagues, the center seeks to further transform the field as well as formalize standards of care that are already serving as models nationally and internationally.

A HISTORY OF SURVIVORSHIP AT MSK

In 2003, oncology nurse Mary McCabe was recruited from the National Cancer Institute, where she was Deputy Director in the Division of Cancer Treatment and Diagnosis, to lead MSK's Survivorship Initiative. Today, she serves as Clinical Director of the Cancer Survivorship Center.

When Ms. McCabe joined MSK, there were few clinicians delivering care for cancer survivors or leading studies to better understand the long-term effects — also called late effects — associated with cancer therapy. Eleven years later, nearly 100 MSK clinicians and researchers are involved in this work.

"Survivorship is now a program of consequence at our institution," she says. "The Survivorship Initiative was established to jump-start the effort, with a strong initial focus on clinical services for patients — but always with an eye firmly fixed on our triple mission as a cancer center. We also wanted to grow our research effort and to focus on education and training."

Looking even further back, in 1990, MSK's Department of Pediatrics established the Long-Term Follow-Up Program, one of the earliest such programs in the nation. Led by pediatric endocrinologist Charles Sklar, who has been working in the field since the 1980s, the program helps children and their families navigate and manage the chronic medical conditions often experienced by survivors of pediatric cancers. (Dr. Sklar also serves as Director of Training and Education in the Survivorship Center.)

"Dr. Sklar headed the pioneering effort and developed a wonderful program to monitor the health of these high-risk children and take care of the late effects of their therapy," says Dr. Oeffinger. "He also led much of the research that helped us understand those risks."

Dr. Oeffinger's Adult Long-Term Follow-Up Program provides follow-up care for adults of all ages who were treated for cancer during their childhood, adolescent, or young adult years. "We take over from Dr. Sklar's program and follow survivors from the age of 18 to, well, age 85-ish or so!" he explains, smiling.

THE CENTER TODAY

Ms. McCabe, Drs. Oeffinger and Sklar, and their colleagues have worked to develop clinical care models for survivors with

different risk levels as well as to foster an active research initiative in areas that now include heart health after cancer treatment; cancer recurrence and the development of second cancers; fertility preservation and sexual health; neurocognitive dysfunction; and lifestyle interventions, such as smoking cessation.

"We're really reaping the rewards of great oncologic care," says Dr. Oeffinger. "In fact, once they have completed treatment, many patients are at low or moderate risk of cancer recurrence but may have many other healthcare needs. And this is where our survivorship clinics come in: Specially trained nurse practitioners and physician assistants see these patients regularly and offer the comprehensive services that survivors need." In 2014, MSK had approximately 11,200 patient visits to its nurse practitioner (NP) and physician assistant (PA) cancer survivorship clinics. For high-risk cancer survivors, MSK has physician-nurse practitioner (MD-NP) clinics, which had approximately 1,500 patient visits in 2014.

As patients complete treatment, they transition from the care of their oncologist to an NP or a PA skilled in disease-specific follow-up. For patients with adult-onset cancers, an NP or a PA is embedded within the clinical team so patients do not need to leave their oncology physician.

"The value of having an NP or a PA as part of the team is twofold," Ms. McCabe explains. "First, team members do not have to 'give up' the patients they have been treating and who are doing well, and that gives them a great deal of personal satisfaction. And, for the patients, they don't have to leave the team that has treated them."

The first clinics based on the NP model began in 2006 for lymphoma, thoracic surgery, and prostate surgery patients. Currently, MSK provides follow-up care for survivors of breast, cervical, colorectal, endometrial, esophageal, head and neck, kidney, lung, ovarian, prostate, and thyroid cancers and melanoma, as well as for those who have undergone blood and marrow stem cell transplantation.

All patients seen in the NP and the MD-NP clinics are given a cancer treatment summary and survivorship care plan, a blueprint for navigating post-treatment life and a communication tool for their primary care physician.





The goal of survivorship care and research is to allow people who have had cancer to live long lives and retain good quality of life through surveillance, health-preserving interventions, and research into the causes of the side effects of treatment.

Left to right

MARY McCABE, RN, MN
Clinical Director,
Cancer Survivorship Center

KEVIN OEFFINGER, MD
Director, Adult Long-Term
Follow-Up Program

CHARLES SKLAR, MD
Director, Long-Term
Follow-Up Program

TO PREVENT AND TO TREAT

Although much is known about cancer survivorship, a great deal remains to be learned. The aim of research is to assess the long-term impact of cancer and its treatment in order to allow clinicians to intervene and minimize or prevent the late effects of therapy.

Physician-scientists from across MSK are conducting numerous ongoing investigations in these areas. This research includes how best to detect early signs of heart disease in survivors of Hodgkin's lymphoma — a result of radiation to the chest and the chemotherapy used in treatment — and studies being done by behavioral psychologist Tim Ahles that focus on how to treat or prevent the cognitive changes associated with chemotherapy for breast cancer. (Dr. Ahles is Co-Director of Research in the Survivorship Center.)

“We’re also doing exciting studies investigating the effects and underlying mechanisms of how targeted, individualized exercise training might prevent tumor progression and metastasis and alter response to cancer therapies, as well as treat late effects,” Dr. Oeffinger says. (Exercise scientist Lee Jones, who co-directs research in the Survivorship Center with Dr. Ahles, is leading

that area of research. To learn more about his work, see page 38. Surgical oncologist Larissa Temple serves as the Survivorship Center’s Director of Clinical Care.)

THE NEXT DECADE

Beyond the institution, MSK clinicians are collaborating with colleagues around the United States and the world.

“We’ve gone from being an initiative in 2003 to a center that today is truly transinstitutional and transdisciplinary,” says Dr. Oeffinger. “Our goal now is to seed and to fertilize — and then to support growth across all areas and at all levels.”

“We have a tremendous opportunity to develop and evaluate our clinical programs in a way that not only contributes to the care that our survivors receive but also helps determine standards for how oncology care is provided in the future,” Ms. McCabe adds. “We’ve worked hard to achieve a certain set of goals during this first decade and have identified a very ambitious set of goals for the next ten years. It’s an exciting time to be at Memorial Sloan Kettering and to be doing this work.” ■



Left to right

LEE JONES, PhD
Director, Cardio-Oncology
Research Program

BHARVI PATEL
Research Study Assistant

JOHN SASSO
Exercise Physiology,
Manager

KRISTEN AUFIERO
Clinical Research Manager

A FIELD IN MOTION: FIGHTING CANCER WITH EXERCISE

*A Conversation
with Exercise Scientist
Lee Jones*

Exercise as a treatment for cancer? Sound too good to be true? It may not be. Exercise scientist Lee Jones, Director of the Cardio-Oncology Research Program (CORP) at Memorial Sloan Kettering, is devoted to teasing out the answer to this and other questions. Using an approach that spans basic and clinical science, his team designs and tests the effects of individually prescribed exercise training to prevent or minimize the adverse cardiovascular side effects of cancer therapy. They're also working to answer this potentially paradigm-shifting question: Can exercise be an effective treatment for cancer itself? Here, Dr. Jones talks about some of this work.

CAN YOU TELL US A LITTLE ABOUT THE RELATIONSHIP BETWEEN EXERCISE AND DISEASE?

If you look at the role of exercise in noncancer chronic diseases such as heart disease or heart failure and type 2 diabetes, exercise is typically part of the standard of care. In fact, exercise is the central piece of treatment for a lot of these diseases. So for example, somebody who's had a heart attack is referred to cardiac rehabilitation, in which exercise therapy is the primary component and everything else is built around it.

An exercise prescription is also one of the front-line therapies for the prevention of many diseases. If you go to your primary care physician and you're at risk for one of the most common chronic diseases such as diabetes or cardiovascular disease, one of the first things he or she will talk to you about is lifestyle interventions, whether that's stopping smoking, modifying your diet, or losing weight — and the conversation always, or should always, include participation in a regular exercise program. For cancer, there's convincing evidence that regular exercise is associated with a significant reduction in the risk of certain types such as breast, colon, and prostate cancer.

SO WHAT DO WE KNOW — AND NOT KNOW — ABOUT THE ROLE OF EXERCISE IN CANCER?

While we've recognized the critical importance of exercise therapy for the prevention and treatment of other diseases for decades, the value of exercise in people with cancer was left largely untouched until recently. The prevailing view was that cancer is associated with poor outcomes, and that patients who either are undergoing or have finished intensive cancer treatments would not be able to participate in or tolerate structured exercise training. Because of this, many patients were — and may still be — advised to rest and avoid strenuous exercise, particularly during treatment.

However, things are now changing radically for a number of reasons. Perhaps the most important is the enormous progress we've made in cancer screening and prevention as well as treatment. In combination, this now means that people are living longer than ever before after a cancer diagnosis, and that accordingly, certain cancer diagnoses are no longer considered a death sentence. Today, with nearly 14 million people in the United States living with a history of cancer, exercise has gained a lot of traction as part of the survivorship movement.



CAN YOU TALK IN A GENERAL SENSE ABOUT THE TYPE OF WORK YOU AND YOUR RESEARCH TEAM ARE ENGAGED IN?

In the CORP, we are essentially focused on two fundamental things. The first is, are there better ways to lessen the immediate and long-term cardiovascular side effects of cancer treatment? Paradoxically, improvements in therapy for cancer have given people sufficient life spans to put them at risk for suffering the [late] effects of therapy, sometimes years after that therapy is over.

As part of their treatment, patients can receive a cocktail of different therapies — surgery, radiation, chemotherapy. We're finding that these treatments, while effective at controlling the growth and progression of cancer cells, also cause damage to the components of the cardiovascular system, especially the heart, as well as the skeletal muscle. Together, this leads to a dramatic decrease in patients' ability to exercise and even perform normal activities of daily living.

What we've learned is that cancer therapy leads to a reduction in a patient's cardiovascular reserve capacity — commonly known as your fitness level — and it appears to stay impaired even years after therapy. In fact, we've found that even a short course of chemotherapy has the same impact on the cardiovascular system as ten years of normal aging. But the good news is that in our clinical trials, we're discovering that these effects can be attenuated in individuals who participate in structured exercise training prescriptions.

Our second major focus is understanding and harnessing the potent therapeutic properties of exercise as a form of cancer treatment to prevent recurrence and even help conventional or novel cancer drug therapies work more effectively. We want to discover if and how exercise impacts tumor biology, both in the early and advanced stages of disease.

We're actually trying to approach the development and investigation of exercise treatment as you'd think about the development of a new drug. The drug we're testing just happens to be called exercise, but I believe that the way we test it should be no different. In our program, we are trying to adopt, whenever possible, the same type of sequential study steps with similar types of endpoints that oncologists and cancer biologists use in the development of new targeted therapies — we think of it as precision exercise treatment.

IS THERE A PROJECT THAT STANDS OUT AS AN EXAMPLE OF THIS APPROACH?

Here's a good example: We're interested in testing the efficacy of exercise across the entire cancer trajectory, from prevention to advanced disease. To this end, we're about to launch a study looking at the earliest stages of cancer development. When we see patients in the clinic — after they've been diagnosed — a lot of the very early events in the development of the disease have already occurred. I want to look at how exercise might be affecting some of these.

To do this, we're going to perform a randomized controlled trial in women diagnosed with atypia [abnormal changes within the breast tissue]. These changes put them at significantly higher risk of developing invasive breast cancer. A total of 100 women will be assigned to a low, medium, or high dose of six months of supervised aerobic training [treadmill walking] — low being 75 minutes a week, medium being 150, high being 300 minutes. The fourth arm, the control group, will be women who will receive the usual standard of care [with no additional prescription for exercise]. All our aerobic training sessions are individualized to participants based on their fitness levels, which we measure at the beginning of the program using a sophisticated exercise stress test.

Before randomization, all women will undergo a battery of assessments including a core biopsy of the normal breast tissue. After six months, the biopsy will be repeated and we'll be able to evaluate, for the first time, whether aerobic training lowers the expression of genes in the normal breast tissue that are known to promote breast cancer, and the optimal dose of exercise to stimulate these changes. What's also unique about this study is that we'll be performing a study in mice that is the mirror image of the human clinical trial, known as a co-clinical trial. Using this approach, we'll be able to learn things in the mouse study that will inform analyses in the human trial. To my knowledge, this is the first study ever to adopt this approach in clinical exercise science in any chronic condition.

Similarly, we're going to be starting a randomized clinical trial in men with early-stage prostate cancer who are part of MSK's active surveillance program. In this approach, treatments such as surgery or radiation therapy are deferred because tests show that the tumor is currently not life threatening or is at low risk of progressing. Our trial is going to test the effect of 24 weeks of supervised aerobic exercise versus the usual care on the prostate microenvironment [the cellular environment in which a tumor exists] and cancer-related anxiety among these men. Again, to my knowledge, this will be the first trial to study the effects of exercise on changes in the tumor itself.

Findings from both these studies will provide unique insights into the effects of exercise on tumor and tissue biology as well as the biologic mechanisms underpinning these effects. This will help us design future studies as well as optimize the efficacy of exercise.

YOU'RE ALSO INTERESTED IN CANCER RECURRENCE AND METASTATIC DISEASE AND THE POTENTIAL IMPACT OF EXERCISE IN THESE CIRCUMSTANCES.

I am. I'm very interested in prevention of recurrence and even the role of exercise in individuals with advanced disease. We're starting to explore if and how exercise might affect the course of disease in these populations.

In terms of metastasis, I think exercise not only changes things like the breast tissue but also alters the microenvironments in tissues such as the lung and bone marrow – those places in the body where metastatic cancer cells may be dormant. I believe exercise may be able to actually change the microenvironment of such tissues to keep metastatic cancer cells asleep for longer – and perhaps even permanently. This is an area we're studying collaboratively with various colleagues at MSK.

YOUR WORK SPANS BOTH LABORATORY AND CLINICAL RESEARCH.

It does. Along with clinical studies in patients, we're also starting to build a robust laboratory research program. Among the things we're doing is working with mouse models as well as zebrafish [in collaboration with physician-scientist Richard White's laboratory in the Sloan Kettering Institute] to study what's going on at the molecular level to better elucidate the effects and underlying mechanisms of exercise training on cancer initiation and progression.

YOU JOINED MSK IN FEBRUARY 2014 AND SO ARE RELATIVELY NEW TO THE INSTITUTION. CAN YOU TELL US HOW YOU FEEL ABOUT YOUR EXPERIENCE SO FAR?

My expectations have already been far exceeded. Across the board – from oncologists to the clinical trials office and various administrative bodies – the support has been nothing short of incredible. I came to MSK because our program goal is to make precision exercise treatment part of the standard of care for people with or at risk of cancer. To accomplish this, we need to do the best science and build a convincing evidence base, and that requires that we be at the best cancer center. MSK is that place! ■

“We’re actually trying to approach the development and investigation of exercise treatment as you’d think about the development of a new drug. The drug we’re testing just happens to be called exercise.”

– LEE JONES





PIONEER/ PRIME MOVER

30 Years of
Changing How
the World
Treats Cancer

A Talk with John Gunn

In March 2015, John R. Gunn retired as Memorial Sloan Kettering's Executive Vice President and Chief Operating Officer. Mr. Gunn joined MSK in 1982 as Vice President of Finance and was a principal MSK leader and a confidant to three successive presidents throughout his long and distinguished service.



Mr. Gunn guided MSK's physical growth beyond the "superblock" at 1275 York Avenue in ways that have set the standard around the country. Starting with the Rockefeller Research Laboratories building (opened in 1989) and the Rockefeller Outpatient Pavilion (opened in the 1990s), and continuing through the current development of the Josie Robertson Surgery Center, he led the transformation of cancer care delivery in the ambulatory setting. With projects that spanned two decades, Mr. Gunn spearheaded efforts that created space to accommodate 21 new operating rooms, state-of-the-art pathology laboratories, and a new family-friendly Pediatric Day Hospital, all without disruption to MSK's ongoing patient-care activities.

The Mortimer B. Zuckerman Research Center, to which Mr. Gunn made significant and creative contributions, has allowed MSK scientists to explore the critical questions of cancer biology and to speed the translation of their discoveries into effective therapies. More recently, he provided leadership during the complex approval process for MSK's planned outpatient center on East 74th Street.

Here, he talks with us about the past 30 years in his own life and the life of MSK, and discusses his contributions to changing the way the world treats cancer.

YOU WERE BORN IN BRITAIN AND EDUCATED IN LONDON. WHY DID YOU COME TO THE UNITED STATES?

As a kid, when I was 11 or 12, I used to go into WH Smith, the newspaper and magazine seller in England. And I bought the *Saturday Evening Post* every week because it serialized stories. I also loved to look at the ads — at the cars and things like that. I promised myself that one day if I ever got the opportunity, I was going to see what the United States was like.

WHEN DID THE OPPORTUNITY PRESENT ITSELF?

In 1969, during the Vietnam War. A lot of young men had been drafted and it was difficult to find young qualified accountants in the United States. I was a chartered accountant in London, and Medicare was just starting. Blue Cross/Blue Shield of Chicago — who had a contract to do the audits — was looking for auditors. So the “Chicago Blues,” as they were known, came to London, recruited about 35 qualified accountants, and flew us over for this one-year project. I decided I should get a green card — which was easy to do back then — in case I liked it here.

During that year, I met some folks at Arthur Andersen, which was the big accounting firm in Chicago, and they asked if I’d like to work for them. I accepted their offer. One of my clients was Michael Reese Medical Center, which was going through fiscal problems. Eventually I got an offer to work in finance at Michael Reese. [Mr. Gunn stayed with Michael Reese from 1974 to 1982, rising to become Vice President of Finance.]

YOU JOINED MSK IN 1982 AS VICE PRESIDENT OF FINANCE. WHEN YOU ARRIVED, WHAT WAS THE BIGGEST CHALLENGE YOU FACED?

I was originally recruited for the purpose of fixing MSK’s accounts receivable. It was a pretty sloppy billing system. At the time, outpatient cancer care was a new activity for MSK, so we were barely collecting any money for our outpatient services. Inpatient was a little more straightforward. Physician billing was also a mess because a lot of it was done by the doctors themselves and some of it was done centrally. Simply put, everyone was doing their own thing.

My role was to try to pull it all together. It was a big issue with the Board. The then-chairman of the Audit Committee was John Reed, who later went on to run Citibank. His feeling was that if we couldn’t run this basic billing operation, how could we run the rest of the place? He worked very closely with me and my colleagues until we got it pretty well fixed.



1997

MSK President Paul Marks (left) celebrates with John Gunn at an awards dinner.



2003

(From left) Mr. Gunn with MSK’s new Chief Operating Officer Kathryn Martin and Douglas A. Warner III, Chairman of the Boards of Overseers and Managers, at the opening of MSK’s new pathology laboratories.



2015

MSK’s current President and CEO Craig Thompson (right) with Mr. Gunn at a reception honoring his retirement.

YOU WERE ALSO DEEPLY INVOLVED IN WORKING TO EXPAND PATIENT ACCESS TO MSK.

Yes. Anecdotally, shortly after I came to MSK, I bought a place in upstate New York. I'll always remember the broker saying, "God forbid anyone I know gets cancer — at least now I know someone at Memorial who'll be able to get us in."

I thought, How odd. Why would you need to know somebody to "get in"? But that was the perception at the time: that in order to become a patient at MSK, you needed to know somebody. I wanted to change that.

In the intervening years we've worked hard to overcome both the problem and the perception. We've definitely made progress with our Physician Access Service, our network of suburban locations, our various community outreach activities — but there's still work to be done to continue to expand access and to let people know that we're not a closed system.

IN THE EARLY YEARS OF YOUR TENURE, MSK WAS PRIMARILY DELIVERING CARE IN A HOSPITAL SETTING. HOW DID YOU BEGIN TO CHANGE THAT?

Except for pediatrics — they'd developed the Pediatric Day Hospital before I got here — you're right that MSK was mostly delivering care on an inpatient basis. So in the early to mid-1980s we started a big test to see if giving patients chemotherapy as outpatients made more sense than admitting them for a three-day hospital stay. The results proved conclusively that we had much happier patients because they got to go home. It was also safe, and it was a much less expensive way to deliver care.

Historically, if you look at MSK's revenue streams, back then it was about 60 or 70 percent inpatient, 20 percent outpatient, perhaps 10 percent doctors. Today, it's completely flip-flopped: It's about 70 percent outpatient, 20 percent doctors, and approximately 10 percent inpatient.

THE LAURANCE S. ROCKEFELLER OUTPATIENT PAVILION — KNOWN FAMILIARLY IN THE HALLS OF MSK AS 53RD STREET — WAS A BIG STEP IN THE FUTURE OF OUTPATIENT CANCER CARE.

True. But even before then we'd already renovated existing floors of the Enid A. Haupt Pavilion in the hospital for ambulatory care. By the 1990s, we'd outgrown those floors and we created the Evelyn H. Lauder Breast Center on East 64th Street.

Then in 1999 came the Rockefeller Outpatient Pavilion. And after that, the Sidney Kimmel Center for Prostate and Urologic Cancers on East 68th Street. And we're still growing. In 2009, we opened the MSK Breast and Imaging Center [which houses the Evelyn H. Lauder Breast Center], and this year we created yet another new outpatient facility on East 60th Street.

Next year, MSK will open the Josie Robertson Surgery Center to accommodate more ambulatory surgeries. [*See more about the JRSC on page 57.*]

A little side note: The 53rd Street building was the only facility Laurance ever agreed to have named after him.

OUR NETWORK OF SUBURBAN LOCATIONS HAS BEEN EXTREMELY IMPORTANT IN INCREASING PATIENT ACCESS TO MSK CARE.

Absolutely. They're a critically important piece of our overall cancer care delivery system. They were designed so that we could extend the highest standards of comprehensive cancer care — and the unparalleled expertise of our staff — to more patients within a unified system.

And we're continuing to expand our ability to treat patients in their own communities, both in terms of facility size and the geographic areas we cover. In 2014, we opened MSK West Harrison to serve residents of the Hudson Valley, and in 2016 we'll open MSK Monmouth, for people who live on the Jersey Shore and beyond.

CAN YOU TALK A BIT ABOUT HOW THE NEW MSK CANCER ALLIANCE CAME ABOUT? YOU WERE VERY INVOLVED IN THAT PROCESS.

Sure. There are two ways to go with the affiliation agreements. You can say, "Give us a million dollars and you can use our name." That's easy. But most of us at MSK think our name is probably our biggest single asset. You know, it's one of the probably five or six name brands in American medicine that's known across the country.

In typical MSK fashion, we took a possible affiliation very seriously and asked, "How can we truly improve cancer care in the community at a distance?" And that required us to make sure that our partner or the affiliate we chose was willing to come and be measured at the bar, so to speak.

And Hartford HealthCare [the first partner in the MSK Cancer Alliance] turned out to be that kind of a place. They took it very seriously and worked with us for almost a year before they got their certification. That required seeing what kind of cancer care they delivered, seeing where we thought it was lacking or where it was acceptable, getting them on a remedial plan to correct what they were doing up to a standard that we felt comfortable with, and then making them an affiliate.

Now, what's really in it for us? Access to a lot more patients. Because in doing clinical research today you need large cadres of patients, many more than we would treat as an individual institution. So one of the things driving the affiliation was how we would be able to do that. In the end, high-quality research yields better outcomes for patients. So far — touch wood — it's working out terrifically. Hartford HealthCare patients will be enrolled in MSK clinical trials that would otherwise have been unavailable to them.

YOU'VE WORKED WITH THREE MSK PRESIDENTS: PAUL MARKS, HAROLD VARMUS, AND NOW CRAIG THOMPSON. THESE ARE THREE VERY DIFFERENT MEN WITH VERY DIFFERENT STYLES. HOW HAVE YOU MANAGED IT?

I honestly don't think I've done many things that differently from president to president. I certainly spent a lot of time with each man and I probably helped grease a few wheels and soothe some ruffled feathers. Change is never easy – there will always be squeaky wheels and ruffled feathers. It may have also been useful that I have a fairly calm personality – my feathers aren't easily ruffled!

HOW HAVE YOU SEEN YOUR ROLE OVER MORE THAN 30 YEARS AT MSK?

There have been so many areas in which I've been involved over the years, but I'd say in an overarching sense my role has been to help our staff to get on and do well at their jobs. It's been to make sure that the voices of all our constituencies are heard and that we act according to their needs and concerns. This includes our patients, our doctors, our nurses, and our scientists.

I used to be involved in recruiting and, in particular, in actually getting people here. Moving to New York is a big deal. And if you're

paying someone a salary and want them to settle in quickly and get on with what they've been hired to do, well, you don't want them worrying about the cost of a roll of paper towels at Gristedes! For those coming from overseas it's even a bigger shock to the system. So to the extent that I've been able to help with that, I have.

One of my ideas that I believe has worked out well has been our employee orientation program, in which all new employees are required to participate before officially joining the MSK family. It came about when my wife and I went down to Disney World to Disney School, where they talked about how to take care of people in Disney World. Every one of their employees went through the orientation, and they were taught that the most important person they'd be dealing with is the customer. And that's what we tell people in orientation here: No matter what you do, the way you do it can have a positive or a negative effect on somebody with cancer – whether you're in research or are a security guard. It matters at all levels.

And one of the things I'm pleased about are the letters I've gotten over the years in which people say, "This was the most unique hospital I've ever been in anywhere in the world. Everybody was so nice – whether it was the lady delivering the food, or the woman coming in to sweep the floors, or the radiation oncology technician, or the nurse who really went out of her way to be helpful."

“From the time John joined us, we’ve been blessed to have had a leader with the wisdom, skill, and imagination to make extraordinary things happen. There are few lives at MSK that he hasn’t touched, including the hundreds of thousands of patients and families who have passed through our doors in the time he’s been with us. He’s guided our institution through good times and bad and has always asked the question – no matter what the issue, no matter how knotty the problem – ‘How can we make this work? How can we make it happen?’ And he has constantly strived to do what is good, and true, and right. John Gunn is a remarkable man. A brilliant, courageous leader. A generous collaborator. And a true friend.”

– DOUGLAS A. WARNER III
Chairman
Boards of Overseers and Managers

YOU'VE CLEARLY MOVED OUTSIDE THE PARAMETERS OF YOUR JOB TITLE!

I've taken on lots of responsibilities over the years to make sure things keep rolling. It's the old make-the-trains-run-on-time syndrome. But it's what I like best: thinking about the future, thinking about how we're going to stay on top. I enjoy challenges of all sorts.

LOOKING BACK, CAN YOU POINT TO A FEW THINGS THAT YOU'RE MOST PROUD OF?

I'm very proud of the fact that we were probably one of the first places in the country to go big into ambulatory chemotherapy because I believe it was good for our patients. I'm proud of 53rd Street, which was way ahead of its time and for which my wife, Clarice [Albright], gets much of the credit. [*Ms. Albright was MSK's Hospital Administrator at the time.*] She was instrumental in the physical design and I think it still holds up and works well to this day.

I'm proud of the Brooklyn Infusion Center because, again, we designed it around patient comfort and convenience.

And the deal with Amgen was pretty special! [*In the 1970s, MSK researchers isolated a naturally occurring protein called granulocyte colony stimulating factor, or G-CSF, that can stimulate bone marrow to produce more neutrophils, a type of white blood cell that fights off infections. The team then demonstrated that filgrastim — which is closely related to G-CSF — can be used to speed up the body's renewal of neutrophils after chemotherapy. Since 1991, filgrastim has been marketed by Amgen as Neupogen®.*] That license agreement, which has produced hundreds of millions of dollars over the more than 20 years we've had it, has been a big source of support for our research operations. [*The agreement is scheduled to end in 2017.*]

DO YOU THINK BEING BRITISH HAS HELPED YOU?

I do think that in New York it helps to sound British — people pay more attention to you! I also think that common sense and fair play have always been characteristics of good British administration. My management style has been to empower people — to set goals and then give people a long leash. Naturally, I believe in hiring good people and I carefully monitor progress, but it's all with the objective of seeing how we can continue to improve our services.

I've always encouraged people to take risks and I've wanted them to succeed with new ideas because it's the new ways of doing things that keep you ahead of the game.

ANY FINAL THOUGHTS FOR US?

There's an enormous responsibility we have at this institution. First and foremost, it involves being supportive of every single patient. Our patients trust us. Their families trust us. We can't let them down. I have been conscious of that every moment of every day I've been here. I'm not able to walk away from problems. I want to fix them.

I'm leaving MSK in the excellent and capable hands of Kathryn Martin, who will succeed me as COO. I've worked with Kathryn since 1999 in her role as Hospital Administrator and, more recently, as Senior Vice President and Hospital Administrator. She's led the hospital alongside Physicians-in-Chief David Golde, Bob Wittes, and José Baselga with vision, creativity, and intelligence.

I also want to mention Michael Gutnick, MSK's Executive Vice President and Chief Financial Officer. During the many years we've worked together, Mike has played a vital role in helping to maintain the financial stability of MSK — and he'll continue to do so with outstanding skill.

I'll miss my colleagues and my friends here, although I'll keep in touch and will follow MSK as it moves into the future. I am much more proud of this place than I am of myself. This is a very unique organization with a great Board, a superb management team, and wonderful people.

I sometimes joke that this is such an extraordinarily strong organization that it's managed to be successful despite me in my role and the three presidents we've had to date [*Mr. Gunn says with a big, dry smile!*] ■■■

“When I think of John Gunn, I think of guidance, inspiration, and creativity. I think of his focus on providing patients with the most advanced, comprehensive, and humane cancer care available. I also think of his equally tireless efforts in championing the programs and facilities that have made possible the research that contributes to that care. John has been one of the chief visionaries behind MSK's expansion plans, both clinical and scientific. He understood our past and our future, and his vision has had a profound and lasting impact on this institution.”

— CRAIG B. THOMPSON
President and CEO



2014
YEAR IN
REVIEW

STATISTICAL PROFILE

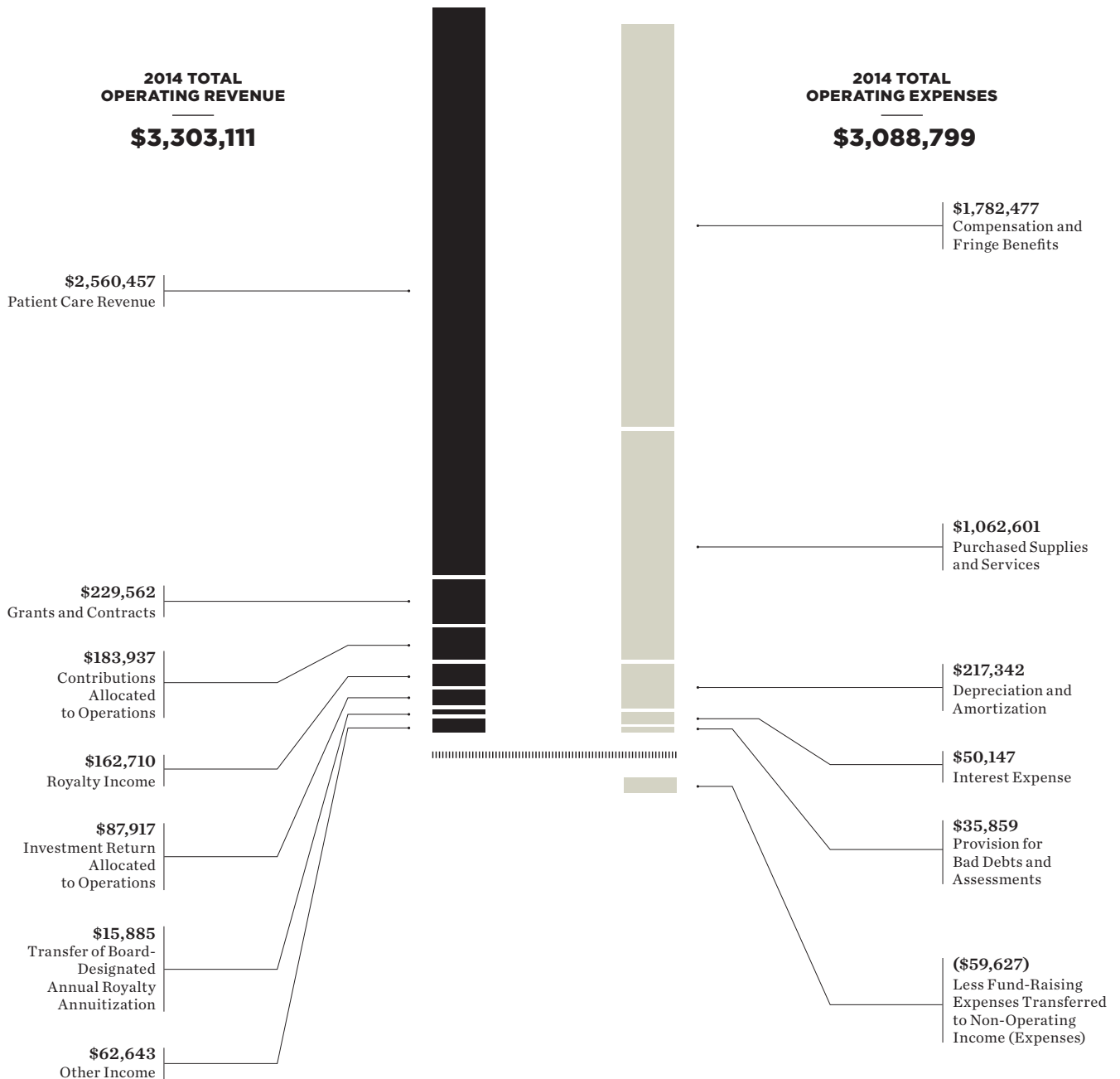
	10	11	12	13	14
PATIENT CARE					
Patient Admissions: Adults	22,852	22,983	23,139	20,773	20,640
Patient Admissions: Children	1,494	1,503	1,459	1,553	1,504
Total Admissions	24,346	24,486	24,598	22,326	22,144
Total Patient Days	143,532	140,990	149,368	144,345	146,855
Average Patient Stay (days)	5.9	5.8	6.1	6.5	6.6
Bed Occupancy Rate (based on adjusted bed count)	83.7%	82.2%	87.0%	83.0%	84.3%
Outpatient MD Visits: Manhattan	418,415	432,802	436,510	463,724	480,260
Outpatient MD Visits: Regional Network	97,658	103,098	104,964	108,198	113,699
Total Outpatient Visits	516,073	535,900	541,474	571,922	593,959
Screening Visits	23,373	20,518	15,519	12,826	10,282
Surgical Cases	19,362	19,374	19,691	20,465	20,420
Radiation Treatments and Implants: Manhattan	59,223	60,393	60,289	61,335	62,375
Radiation Treatments and Implants: Network	47,926	51,615	50,476	53,660	55,229
Total Radiation Treatments and Implants	107,149	112,008	110,765	114,995	117,604
Diagnostic and Interventional Radiology Procedures	362,609	377,360	391,187	416,360	435,501
Clinical Investigation Protocols (excludes studies closed to accrual)	552	552	657	735	776

	10	11	12	13	14
STAFF					
Sloan Kettering Institute Members	142	143	146	143	140
Hospital Attending Staff	804	834	876	935	995
Registered Nurses	1,945	2,018	2,133	2,221	2,373
Administrative and Support Staff	8,613	8,989	9,281	9,707	10,223
Total Staff*	11,469	11,950	12,402	12,975	13,699
Volunteers	942	1,058	1,018	1,004	902
EDUCATION					
Residents and Clinical Fellows — Positions	447	440	445	464	465
Residents and Clinical Fellows — Annual Total	1,625	1,676	1,682	1,691	1,674
Research Fellows	295	321	320	323	351
Research Scholars	132	131	124	133	110
Research Associates	94	82	89	91	95
Graduate Research Assistants	23	29	39	41	47
PhD Candidates	231	225	222	227	239
MD/PhD Candidates	26	21	21	19	18
Registrants in CME Programs	2,554	2,533	3,968	3,681	5,614
Medical Observers	541	526	566	630	579
Medical Students	391	419	431	392	505
Nursing Students	105	142	178	179	257
Social Work Students	6	6	6	7	7
Radiation Oncology Technology Students	14	14	13	15	15
Physical Therapy Students	3	4	7	2	6
Occupational Therapy Students	3	3	4	2	3

*In 2014, 32 staff members held appointments in both the Institute and the Hospital.

FINANCIAL SUMMARY

(in thousands)



	10	11	12	13	14
OPERATING REVENUES (in thousands)					
Patient Care Revenue	\$ 1,854,776	2,141,421	2,201,941	2,367,731	2,560,457
Grants and Contracts	186,327	190,948	185,160	202,061	229,562
Contributions Allocated to Operations	117,323	130,791	144,497	164,943	183,937
Royalty Income	68,663	77,510	78,350	94,058	162,710
Other Income	44,874	48,351	51,167	57,150	62,643
Investment Return Allocated to Operations	100,389	104,699	75,877	82,028	87,917
Transfer of Board-Designated Annual Royalty Annuitization	41,578	46,417	51,709	57,495	15,885
Total Operating Revenues	\$ 2,413,930	2,740,137	2,788,701	3,025,466	3,303,111
OPERATING EXPENSES (in thousands)					
Compensation and Fringe Benefits	\$ 1,361,032	1,466,667	1,582,212	1,689,501	1,782,477
Purchased Supplies and Services	772,968	835,621	879,219	924,691	1,062,601
Provision for Bad Debts and Assessments	11,046	18,285	17,541	19,969	35,859
Depreciation and Amortization	175,494	195,461	210,810	210,373	217,342
Interest Expense	47,931	57,098	54,894	55,039	50,147
Less Fund-Raising Expenses Transferred to Non-Operating Income (Expenses)	(43,926)	(44,665)	(47,305)	(52,470)	(59,627)
Total Operating Expenses	\$ 2,324,545	2,528,467	2,697,371	2,847,103	3,088,799
Income from Operations	\$ 89,385	211,670	91,330	178,363	214,312
PHILANTHROPY (in thousands)					
Philanthropy	\$ 237,666	301,374	231,159	380,500	376,533
CAPITAL SPENDING (in thousands)					
Capital Spending	\$ 262,371	223,251	258,613	315,282	473,859
BALANCE SHEET SUMMARY (in thousands)					
Assets	\$ 6,448,415	6,790,005	7,795,606	8,481,418	8,980,672
Liabilities	2,550,889	2,848,843	3,562,546	3,337,444	3,614,264
Net Assets	\$ 3,897,526	3,941,162	4,233,060	5,143,974	5,366,408

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FACILITIES UPDATE

The Memorial Sloan Kettering Josie Robertson Surgery Center is a first-of-its-kind freestanding outpatient and short-stay cancer surgery facility. It will offer a seamless experience for both patients and their caregivers, providing them with exceptional care using the latest in surgical technology — all in a serene and beautiful environment.



The Josie Robertson Surgery Center (JRSC), made possible by a generous commitment from the Robertson Foundation, will open in 2016. This 16-story, 179,000-square-foot building on York Avenue between East 61st and 62nd Streets will feature 12 operating rooms equipped to provide technologically sophisticated surgical care — including minimally invasive and robot-assisted procedures — on an outpatient basis.

This technology and the expertise of our surgeons and support staff will allow us to perform cancer surgeries that have typically required hospitalization but that now can be performed safely on an outpatient basis, with a single overnight stay. MSK is one of only a handful of cancer hospitals offering this type of leading-edge surgery.

Patient and family engagement is central to the JRSC experience. Education, preoperative preparation, and technological innovation will help patients and families participate in their own care. For example, an online patient portal and mobile device application will help them prepare for the day of surgery, permitting interactions with their team of healthcare professionals as well as giving them the ability to ask questions and monitor their post-surgery progress.

A real-time location system will enable patients and caregivers to move freely around the JRSC rather than remain tethered to waiting rooms. Twenty-eight private postoperative recovery rooms with private bathrooms will offer sleeper sofas and recliners for caregivers.

The facility is designed to encourage patients to get out of their rooms and walk as well as to engage them and their families in actively participating in their care, both in the facility and at home after discharge.

Top: An exterior view of the Josie Robertson Surgery Center as it nears completion.
Middle: A waiting area with a view of the Queensboro Bridge through floor-to-ceiling windows.
Bottom: A café where patients and caregivers can purchase food, eat, and relax.

THE CAMPAIGN FOR MEMORIAL SLOAN KETTERING

Memorial Sloan Kettering benefited enormously from the generosity of thousands of donors who made contributions large and small to the Campaign.



Douglas A. Warner III Louis V. Gerstner, Jr. Craig B. Thompson

Fueled by over a million gifts received from supporters around the world, the Campaign for Memorial Sloan Kettering maintained its strong forward progress in 2014. As of December 31, the Campaign had recorded \$3.53 billion in gifts and pledges, with two years still remaining in the historic fundraising effort.

From its outset, the Campaign has benefited from the leadership of co-chairs Douglas A. Warner III and Louis V. Gerstner, Jr., who work closely with President Craig B. Thompson and their colleagues on the MSK Board to generate philanthropic support for MSK's most pressing needs.

The Campaign achieved impressive results at every gift level during the year, which ended on a high note: A total of \$83.4 million in gifts and pledges were recorded in December. Under the direction of Anne M. McSweeney and Richard K. Naum, the MSK Development Office has built a solid foundation for ongoing achievement that will be crucial in the years ahead.

It was another standout year for MSK's athletic fundraising initiatives, including Cycle for Survival and Fred's Team, which help spread the word about the important work being done at MSK while engaging thousands of supporters in the fight against cancer. Together with Equinox, the event's founding partner, Cycle for Survival has become the fastest-growing such event in the country, attracting 85,000 new donors in 2014 — an increase of 22 percent over the previous year. Since its founding in 2007, Cycle for Survival has raised more than \$76.4 million for research into rare cancers.

The Campaign's strong continued achievement is inspired by the extraordinary accomplishments of MSK's talented physicians and scientists, and the generous support that benefactors provide is helping to drive further progress, now and in the years to come.



Top: Cycle for Survival's national events culminate with several rides throughout New York City, including this one at Equinox's Bryant Park location.
Bottom: MSK nurse and Fred's Team member Anna Giallo-Uvino running the TCS New York City Marathon.

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THE SOCIETY OF MEMORIAL SLOAN KETTERING CANCER CENTER

“For nearly 70 years, members of The Society of MSK have made a difference in the lives of our patients. We’re grateful for the personal dedication they demonstrate and the important programmatic activities they enable.”

– CRAIG B. THOMPSON
President and CEO

“The Society is a unique part of the MSK team,” says Martha Vietor Glass, The Society President from 2013 to 2015. “We enjoy a dynamic partnership with MSK leadership to identify special needs of an immediate and long-term nature in both research and patient care. After we raise support through our members, our Administrative Board is excited to be able to fund projects that strengthen and enhance MSK’s mission.”

SUPPORTING RESEARCH

One of The Society’s central focuses is funding nascent research that is often too early to receive support from conventional sources. By sponsoring new and innovative research, The Society has helped launch the investigations of young scientists and has provided an opportunity for established researchers to explore leading-edge ideas.

In 2014, The Society’s Special Projects Committee funded the research of five MSK scientists. The projects included the development of a new way to combat drug resistance in cancer and a study using mouse models — complemented by analysis of human genetic data and tumor samples — to identify pathways that drive tumor progression in a childhood brain cancer called medulloblastoma.

The Society’s Research Grants support clinical and translational research projects, many of which go on to become permanent programs and features of MSK. In 2014, the grant program funded seven proposals. These included a study to evaluate whether genetic mutations can explain why some patients with lung cancer respond to immunotherapies while others don’t, a study that aims to enable clinicians to detect heart damage from chemotherapy before it becomes permanent, and research that will develop a novel pharmaceutical approach to ameliorate graft-versus-host (GvHD) disease in patients after allogeneic stem cell transplantation. GvHD occurs when a donor’s immune cells attack cells in a recipient’s body and can be a fatal complication of transplantation.

The Society also supports research through the Associates Committee Fall Party, which in 2014 raised funds to accelerate the launch and support of clinical trials of a treatment that promises to change the future of pediatric sarcoma.

The Annual Appeal, a tradition since 1946, supports research and sometimes patient care programs through a personal letter-writing campaign. This year, the Annual Appeal directed its efforts to funding research in leukemia and an exciting new way to fight the disease.



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SUPPORTING PATIENT CARE

If any Society member were asked to define the other key purpose of the organization, the words “patient care” would echo again and again. The group has had a long-time commitment to enhancing the patient experience by providing activities and events outside of the treatment routine.

Patient programs that support artistic expression, special projects that brighten the patient environment, visits from Big Apple Circus clowns to the Department of Pediatrics, flowers in waiting areas, and festive holiday activities throughout the year are just some of the ways that The Society improves the days of MSK’s patients.

For decades, some of the most celebrated Society traditions have centered on making the winter holidays a joyful time for Memorial Hospital inpatients by sponsoring parties for both children and adults, complete with overflowing gift bags.

In May 2014, The Society hosted its seventh annual Spring Ball. The event raised funds for The Society’s Patient Assistance Program initiative, which provides emergency financial assistance to MSK patients to help with nonmedical expenses.

And in June, more than 200 pediatric patients — from toddlers to teens — partied up a storm at the annual Pediatric Prom. The event, hosted by The Society’s Children’s Committee, enables children and young adults who are being treated for cancer to celebrate with family, friends, and pediatric medical and support staff.

To increase accessibility and encourage support for its mission, The Society introduced its newest donor group, The Society Circle, in 2014.

1. The 24th annual Bunny Hop benefited MSK’s Department of Pediatrics.

2. (Left to right) Debra Pipines, 2014 Society Finance Committee Chairman; 2014 research grant recipients Matthew Hellman, MD, Paul Paik, MD, Sean McBride, MD, MPH, and Andrew Plodkowski, MD; MSK President and CEO Craig Thompson; MSK Physician-in-Chief José Baselga; Martin Voss, MD, Robert Young, MD, and Johannes Zakrzewski, MD, also recipients of 2014 research grants; and Society President Martha Vietor Glass.

3. Santa comes to MSK bearing holiday gifts.

4. Ms. Vietor Glass (center, in red) joins Spring Ball Chairmen (left to right) Alexi Meyers, Claudia Overstrom, Maria Villalba, and Lisa McCarthy.

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