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MSKNews

MEMORIAL SLOAN KETTERING CANCER CENTER

Targeting Cancer's Habitat

MSK's Bold New
Project To Help
More People
Like Bridget

ALSO INSIDE

Making Immunotherapy
Work for More Patients

The Microbiome and Its
Role in Cancer

Meet Tracy Gosselin:
MSK's New Chief Nurse



Memorial Sloan Kettering
Cancer Center

Dear MSK Community,

We are poised at a pivotal moment in cancer research.

For the past few decades, researchers have focused on identifying gene mutations associated with cancer and have developed highly effective drugs to target them. This revolutionary approach, called precision oncology, has saved countless lives. Yet too many people still die from cancer, and we now know that addressing genetics alone cannot save most of them.

Up to 90% of the 600,000 Americans who will die from cancer this year will die from metastasis, when cells from a primary tumor spread to other parts of the body. Precision oncology cannot cure metastatic cancer because, to our knowledge, there are no gene mutations that specifically drive metastasis.

The next treatment revolution will come from understanding cancer as a systemic, rather than a predominantly genetic, disease — one that begins in a single location but relies on conditions throughout the body to spread. Just as invasive plants or fish can only thrive in a nurturing habitat, cancer too requires the right conditions to flourish in the body's complex ecosystem. Immunotherapy, developed at Memorial Sloan Kettering Cancer Center (MSK), already provides an example of how to leverage a component of the patient's body, the T lymphocytes, to attack cancer.

This issue of *MSK News* will report on the mission of the new **Marie-Josée and Henry R. Kravis Cancer Ecosystems Project**, an ambitious program to investigate cancer beyond genetics. This \$100 million initiative will explore how tumors interact with the nervous, endocrine, and immune systems; the gut microbiome; and lifestyle factors like stress and obesity.

The research supported by the Kravis Cancer Ecosystems Project is categorized as “basic science” — meaning it seeks to answer fundamental biological questions rather than test therapies in patients. Basic science is anything but simple or ordinary. It unravels how living systems work. This knowledge leads to better ways to predict, prevent, diagnose, and treat disease. Every breakthrough in cancer therapy started out years — even decades — earlier in the bustling lab of a scientist who was curious about an unexplained phenomenon. With a hunch and a hypothesis, basic researchers follow the science wherever it leads. The end results can be spectacular. Without someone asking why our bodies are able to fight off sickness, we would not today have cancer immunotherapy.

Our commitment to basic science distinguishes MSK from all other cancer hospitals conducting research. The investigators at the Sloan Kettering Institute are like artists and inventors, engaged in a fundamentally creative process that doesn't always progress in a straight line.

This generous gift will give our scientists the freedom they need to take risks and test bold ideas. Their achievements are sure to benefit people with cancer around the world.



Sincerely,

Joan Massagué

Marie-Josée and Henry R. Kravis
Foundation Chair
Director, Sloan Kettering Institute

MSKNews

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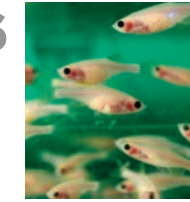
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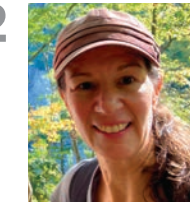
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MSK investigators are leading the way with approaches so bold they

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MSK's new nursing executive shares her mantra for leading nurses and listening to patients: “Keep calm and hurdle on.”

BACK COVER Transformative Giving: Marie-Josée and Henry R. Kravis

Their philanthropy has already revolutionized cancer research. Now they are doing it again, by supporting the exploration of the complex ecosystem that permits cancer to thrive — or not — in the body.

Congratulations!

These prestigious honors will be awarded in early June by ASCO, the American Society of Clinical Oncology:

Fumiko Chino, MD, will receive the inaugural Excellence in Equity Award for increasing access to care.

Craig B. Thompson, MD, will receive the Science of Oncology Award for his basic and translational research.

Jedd D. Wolchok, MD, PhD, will receive the David Karnofsky Award for his contributions to the diagnosis and/or treatment of cancer.



Scan the QR code with your smartphone's camera to read more.

Weeds in the Garden

The Bold New Project To Uproot Cancer's Ecosystem

When the ambitious effort to sequence all the DNA in the human genome completed its first draft in 2000, scientists and government officials around the world heralded the achievement of the Human Genome Project.

"Without a doubt, this is the most important, most wondrous map ever produced by humankind," said President Bill Clinton, likening it to the American frontier map created by explorers Meriwether Lewis and William Clark in 1806. "With this profound new knowledge, humankind is on the verge of gaining immense new power to heal."

Indeed, the Human Genome Project led to many important scientific and therapeutic advances. Thanks to the technology spurred by the project, it eventually became possible to sequence the genomes of tumors, too. Scientists discovered specific changes in the DNA sequence of genes — specific mutations — that transformed normal cells into cancer cells. In turn, this led to the development of drugs that target tumors with these mutations in order to save more lives.

However, two decades later, scientists have also uncovered what genes do not control, and what they cannot explain about health and illness.

The more scientists learn about genetic mutations, the more they are coming to understand that such DNA changes alone do not cause cancer. A recent study of more than 25,000 MSK patients found no single gene that, when mutated, would predict whether a tumor will metastasize to a particular organ.

"Specific mutations do little to explain how individual cancers spread," says **Joan Massagué, Director of the Sloan Kettering Institute and the Marie-Josée and Henry R. Kravis Foundation Chair.** "It's all about adaptation of the spreading tumor to the organs it travels to."

In fact, scientists now know that the same genetic mutation that promotes cancer in one tissue may leave another unscathed, highlighting the need to understand what else is going on.

This need to look beyond genes, to the interactions among genes, cells, tissues, organs — even whole-body systems — is the mission of the newest scientific initiative from Memorial Sloan Kettering Cancer Center (MSK): The Marie-Josée and Henry R. Kravis Cancer Ecosystems Project.

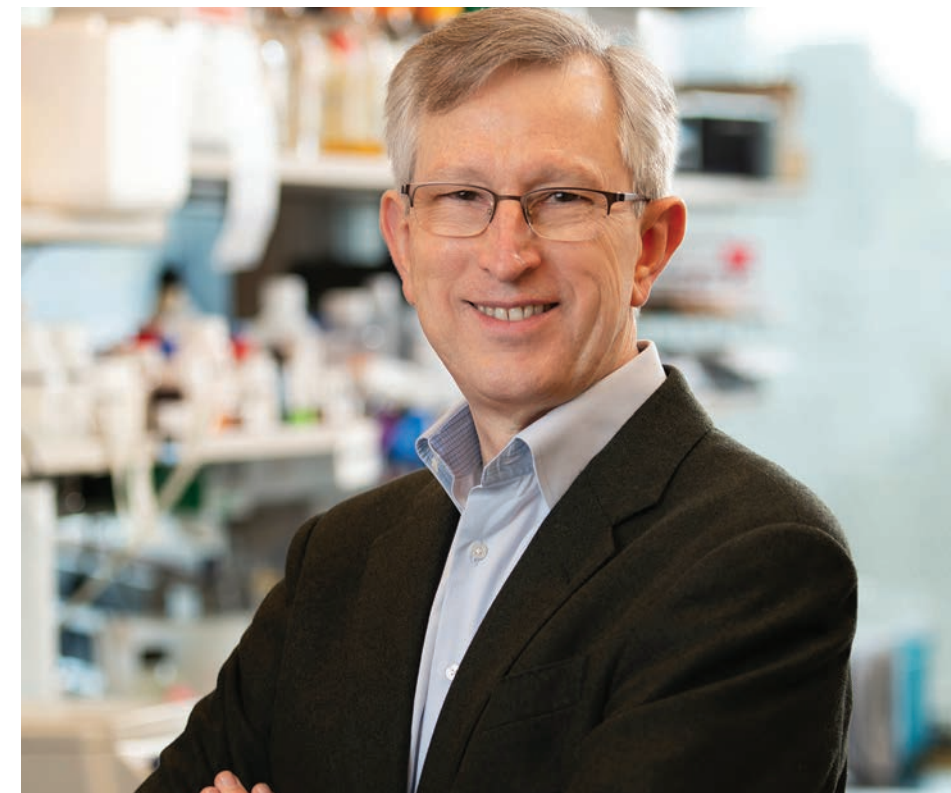
"It is for us, as scientists and physicians, a watershed moment in cancer research," says Dr. Massagué, who will oversee the project. "We are shifting the focus from mutant genes in the context of cancer genomes — a staple of research over the past decade and a great source of therapeutic as well as diagnostic insights — to a focus on cancer cells in the context of biological ecosystems."

As its name implies, the Kravis Cancer Ecosystems Project will galvanize a more global and systemic approach to cancer research than has previously been undertaken, with the aim of tackling the most difficult remaining cancer challenges, including that of metastasis. But first, what exactly do scientists mean by the cancer ecosystem?

Cancer's Habitat

Consider the ecosystem that we are all more familiar with — the one outside our doors. That ecosystem is made up of the plants and animals that make their home there. It also includes the food they consume, the elements and minerals that are recycled when organisms die, and the nonliving parts of the environment (like precipitation and temperature) that affect the climate. The parts of an ecosystem are all inter-connected; changing one part can have a cascading effect on the others.

Likewise, tumors are part of a wider ecosystem that determines how they grow. They are affected not only by the genes they carry but also by the environments they encounter as they develop and spread. Cancer is not just a disease of a tumor but a disease of the whole organism that has it.



Joan Massagué, Director of the Sloan Kettering Institute, will oversee the new Kravis Cancer Ecosystems Project.

More than a century ago, the English doctor Stephen Paget proposed the "seed and soil" hypothesis to explain how cancer spreads. The idea was that cancer cells are like seeds that require a fertile and compatible soil in order to grow.

The Kravis Cancer Ecosystems Project takes an even wider, more comprehensive view. If a tumor is like a weed, then the weed's ecosystem includes the soil the weed finds itself in, the nutrients that flow in and out of that soil, the competition from nearby plants that also require those nutrients to grow, the sunlight that warms and feeds the plant or is blocked by trees, the predatory insects that feed on the weed's leaves, and even the animals that help disperse seeds. All these factors influence whether the weed thrives or succumbs to heartier vegetation.

"It is for us, as scientists and physicians, a watershed moment in cancer research to focus on cancer cells in the context of biological ecosystems."

—Joan Massagué

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Understanding the Cancer Ecosystem

There are many similarities between nature's ecosystem (left page) and your body's ecosystem (right page). Think of a tumor like a weed, whose growth depends on many factors.

Temperature

Precipitation

Photosynthesis

Respiration

Decomposition



Weed

Removal/Destruction

Predatory insects eat and may kill a growing plant, similar to how macrophages and other immune cells attack a growing tumor.

Competition

Other plants and animals compete with the weed for space and resources, just as normal cells compete with a tumor.

Microenvironment

The pH of the soil, like that of the tumor microenvironment, can affect growth.

Energy

Plants obtain their energy from the sun, while tumors burn glucose and fats for energy.

Dispersal

Tumor cells continually break off from a primary tumor and spread to other locations, like plant seeds dispersed by wind.

Growth

Hormones from the endocrine system and messages from the nervous system provide growth signals for the tumor, in the same way that plant hormones trigger germination.

Microbiome

Our digestive system contains microbes that help us digest nutrients, much the way fungi and other decomposers recycle nutrients in a forest.

Nutrients

Tumors get nutrients from blood vessels much like roots get nutrients from the soil.

Nerve

Immune cell

Tumor

Nervous System

Endocrine System

Immune System

Circulatory System

Digestive System

Targeting the Ecosystem

The more scientists understand about the cancer ecosystem, the more they can begin to think about therapies designed to block parts of it — depriving a pesky weed of the opportunity to take over your garden.

In concrete terms, that means understanding more about several key biological processes. Perhaps the most immediate is understanding cancer's metabolism: how it takes in and uses nutrients for energy and building blocks. Scientists at MSK, including **cell biologist Lydia Finley** and **cancer biologist Craig B. Thompson** (Douglas A. Warner III Chair), are learning that cancer cells can adapt their metabolism in ways that give them the unusual capacity to reproduce endlessly. Not only that, but the particular metabolic pathways they use can alter their identity in ways previously unrecognized — for example, making them more like stem cells, with the potential to develop into many different types of cells in the body.

Also crucial to understanding cancer are the interactions between tumor cells and other cells in the immediate environment, most especially immune cells. **Immunologist**

Andrea Schietinger (Catherine and Frederick R. Adler Chair for Junior Faculty and former Josie Robertson Investigator), is laser-focused on understanding why immune cells often fail to stop cancer from growing in their midst (see page 9). Collaborating with her are the many clinicians and translational researchers at MSK who work with patients and patient-derived tissue samples.

Cancer biologists Joan Massagué, Adrienne Boire (Geoffrey Beene Junior Faculty Chair), and **Karuna Ganesh** (Josie Robertson Investigator) are dedicated to studying the deadly process of metastasis and the question of how cells that are shed from tumors can make their way in often hostile new environments. They are learning that metastatic cells co-opt the normal processes of wound healing to take root in new organs.

SKI scientists Justin Perry, Alexander Rudensky, and **Philipp Niethammer** are determined to understand the role of inflammation in nurturing tumor growth, while **cancer biologist Scott Lowe** (Geoffrey Beene Chair) and **computational biologist Dana Pe'er** (Alan and Sandra Gerry Chair)

are exploring the role of the tumor stroma in doing the same.

Figuring out how cancer hijacks normal development pathways is the mission of **developmental biologists Anna-Katerina “Kat” Hadjantonakis** (Alfred P. Sloan Chair), **Charles Sawyers** (Marie-Josée Kravis and Henry R. Kravis Chair in Human Oncology and Pathogenesis), and **Danwei Huangfu**. And that's just the tip of the iceberg.

In fact, the more scientists learn about cancer, the more they are realizing that nearly every system in the body — from the endocrine system to the nervous system to the digestive system — can affect cancer growth. With that knowledge comes the hope that each of these systems could one day become a target for cancer therapies.

“Immunotherapy has shown us the tremendous power of treatments that leverage components of the cancer ecosystem to attack tumors,” Dr. Massagué says. “We believe that new findings to emerge from the Kravis Cancer Ecosystems Project will allow us to leverage other components of the ecosystem to the same end.”

And so a new era begins. •

Making Immunotherapy Work for More People

Symantha Wilson knows she is one of the lucky ones. The 26-year-old Long Island resident was nearing the end of a six-month chemotherapy regimen for stage 2 Hodgkin lymphoma last June. The treatment had been very effective, wiping out most of the cancer cells. But with just over a month left in her regimen, she was crushed to learn that her blood cancer was growing resistant to the therapy.



The more scientists understand about the cancer ecosystem, the more they can begin to think about therapies designed to block parts of it — depriving a pesky weed of the opportunity to take over your garden.

Memorial Sloan Kettering Cancer Center (MSK) is grateful to **Alan and Sandra Gerry** and **Marc and Jennifer Lipschultz** for their support of metastasis research at MSK.

“To be so close to thinking that I beat it and then get that news was devastating,” Symantha says. “I felt like, ‘Maybe this is it for me. I don’t stand a chance.’”

Her doctor on Long Island referred her to Memorial Sloan Kettering Cancer Center (MSK), where she joined a clinical trial led by **medical oncologist Alison Moskowitz**. The study was testing a drug that works by harnessing the immune system to fight the cancer. Doctors would combine this drug, called pembrolizumab (Keytruda®), with a different chemotherapy regimen and then perform a stem cell transplant.

Pembrolizumab is known as a checkpoint inhibitor. It works by releasing a natural brake that the immune system places on powerful immune T cells so they don’t accidentally attack normal cells. Cancer cells hide from attack by tripping the brake, hoping to fool T cells into believing they are normal. But checkpoint inhibitors release the brake, allowing the T cells to activate, recognize, and attack tumors.

Symantha began the treatment in September. After only six weeks, her

cancer was undetectable, and she was able to have the stem cell transplant. Four months later, she remains cancer-free. Her doctors say her outlook is excellent.

“It was so scary and discouraging to hear my cancer was growing even as I was getting chemotherapy,” she says. “Then to fast-forward six weeks and not have cancer at all — thanks to science and God’s help — it was truly amazing.”

Why Doesn’t Immunotherapy Work for More Patients?

Immunotherapy has undoubtedly saved many people. But the sobering truth is that cases like Symantha’s are still the exception. Far too often, immunotherapy does not work. Checkpoint inhibitors fail to be effective in up to 80% of patients. The success rate is not much better with chimeric antigen receptor (CAR) T cells, which engineer a patient’s own cells to attack the cancer. CAR T therapies are difficult to administer and so far, have only worked for certain blood cancers.

“It was so scary and discouraging to hear my cancer was growing even as I was getting chemotherapy. Then to fast-forward six weeks and not have cancer at all — thanks to science and God’s help — it was truly amazing.”

—Symantha Wilson



Santosha Vardhana has discovered that T cell behavior is greatly affected by nutrients in the surrounding environment, an important insight into the ecosystem of cancer in the human body.

“We haven’t really understood how or why T cell exhaustion happens, which is critical to making immunotherapy work for more people.”

—Santosha Vardhana

Sadly, many people initially respond to immunotherapy only to find the benefits are fleeting.

“One tragic element of the immunotherapy revolution is how it changes the expectation for even some of our very sick patients,” says MSK **physician-scientist Santosha Vardhana** (Josie Robertson Investigator), who treats people with lymphoma. “Many of them experience a brief wisp of promise. They just start to experience the possibility of joy and then have it taken away.”

When Immune Cells Stop Working

The immune system does its best to fight cancer cells naturally: T cells sense danger, flock to tumors, even invade them. But then they lay down their arms. Something causes the T cells to become dysfunctional. They enter an exhausted state in which they can no longer self-renew and give rise to cells to keep the attack going. It’s called “T cell exhaustion.” Immunotherapy seeks to boost the immune system to keep up the fight, but too often, it doesn’t work.

MSK researchers, including Dr. Vardhana, are trying to unravel the mystery. It’s proving to be extraordinarily complex.

“We haven’t really understood how or why T cell exhaustion happens,” Dr. Vardhana says. “Because of that, we don’t

really have good strategies that reverse it, which is critical to making immunotherapy treatments work for more people.”

Thinking Outside the Box

Also keenly interested in understanding T cell exhaustion is **Andrea Schietinger, an immunologist in the Sloan Kettering Institute** (Catherine and Frederick R. Adler Chair for Junior Faculty and former Josie Robertson Investigator). In 2017, her lab reported in *Nature* that T cells become dysfunctional through successive waves: When T cells enter tumors, they quickly lose their ability to kill cancer cells, but their fate is plastic — there is an early window in which they can still be reactivated. But with time, the T cells become exhausted and settle into a fixed state in which they cannot be reprogrammed. Presumably then, checkpoint inhibitors work when they catch the T cells early enough — in their plastic state.

But Dr. Vardhana says it’s becoming clear the drugs don’t actually reverse T cell exhaustion. Instead, checkpoint inhibitors seem to “extract the remaining juice” out of exhausted T cells. Furthermore, the drugs seem to work only if the tumor has a lot of mutations that the T cells can attack, or if the tumor is small enough that the T cells don’t have as much work to do.

In 2019, Dr. Schietinger discovered something even more surprising about T cells in tumors: They enter the exhausted state to save themselves. They stop fighting to avoid becoming overstimulated and dying. It’s about their own survival, Dr. Schietinger reported in a study published in *Nature*.

All together, these findings show, simply “taking the brakes off” the immune system with checkpoint inhibitors won’t suffice. “We need to look at everything causing T cell exhaustion and find ways to prevent or undo it,” Dr. Schietinger says.

How the Ecosystem Could Help T Cells Keep Fighting

MSK scientists are laser-focused on understanding cells in the ecosystem around tumors, because those surrounding cells send various signals to the T cells. Investigating how those signals are then processed or metabolized by the T cells is the focus of research funded by a prestigious grant received by Dr. Vardhana — the 2022 Damon Runyon Cancer Research Foundation-Rachleff Innovation Award. He is studying lung cancer and

mesothelioma, because in both diseases there is a buildup of fluids and cancer cells in the pleura, a thin layer of tissue between the chest wall and the lung.

“We focused on these cancers because we wanted to be able to sample the environment a T cell is living in,” he says. “It’s really hard to get samples from most tumors, which are tightly packed, but the pleural fluid offers a very clean way to look at the environment where T cells have to live and function as they try to respond to tumors.”

Much to their surprise, his team found that T cells in the pleural fluid are not capable of mounting an immune response. Once they enter this space, they are instantly told to stand down, so immunotherapies don’t work. This suggests that certain ecosystems in the body may naturally suppress all T cell function.

“The fundamental decision a T cell has to make is whether to turn on and attack when it detects something that seems to be foreign, like a cancer cell,” says Dr. Vardhana. “We’re learning that the environment around the T cell can fine-tune its behavior.”

Dr. Vardhana’s lab has found evidence that T cells can change their entire state — becoming dormant or active — based on how they metabolize nutrients obtained from their environment. Therefore, adding or depleting nutrients in their ecosystem could theoretically activate T cells to attack the cancer.

“We’re excited to probe this further because it could have broad implications for improving immunotherapy in many cancers,” he says.

Learning From Autoimmune Disease — When T Cells Go Into Overdrive

Another way to combat T cell exhaustion could be changing the T cells themselves. In a bold study launched four years ago, Dr. Schietinger’s team took a cue from immune cells in autoimmune diseases, where the immune system goes into overdrive and attacks the body’s own organs

relentlessly. Dr. Schietinger asked: “What is it about autoimmune T cells that they never give up? Why don’t they get exhausted?”

“We thought if we could figure out how autoimmune T cells are programmed, we could take that information and apply it to tumor-specific T cells to make them more effective cancer killers,” she says.

It was an out-of-the-box idea. To pursue this ambitious research project, Dr. Schietinger also received a prestigious grant — the National Institutes of Health Director’s New Innovator Award in 2017. Her team studied mice that spontaneously develop type 1 diabetes, an autoimmune disease where T cells destroy insulin-producing cells in the pancreas. Their surprising findings were published in 2021 in *Nature*: There are stem-like T cells in lymph nodes that can generate billions of new highly functional killer T cells, so they are constantly resupplied. That’s why the T cell destruction of the pancreatic cells never stops.

“This was quite a breakthrough for me as a tumor immunologist, because we can take this information and think about how we can potentially engineer stem-like T cells and their environment for the fight against tumors, using the autoimmune stem cells as a model,” Dr. Schietinger says.

The Road Ahead

Whether reprogramming T cells directly or changing their environment, MSK researchers are determined to make immunotherapy more successful for more patients. They want far more people to experience the joy and relief felt by Symantha — keeping cancer at bay with a lasting remission.

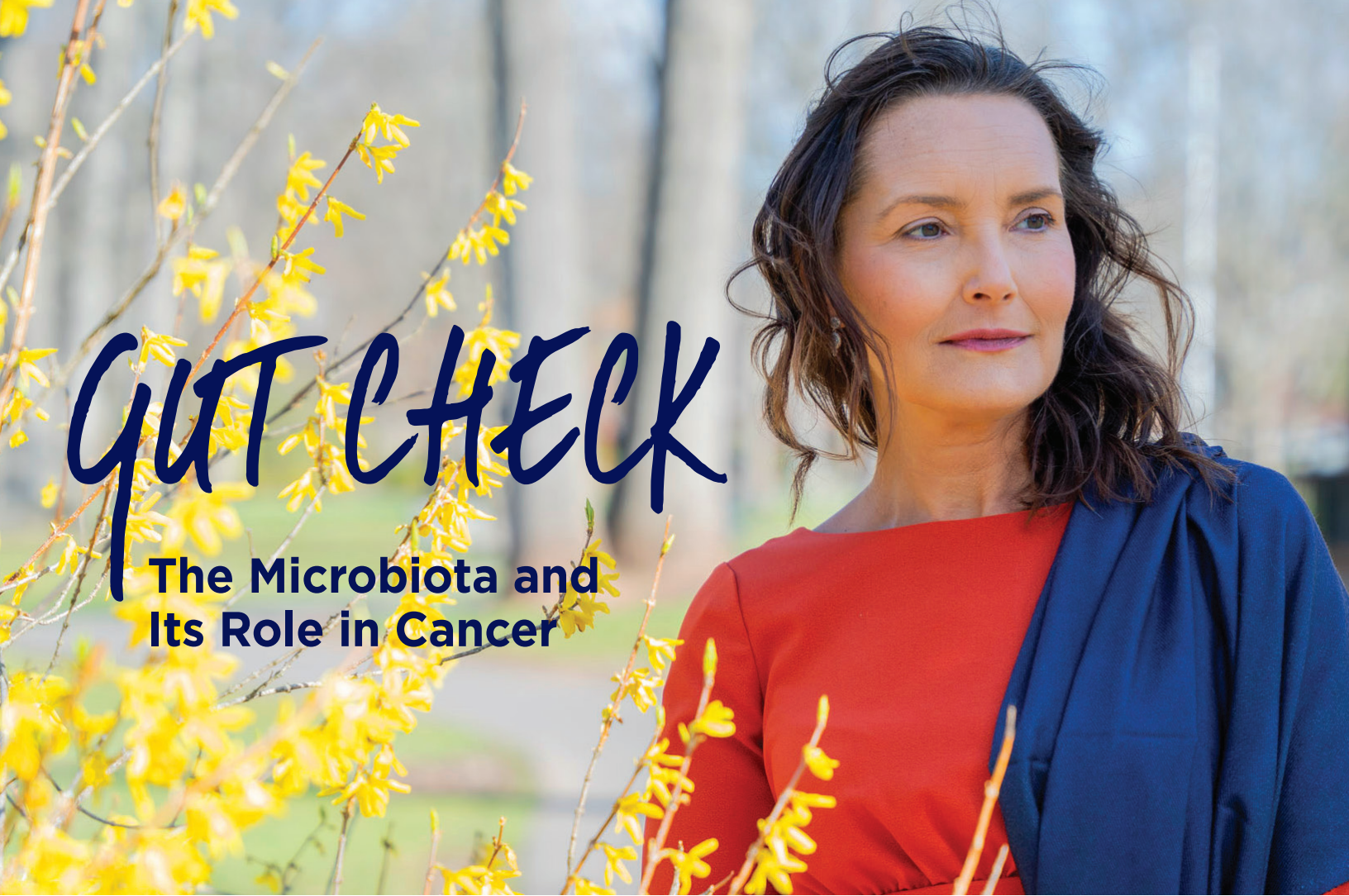
“Seeing patients who thought the improbable had occurred — only to slip back into that unfair and harsh reality — has been among the most difficult experiences in my professional life,” Dr. Vardhana says. “I want to see patients gain hope without it being taken away. They’re always in my mind when I think about the road we have ahead of us.” •



“This was quite a breakthrough for me as a tumor immunologist, because we can take this information and think about how we can potentially engineer stem-like T cells and their environment for the fight against tumors.”

—Andrea Schietinger

Dr. Schietinger’s and Dr. Vardhana’s work is made possible by the generosity of the **Carson Family Charitable Trust, Pershing Square Sohn Cancer Research Alliance, Gateway for Cancer Research, Cancer Research Institute Lloyd Old STAR Award, AACR Bristol Meyers Investigator Award**, and other members of the MSK donor community.



GUT CHECK

The Microbiota and Its Role in Cancer

Bridget Anderson had been looking forward to attending a concert at the Red Rocks Amphitheatre in Colorado with college friends. But a few days before her trip, she'd gone to her doctor in Newark, New Jersey, complaining about fatigue. Blood tests revealed devastating news: She had acute lymphoblastic leukemia.

"I was admitted on my 45th birthday," she says. "Talk about putting the aging process in perspective."

She needed a transplant to replace her own blood stem cells, which were being destroyed by the leukemia. She was given a 50% chance of survival. She was also given the opportunity to participate in a study led by **infectious disease expert Ying Taur** testing the impact of manipulating the ecosystem of her gut. There is growing evidence that patients having stem cell transplants benefit from fecal microbiota transplants — known more commonly as poop transplants.

"When I learned I'd been selected for the test group of the trial, I told my boyfriend, Charlie, that I never in a million years thought I'd be rooting to have my feces put back inside me," Bridget remembers.

This procedure may sound off-putting, but it's a cutting-edge way to manage a critical system in the body. The microbiota is the ecosystem of microorganisms that swarm our gut, live on our skin, and thrive in our respiratory airways. This ecosystem plays a vital role in maintaining good health. In the gut, these bacteria train our immune system and help us obtain nutrients from our food, but they can also cause inflammation and suppress the immune system.

For these reasons, scientists at MSK are searching to uncover the role the microbiota plays in cancer. Researchers throughout the institution are focused on how managing the microbiota can improve patient care as well as someday even potentially prevent certain cancers, like colorectal cancer, from ever developing in the first place. We've learned the microbiota can also impact how well

a patient responds to treatments with immunotherapy. That makes sense, because about half of your immune cells live in your gut and are in contact with your microbiota.

"My doctors explained that when you have any kind of stem cell or bone marrow transplant, the treatment kills a lot of the healthy bacteria that you need in your gut," Bridget says. "They thought that storing it and later putting it back might reduce some of the side effects from the transplant. I thought, 'Why not? I'll give it a try.'"

Before she began her transplant in October 2015, a sample of Bridget's stool was collected and frozen. Later, after she received chemotherapy and infusions of umbilical cord blood to replace her own blood stem cells, her stool was thawed out and returned to her body.

Always an optimist, she says, "I never once thought my cancer treatment would not be successful."

A Treasure Trove of Data on Transplant Patients

For more than a decade, MSK has been at the forefront of studying gut microbiota in people receiving stem cell and bone marrow transplants (BMTs). This initiative has been led by physician-scientist **Marcel van den Brink, Head of the Division of**



Systems biologist Joao Xavier (right), shown here with postdoctoral research fellow Ana Djukovic, combines computational and experimental approaches to study the microbiota.

Hematologic Malignancies and a member of the Immunology Program at the Sloan Kettering Institute (SKI).

Dr. van den Brink and his team have now amassed biological samples and comprehensive records for more than 1,400 patients. "We have a wealth of clinical data on these patients, including every drug they took and, in some cases, even what they ate," says **Dr. van den Brink** (Alan N. Houghton Chair). "Having all of

these details allows us to do research that wouldn't be possible anywhere else."

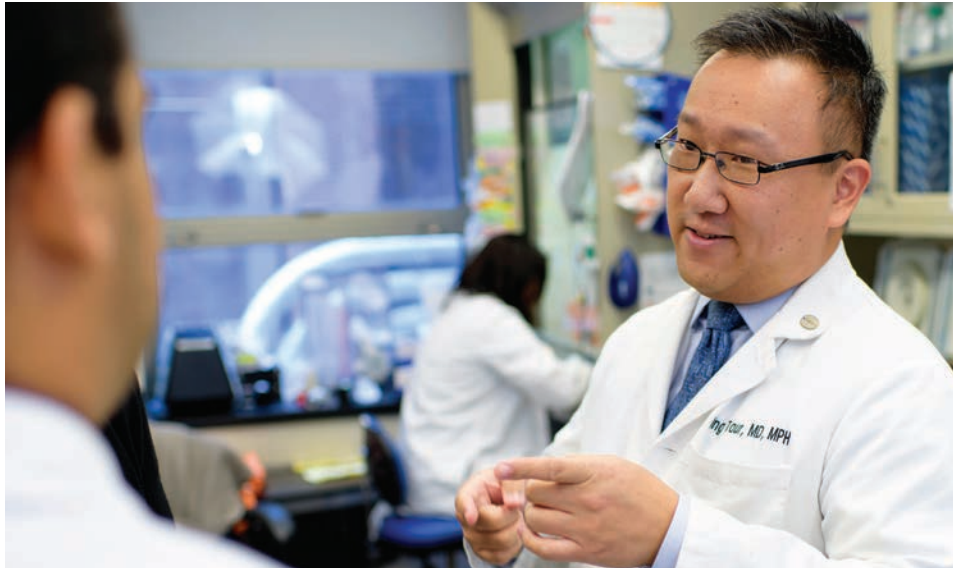
Scientists have learned that the microbiota can be thrown out of balance by the large doses of antibiotics given to patients to protect against infections while their immune cells are wiped out during a BMT. They've also discovered that patients with a less diverse microbiota are more likely to suffer graft-versus-host disease (GVHD), a potentially deadly side effect in



"Having all these [patient records and biological samples] allows us to do research that wouldn't be possible anywhere else."

—Marcel van den Brink

Physician-scientist Marcel van den Brink has long been at the forefront of studying how the microbiota affects patient outcomes after stem cell and bone marrow transplants.



Infectious disease doctor Ying Taur led a study looking at the benefits of fecal microbiota transplants.

which the donor's immune cells attack the recipient's healthy tissues.

In *The New England Journal of Medicine* in 2020, Dr. van den Brink and his colleagues reported that the diversity of the gut microbiota can predict a patient's survival after a BMT. The research — a multicenter study involving cancer centers in Germany, Japan, and North Carolina — showed that the link between bacteria in the gut and patients' outcomes is important across the globe.

Figuring out which gut bacteria matter the most could be a game changer: It might help predict which patients will benefit from certain types of cancer treatment and improve care for more of them by adjusting their microbiota.

Microbes and the Immune Cells: A Complex Relationship

Teasing apart the complexity of the microbiome requires a lot of expertise and computing power. **SKI systems biologist Joao Xavier** develops mathematical models to untangle this complexity. In a landmark study in *Nature* in November 2020, Dr. Xavier and his colleagues showed for the first time how the gut microbiota directly shapes the makeup of the human immune system. "During BMTs, the immune system and the microbiota are both damaged," Dr. Xavier says. "Being able to track their parallel recovery gives us a unique opportunity to test the associations between the two of them."

Understanding how the microbiota teaches immune cells is the focus of research by **SKI immunologist Gretchen Diehl**. "A lot of what I'm interested in is how specific microbes regulate the immune system," says Dr. Diehl (Catherine and Frederick R. Adler Chair for Junior Faculty).

Using mouse models, her team has discovered that gut bacteria travel to the thymus — the organ that makes immune cells called T cells. The bacteria train the cells to distinguish between friend and foe. Their research was published in *Nature* in May 2021.

The gut microbiota's connection to the immune system may offer clues explaining how colorectal cancers develop, including those in younger patients. "It's possible that certain microbes activate signaling in the lining of the gut, which

could promote cancer," Dr. Diehl says. "It's important for us to understand the more mechanistic interactions between microbes and the intestine to get at why this might happen."

Bridget's Poop Transplant

Bridget's fecal microbiota transplant was autologous, which means that she was given back her own microbiota. It had been stored at the start of the study, before she got her cord blood transplant. Studies at other hospitals have looked at the benefits of transplanting donor stool. But because people having BMTs are so susceptible to infections, MSK researchers wanted to take a safer route and avoid transferring potentially dangerous strains that could be present in donors.

"The gut microbiota is kind of a black box," Dr. Taur says. "We don't always know exactly what it contains or which individual species will be the most beneficial."

In 2018, Dr. Taur and his colleagues published results in *Science Translational Medicine* that confirmed autologous fecal transplants help restore a healthy microbiota. A preliminary analysis suggests that people who received the fecal transplant after their BMT had lower rates of viral infections and graft-versus-host disease. "Viral infections and GVHD are the top two complications that BMT patients face, and both are related to the immune system," Dr. Taur says. "We know that the immune system does a better job of rebuilding itself in the presence of a healthy, diverse microbiota."

Six months after her fecal transplant, Bridget learned that her gut had been successfully recolonized by healthy bacteria. Having her ecosystem back in balance helped her through her transplant journey, which took months. "Throughout the whole process, I really didn't have any serious infections," she says.

MSK researchers are looking at other ways to keep a healthy balance of microbes in people having BMTs. There's an experimental microbiota pill being



After recovering from her cord blood transplant, Bridget Anderson, shown here with now-husband Charlie Gerstung, was finally able to travel to Red Rocks in Colorado.

tested by **hematologic oncologist Doris Ponce** and **medical oncologist Miguel-Angel Perales, Chief of the Adult BMT Service**. MSK **physician-scientist Jonathan Peled** played an important role in the design of this pill and the trial. Investigators are also studying whether more careful use of antibiotics during the BMT process can protect healthy microbes and prevent harmful ones from taking hold.

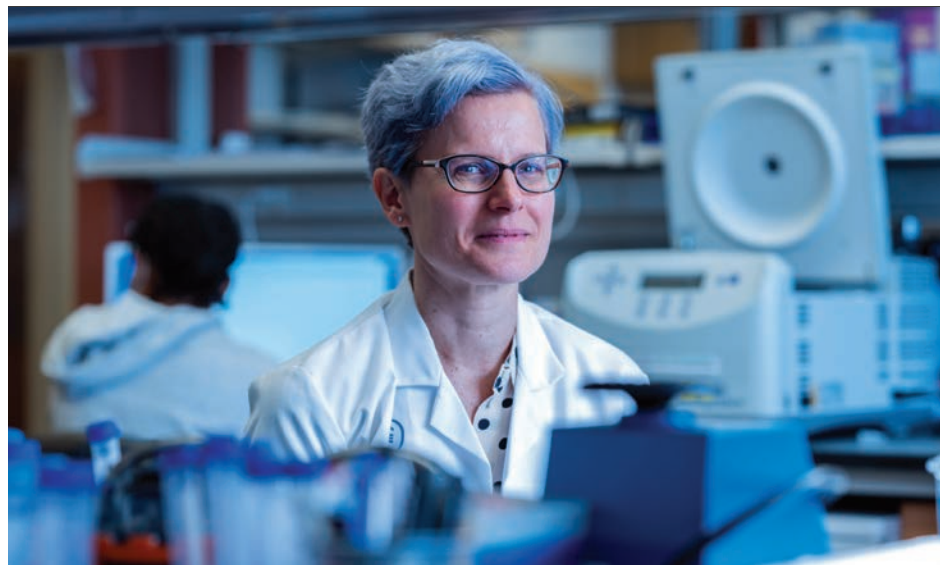
It's been almost seven years since Bridget had her transplant. She's healthy

and grateful to Dr. Taur and **hematologic oncologist Juliet Barker**, her transplant doctor. In August 2021 she married Charlie Gerstung, the boyfriend who stayed by her side throughout her treatment.

She also finally made that trip to the Red Rocks Amphitheatre. "Amongst the mountains of the Colorado night sky on a summer night," she told a group of BMT patients, "I closed my eyes and looked up to God and the universe and said, 'Thank you.'" •

"I closed my eyes and looked up to God and the universe and said, 'Thank you.'"

—Bridget Anderson



Immunologist Gretchen Diehl uses mouse models to study the connection between bacteria and the immune system.

Microbiome research at MSK is supported by **Anthony B. and Judith W. Evnin** and the **Tow Foundation**. Dr. van den Brink's microbiome research is supported by the **Peter and Susan Solomon Family Foundation** and the **Paula and Rodger Riney Foundation**.

School of Fish

What Fish Fins Are Teaching Scientists About Human Melanoma

Five years ago, MSK physician-scientist Richard White learned about a woman with a rare form of skin cancer on her foot. Called acral melanoma, this type forms on the palms of the hand and soles of the feet and is typically very aggressive. It killed reggae singer Bob Marley.

As a melanoma researcher, Dr. White was intrigued by this patient's case, particularly when genetic testing revealed that the woman's tumor had an unusual genetic alteration.

"Melanomas that occur on the face, trunk, or back usually have DNA alterations in a gene called *BRAF*," Dr. White says. "But this patient had an alteration in a gene called *CRKL* [pronounced 'crackle']."

Dr. White was curious about why the same type of cancer — melanoma — would be associated with different alterations in different parts of the body. Why do some DNA changes cause cancers to take root in the hands and feet, but not elsewhere? Why do most skin cancers never appear on the hands and feet? And what does that location have to do with the ability of a genetic change to cause cancer?

To get to the bottom of the mystery, he and an MD-PhD student in the lab, Joshua Weiss, decided to do some experiments using their favorite model organism: zebrafish.

Zebrafish are translucent, which means they are a great tool for studying cancer because you can actually see tumors forming beneath the scales. They are also easy to genetically engineer.

"We can take a cancer gene from a human and put it into a fish, and the fish will get cancer — allowing us to really understand how these genes work," Dr. White explains.

For this study, Dr. Weiss engineered zebrafish to contain either extra *CRKL* genes or a mutant *BRAF* gene. Then, he monitored them for about a year. Along the way, he noticed something intriguing: Most of the fish with a *BRAF* mutation developed tumors on their body. Those with *CRKL* developed tumors on their fins. It was a mirror of what they saw with their patient — only instead of a foot it was a fin.

That initial observation was the start of a five-year-long research investigation that would eventually lead to a paper published in *Nature*. Somewhat surprisingly, it may also lead to an entirely new treatment approach.

"It's very rare for a basic laboratory finding to have immediate therapeutic implications," Dr. White says. "But this one does. Not only for this patient, but for other patients as well."

Location, Location, Location

Like many of his SKI colleagues, Dr. White is interested in exploring the factors — beyond just genes — that influence whether cancer does or does not form in the body. In other words, he's interested in the cancer ecosystem.

That interest comes in part from realizing that the same mutation that causes cancer in one tissue may leave another tissue completely unscathed. Take an ordinary skin mole. Typically, moles on the skin have a *BRAF* mutation, but most of the time they don't turn cancerous.

In a paper published in the journal *Science* in September 2022, Dr. White and fellow SKI colleague Lorenz Studer discovered why that is. The ability of a *BRAF* mutation to cause melanoma, they found, depended on the developmental state of the cell containing it. The stem-like skin cells with a *BRAF* mutation readily turned cancerous. But the fully mature skin cells called melanocytes did not turn cancerous. Instead, they formed moles. To explain why not all mutated cells cause cancer, Drs. White and Studer coined the term "oncogenic competence."

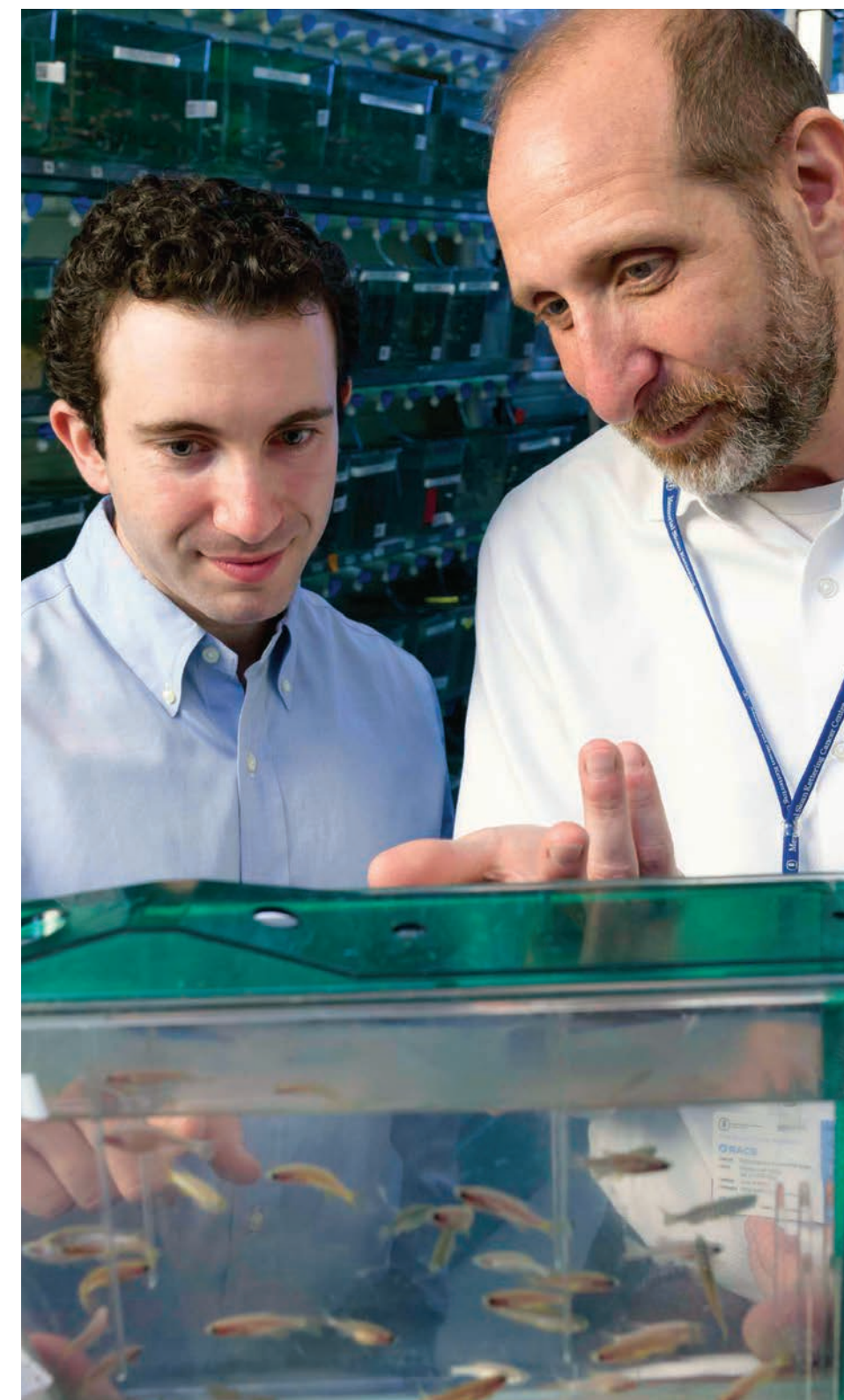
Now, in his most recent work on *CRKL*, Dr. White and his team say oncogenic competence of a cell is also determined by something else — its location in the body.

"Not only can a DNA mutation behave differently depending in the type of cell it finds itself in, but different parts of the body are susceptible to different mutations," Dr. White says.

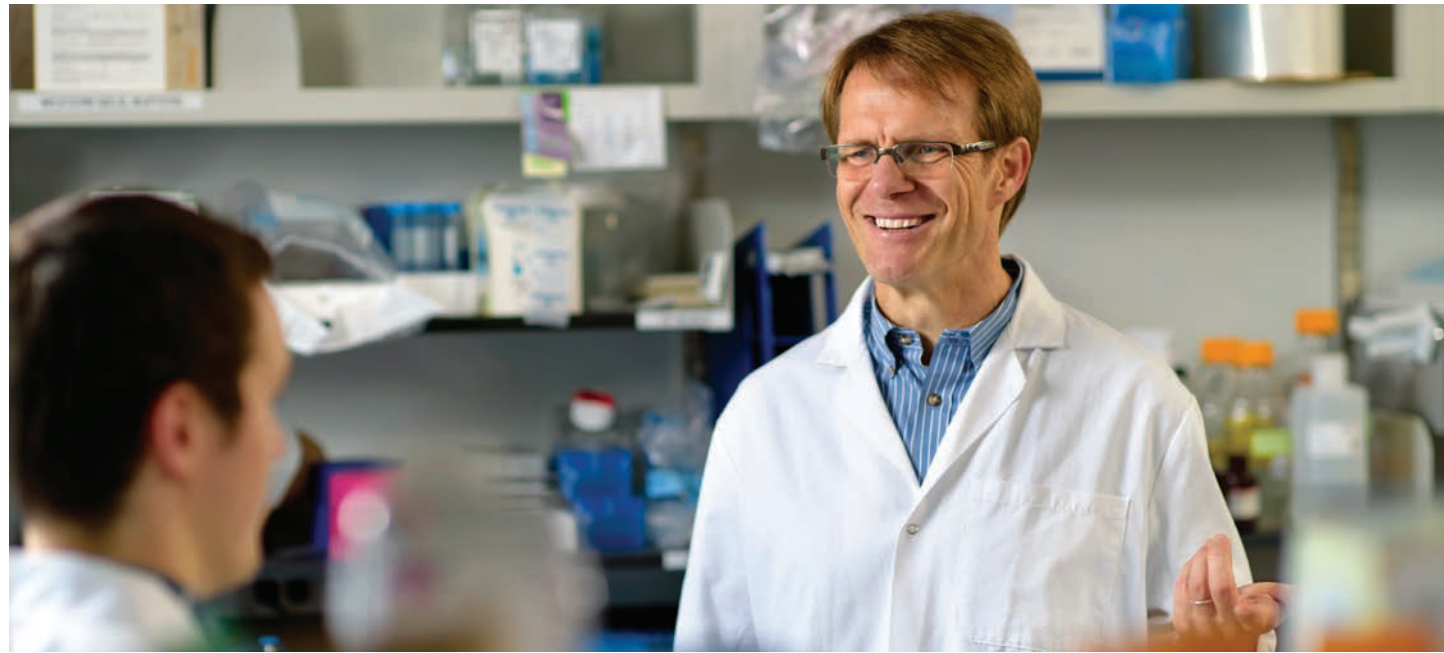
Treating the Location, Not the Cancer

The typical way of treating cancer is to target a mutated gene with a drug — for example, when a person with a *BRAF* mutation is prescribed the targeted drug vemurafenib.

But if the ability of genes to cause cancer also depends on location, then



SKI cancer biologist Richard White (right) with MD-PhD student Joshua Weiss



SKI developmental biologist Lorenz Studer is creating tools that could one day aid personalized medicine.

“It’s very rare for a basic laboratory finding to have immediate therapeutic implications, but this one does. Not only for this patient, but for other patients as well.”

—Richard White

it might be possible to blunt cancer development by blocking location cues.

“It leads to the interesting idea that instead of treating the oncogene — or the tumor even — we can treat patients who have these tumors based on their anatomic location.”

To identify potential “location” drugs, Dr. White’s team is taking advantage of a technology developed with Dr. Studer for the previous study. Scientists take genes from a patient’s tumor, put them into human embryonic stem cells, and grow these stem cells into skin cells to create a custom-made model of the patient’s tumor in a dish.

With this model, the scientists can then test a battery of chemicals on the cells to see which might make good medicines. Once they find candidate drugs, they can go back to the fish and test them in a living animal to see if they are safe and effective.

That’s exactly what they are doing for the patient from five years ago. Using these innovative methods, they have found — and are now testing — a handful of drugs that may be effective at treating that woman’s *CRKL* tumor.

Your Own Ecosystem

The melanoma patient who sparked Dr. White’s research doesn’t have a need for these drugs right now. She is still doing well following surgery to remove her original tumor. But should the cancer relapse, these drugs will be there waiting for her.

Dr. White hopes that this approach to drug development will become a reality for more and more patients. It would mean the beginning of a new era of personalized medicine. No longer only available off-the-rack, drugs would be tailor-made and tested for you, depending on your personal ecosystem. ●

Quantum Leap

How MSK Researchers Use New Technology To See Cancer Like Never Before

To study a complex ecosystem, researchers often deploy an armada of high-tech tools.

On the African savanna, for example, drones track migrating elephants. Infrared sensors spy on leopards as they prowl at night. And DNA tests reveal the unique genetic fingerprints of plant and animal species. Analyzing all this data requires enormous computing power.

And so it is for MSK researchers, as they investigate the hugely complex ecosystem of cancer in the human body. To advance their understanding, MSK scientists are pushing the frontier of what technology can see, on a scale that stretches from the atom to the entire human organism.

What they are discovering is already changing how MSK — and the world — treat cancer.

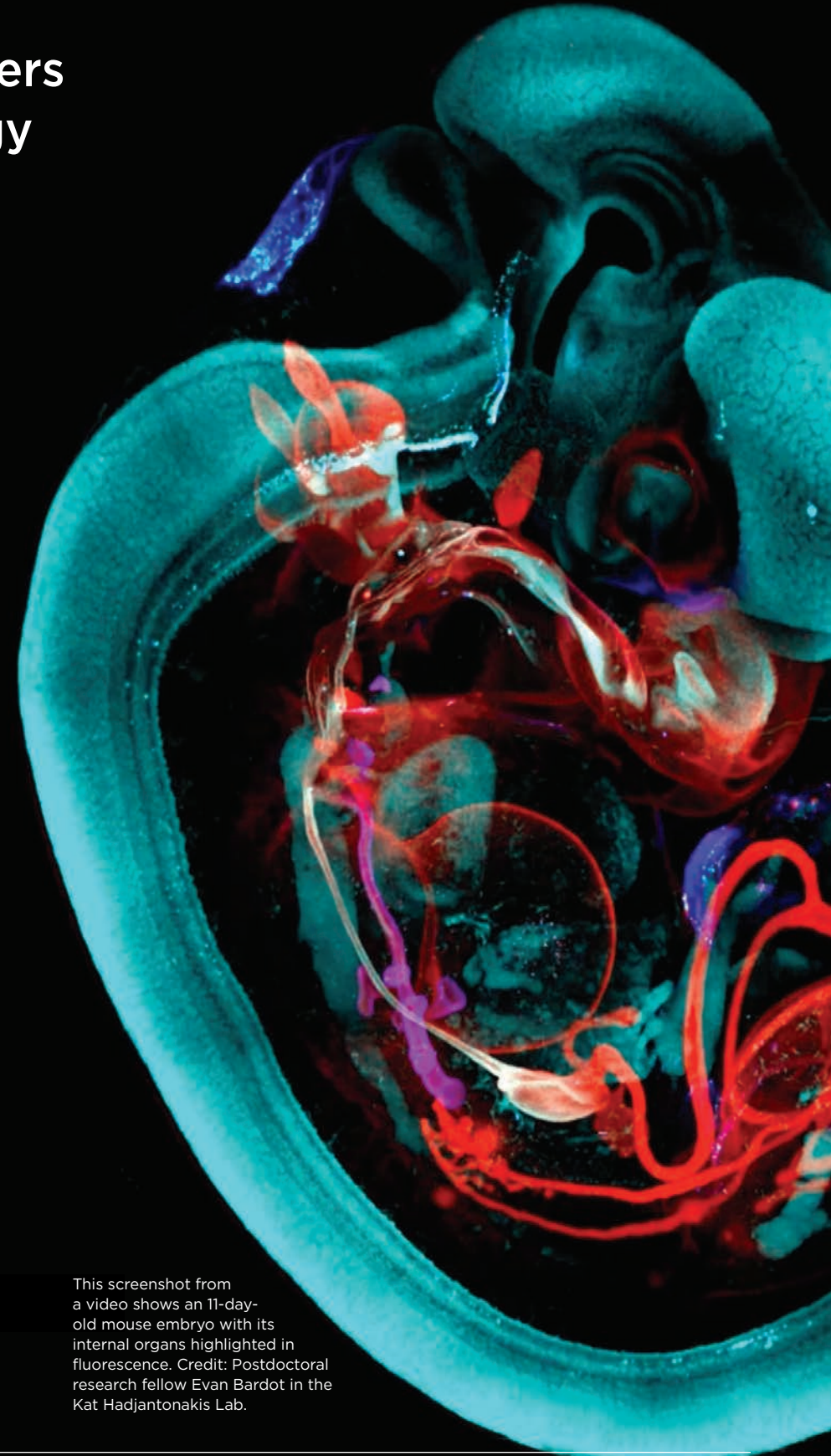
Guided Tour

“This is an image that I probably couldn’t have shown you a year ago,” **Anna-Katerina “Kat” Hadjantonakis** tells an audience on a February afternoon. She is the **Chair of Developmental Biology at the Sloan Kettering Institute (SKI)** and Alfred P. Sloan Chair and is leading a guided tour through a 3D image of a mouse embryo.

“The mouse tissue is dense and opaque,” says Dr. Hadjantonakis. “But the resolution of the imaging is so high that we can zoom in to see any individual cell in the context of the tissue surrounding it.”

That means, she explains, that “we can study cells not just one at a time, but by the tens of thousands. We can see all the cells that make up an organ at the same time.”

She continues that “the tissues of our body are infiltrated with blood vessels and lymphatic vessels and the immune system, to name just a few. They are very complex. Now we can look at all these different features at once — and over time.”



This screenshot from a video shows an 11-day-old mouse embryo with its internal organs highlighted in fluorescence. Credit: Postdoctoral research fellow Evan Bardot in the Kat Hadjantonakis Lab.

Supporters of Richard White’s research include the **Melanoma Research Alliance**, **Pershing Square Sohn Cancer Research Alliance**, and **Mark Foundation for Cancer Research**.

Lorenz Studer’s research is supported by **Aligning Science Across Parkinson’s** (with **The Michael J. Fox Foundation for Parkinson’s Research**) and the **JPB Foundation**.



“We can study cells not just one at a time, but by the tens of thousands. We can see all the cells that make up an organ at the same time.”

—Kat Hadjantonakis

(From left) Kat Hadjantonakis, PhD, and research assistant Ying-Yi (Beth) Kuo

Movie Magic

This breakthrough is achieved by microscopes that look nothing like the device many people peered through in high school.

The 3D mouse image was produced by the Bruker Luxendo MuVi SPIM light-sheet microscope. It works by taking thousands of scans using a sheet of laser light at different depths, and from different positions, and then digitally compiling them into a single 3D image. Dr. Hadjantonakis compares the resulting image to a movie — while older technologies produced snapshots.

“Imagine a 90-minute movie on Netflix,” she says. “If you were only given one snapshot of the movie every five minutes, it would be very difficult to piece together the story.” With the new technologies, however, “we can look at all the actors together and see how they interact. And we can look at them over time to see how the story unfolds. That means we can make new insights and raise new questions.”

As a developmental biologist, one of the big questions that fascinates Dr. Hadjantonakis is the process by which normal cells grow and work together to build organs — and “how those processes are disrupted or hijacked in diseases like cancer.”

She points out that “tumors are not entirely composed of cancer cells. They

are actually an integration of tumor and normal cells. It’s really important that we understand how both normal and cancer cells arise — and how they interact in a tumor.”

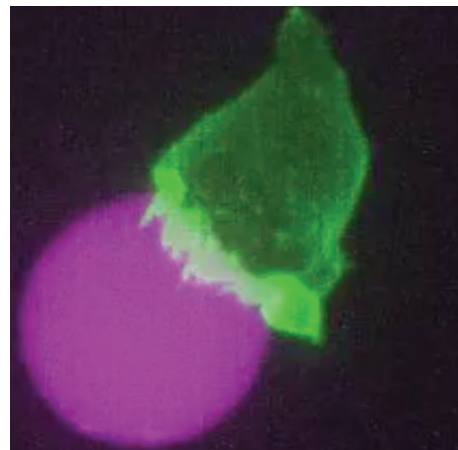
The goal, she says, “is to understand what’s normal, what’s going wrong in disease, and how we can intervene.” Long-term, the insights gained into how single cells develop into tissues may provide the ability to “repair, replace, or regenerate an organ damaged by cancer, so we can restore patients to their normal lives.”

How Immune Cells Sink Their Fangs

Morgan Huse, a member of the **Immunology Program at SKI**, wields cutting-edge imaging tools to study another key component of the cancer ecosystem — the interaction between tumors and the immune system.

One of his focuses is the immune system soldier called a T cell, which attacks harmful pathogens, including cancer. Dr. Huse explains that “the notion had been that a T cell stuck itself onto the target cell and kind of vomited toxic molecules onto the surface of the target cell, hopefully killing it.”

However, that idea was challenged when Dr. Huse and his team, armed with super-resolution microscopes like the Zeiss Elyra, looked more closely at T cells



This still from a video shows a T cell (green) attacking a simulated tumor cell. The T cell extends spike-like extensions as it tries to “kill” it. Credit: Miguel M. de Jesus in the Morgan Huse Lab.

in the act of killing. They found that T cells actually exert mechanical force against target cells, squeezing them “like a stress ball,” according to Dr. Huse. The T cell inserts its toxin very precisely into the target cell using “a highly evolved physical delivery system,” not unlike how a snake uses its fangs to inject venom.

The result, says Dr. Huse, “is that the T cell maximizes its killing power while using less toxin and lowering the chance that the toxin will leak out and hurt an innocent bystander cell.”

Finding Vulnerabilities

To capture these “very small and very fast interactions,” the Zeiss Elyra microscope casts light into a pattern like a crisscross lattice, then rapidly moves the pattern and combines all the resulting images to extract a higher-resolution image.

Having revealed a critical mechanical dimension to T cell killing, Dr. Huse’s research is now investigating the implications. “It turns out that metastatic cancer cells need to physically stiffen in order to colonize new organs. In collaboration with **Joan Massagué’s** group, we recently showed that this stiffening makes the cancer cells more vulnerable to T cells.”

This new type of biomechanical vulnerability could perhaps be given a boost by medicine in the never-ending arms race between the immune system and cancer. (You can learn more about Memorial Sloan Kettering Cancer Center efforts to strengthen the immune system to fight cancer on page 9.)

An Intersection of Revolutions

This new world of research relies on one of the fastest-growing fields in biomedical science: computational biology and related disciplines. Dr. Hadjantonakis points out that it takes “very sophisticated computational methods to analyze all

the data we’re generating — a computer may extract patterns that I may not see.”

That’s where computational biologists come in, like **Christina Leslie**, a member of the **SKI Computational and Systems Biology Program**. Trained as a mathematician, she helped develop crucial artificial intelligence and machine learning methodologies that make sense of the enormous data sets generated by research into cancer genetics and the human genome — the blueprint of genetic instructions.

Today, Dr. Leslie’s field will be just as important in unlocking the secrets hidden in the mountain of data generated from the focus on the cancer ecosystem. She says: “I think we’re at the intersection of multiple revolutions. There’s a revolution in single cell genomics. There’s a revolution in genome editing, which allows us to study the consequences of genetic changes. There’s a revolution in data science. And it’s all moving really fast.”

Investment for the Future

Staying ahead of the revolution is the purpose of the **Research Technology Transformation (RTT)** initiative at SKI, which relies on generous support from donors, including the **Friedman Family Foundation** and **Cycle for Survival**®. The RTT seeks to get the best new technology

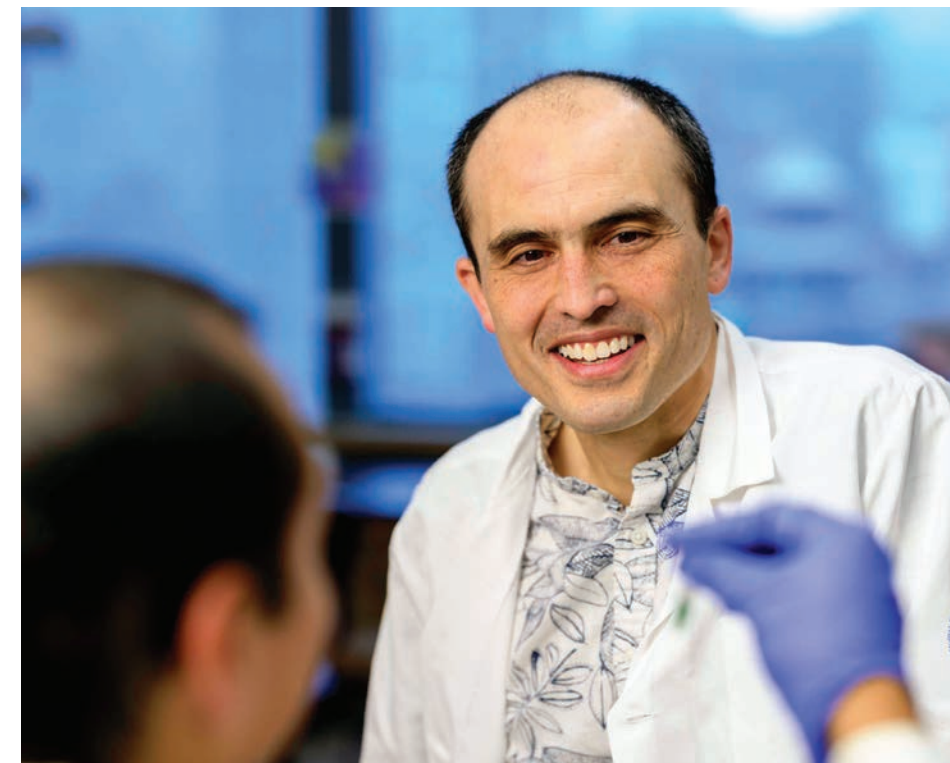
into researchers’ hands quickly and share resources when possible. That provides a competitive edge that is essential to recruit and train the best and brightest of tomorrow.

Dr. Hadjantonakis says: “I don’t think we would have been able to bring in these instruments that will allow us to make these scientific advances without the RTT. It puts us five years ahead of the curve of other institutions.”

Several high-profile projects in the pipeline include:

- Triple Quadrupole Mass Spectrometry, led by **Derek Tan** (Eugene W. Kettering Chair), which will cut sample processing time from 10 minutes to as little as six seconds.
- Expanding the Single-cell Analytics Labs (SAIL), led by **Dana Pe’er** (Alan and Sandra Gerry Chair) and **Ronan Chaligné**.
- Organoid Innovation Lab, which will create disease models using patients’ own cancer cells, under the direction of **Scott Lowe** (Geoffrey Beene Chair), **Lorenz Studer**, and **Charles Sawyers** (Marie-Josée Kravis and Henry R. Kravis Chair in Human Oncology and Pathogenesis).

Together, all these resources will search for vulnerabilities in the hugely complex ecosystem of cancer in the human body, another major step forward in the effort to ensure that cancer is no longer the king of the jungle. •



Morgan Huse is a member of the Immunology Program at SKI.



Christina Leslie is a member of the SKI Computational and Systems Biology Program.

Meet Tracy Gosselin

MSK's New Chief Nurse



Dr. Gosselin (left) took her own advice to “keep calm and hurdle on” while at Duke during the height of the pandemic.

Tracy Gosselin says she was taken by surprise when she got the call asking her to consider applying for the top nursing job at Memorial Sloan Kettering Cancer Center (MSK).

“I laughed and said, ‘I can give you lots of names,’” she recalls. After careful thought and consultation, she ultimately decided to apply. She got the job not only because she had the experience; she also has the heart and soul of an oncology nurse.

Dr. Gosselin joined MSK in November 2021 as **Senior Vice President, Chief Nurse Executive, and Chair of Nursing**. Her credentials are impressive — PhD, RN, AOCN, NEA-BC, FAAN — plus 28 years in nursing at Duke University Hospital. But Dr. Gosselin says she is stepping into the shoes of a luminary in the field — Elizabeth McCormick. Under her leadership, MSK’s

nursing staff twice received Magnet® recognition, the nation’s highest honor for exceptional nursing care.

“It’s really about building upon the excellence that’s already here,” Dr. Gosselin says, taking a sip of her Diet Coke. It’s 3:30 p.m. on a Friday, and she is just sitting down to lunch. After nearly 30 years as a nurse, a busy schedule doesn’t faze her.

A Calling to Cancer

She grew up in Sutton, Massachusetts, 50 miles outside Boston, and says she found her passion for nursing when she was a teenager volunteering at a local hospital.

Delivering flowers to patients, rocking babies in the nursery, and assisting nurses on nonclinical tasks focused her ambition and taught her the value of human connection. She called it an honor “being present and learning how people navigated whatever it was that brought them in.”

She was inspired to enroll in a five-year program at Northeastern University. When she started to care for people with cancer, she knew she had found her vocation. “I loved getting to know their stories and who they were as people,” Dr. Gosselin says.

To the surprise of no one in her life, she received multiple job offers upon graduating. She chose Duke, which was opening a new solid tumor oncology unit that emphasized continuity of care: one nurse providing top-to-bottom care for a small group of patients. Dr. Gosselin packed her things and moved 700 miles south. North Carolina, she admits, took some getting used to.

“I thought I could ride my bicycle to work because in Boston, there were buses, there was the T, and people knew how to take care of snow,” she says with a laugh. “The recruiter took one look at me and said, ‘You need to get a car.’”

‘Keep Calm and Hurdle On’

But just as she defended her PhD, she got heartbreaking news: Her father was diagnosed with stage 4 gastroesophageal cancer. Suddenly, she saw cancer from the other side of the bed, as a patient’s loved one. Sometimes, Dr. Gosselin had trouble switching off her “nurse brain.”

“I will never forget what the hospice physician told me,” she says. “He said, ‘Tracy, you just need to be a daughter right now.’”

Her father’s illness and death taught her the importance of simply sharing in her patients’ grief, to just be present and say nothing at all. She says it’s a challenge for anyone who takes care of patients because “all we want to do is make things better, and sometimes hope of cure changes to hope for a peaceful death.” She developed a mantra she uses to this day: “Keep calm and hurdle on.”

“It’s about helping people through those challenging moments,” she says. “How do you listen and figure out what they need, and help them through that next hurdle?”

Even as the executive in charge of 5,000 nurses, Dr. Gosselin checks in on

patients when she’s rounding the halls to ask about their care.

‘Oncology Chose Me’

She’s also making the rounds to listen to nurses. When she started, she set out to meet as many as possible, spending time in inpatient units and at each of MSK’s seven regional locations. “I think it’s important to see people and thank them, because it’s not easy,” she says. “There’s a big push around self-care, but people want more than that. People want to be seen, heard, and valued for their contributions.”

Long-term, her priorities are to recruit top-tier talent and to ensure care is accessible to people outside of New York City. She’s also looking forward to mentoring the next generation of MSK nurses. She says, “You just try to pay it forward for what other people did for you early on.”

When the workday ends, she enjoys exploring the city with her husband, John. They love walking in Central Park, going to museums, and seeing Broadway shows.

It’s an exciting new chapter for Dr. Gosselin and one she never imagined. “Growing up, I didn’t know much about cancer,” she says. “But oncology chose me, and I keep choosing it, over and over again.” •



In her early days as a nurse, a pediatric patient came to visit dressed as the Cat in the Hat.



Dr. Gosselin’s pups, Bella and Luna, are sisters who were rescued from Puerto Rico after back-to-back hurricanes.



Dr. Gosselin (pictured with her husband, John) says that her role at MSK is “really about building upon the excellence that’s already here.”



TRANSFORMATIVE GIVING: Marie-Josée and Henry R. Kravis

Marie-Josée and Henry R. Kravis have already revolutionized cancer research. Now with a transformational gift of \$100 million to establish The Marie-Josée and Henry R. Kravis Cancer Ecosystems Project at Memorial Sloan Kettering Cancer Center (MSK), they are committed to advancing the field even further and saving more lives.

In 2014, the Kravises made a gift to establish the **Marie-Josée and Henry R. Kravis Center for Molecular Oncology (CMO)**, a first-of-its-kind research powerhouse dedicated to understanding the molecular drivers of cancer. With the couple's support, the CMO developed the first FDA-authorized tumor-sequencing test, MSK-IMPACT®, which can detect cancer-associated mutations in hundreds of genes. This breakthrough allows doctors to match patients with drugs that can effectively target and treat their cancer. And in just a few years, the CMO's work has led to the creation of many life-changing therapies for people with cancer.

But genes are only one piece of the cancer puzzle. Once again, the Kravises,

whose philanthropy is informed by decades of experience in finance, analysis, and strategic planning, are helping MSK's doctors and scientists accelerate progress in cancer care. **The Marie-Josée and Henry R. Kravis Cancer Ecosystems Project** will tackle the biggest challenges in cancer today, including metastasis, the cause of the vast majority of cancer deaths. Building on the momentum of the past two decades of cancer research, the project will unite specialists across MSK to investigate the complex factors beyond genetics that allow cancer to flourish in the body and to develop treatments to combat its spread.

As **Vice Chair of MSK, Chair of the Sloan Kettering Institute**, and **Chair of the Joint Science Committee of the Boards**, Marie-Josée, with her husband, Henry, are helping to shape the future of oncology. "This is a time of extraordinary potential for cancer research," she says. "I have had the

privilege of witnessing MSK lead a revolution in cancer genomics in the past decade, and we are honored to help usher in a new era of ecosystems research that will benefit so many people with cancer."

Research initiatives are already underway across MSK that use advanced imaging tools and computational techniques to predict where tumors are most likely to spread and to identify environmental factors that spur cancer growth. The Kravis family's gift will allow MSK to bring new treatments to patients faster than ever before.

"We are profoundly grateful to Marie-Josée and Henry Kravis for their generosity," says **Joan Massagué, Director of the Sloan Kettering Institute and Marie-Josée and Henry R. Kravis Foundation Chair**. "Through their partnership, MSK will be able to pursue innovative projects that will help the next generation face every cancer diagnosis with hope and confidence."

Visit mskcc.org/ecosystems-project to read more about The Marie-Josée and Henry R. Kravis Cancer Ecosystems Project. •



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