SPECIAL ISSUE

SUMMER 2021

MSK News

MEMORIAL SLOAN KETTERING CANCER CENTER

Defeating Cancer's Spread

On the 50th anniversary of the War on Cancer, this **SPECIAL ISSUE** focuses on metastasis: What's available now — and on the horizon — for patients like Ilene Thompson facing advanced disease.

ALSO INSIDE:

A Major Advance for Prostate Cancer Patients

Seed and Soil: A Cancer Cell's Journey

How to Outsmart Tumor Evolution

Memorial Sloan Kettering Cancer Center

Dear MSK Community,

These are the four most frightening words for a patient to hear: “Your cancer is back.”

As we mark the 50th year of the War on Cancer and look to the future, our mission at Memorial Sloan Kettering is nothing less than conquering the most urgent challenge: preventing cancer’s spread. Also called metastasis, it causes 90 percent of cancer deaths. It’s why we are devoting this entire issue to reporting on how we offer hope and help to patients whose cancer has spread. In the clinic, we are developing more targeted drugs, more precise radiation, and more sophisticated surgical techniques to treat our patients. In the lab, we are learning more every day about why cancer cells metastasize and how to stop them.

Our vision to save more lives requires a commitment to hire and train the brightest minds and a significant investment in four key areas of technology, which are already bringing about astonishing advances:

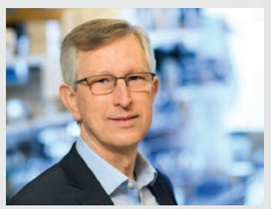
- **Better models to study cancer:** Conducting research in mice is time-consuming and doesn’t necessarily reflect cancer biology in humans. New technology makes it possible to grow samples of a patient’s own tumor in a dish in order to understand its evolution and test its response to a cancer drug — getting results faster than ever before.
- **Visualizing cancer at every level from atoms to organs:** State-of-the-art imaging equipment can be used to visualize single cells moving and reacting in real time; observe how cancer cells behave and find them before they take root in new places; inspect fragile tissue samples; and spot tumors in the body.
- **Analyzing cells one at a time:** We’ve made great progress understanding how genetic mutations can drive cancers. But they don’t account for all tumor behaviors, particularly metastasis. Sophisticated equipment helps us understand how cancer cells adapt to new environments as they break free from their original tumors.
- **Using computers to decode cancer’s behavior:** Through all of our new technologies, we are gathering more data than ever before. We need to improve our computational methods to organize, describe, and find patterns in this data that can unlock the reasons cancer spreads.

Our patients choose MSK because our compassionate care is powered by innovative research that we conduct through a major investment of resources. Our scientists and physicians have helped develop and test groundbreaking chemotherapy drugs, immunotherapies, surgical and radiation techniques, and countless other treatments that have saved lives. And we share our work with the world.

We know that with enough resources, we will stay on a path of relentless discovery, leading the way and protecting our patients from hearing those four frightening words.

CRAIG B. THOMPSON
President and
Chief Executive Officer

LISA DEANGELIS
Physician-in-Chief and
Chief Medical Officer



JOAN MASSAGUÉ
Director,
Sloan Kettering Institute

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A Major Advance

Tracking and Treating Hidden Prostate Cancer Cells

A transformation is coming for patients with prostate cancer, says Memorial Sloan Kettering medical oncologist Michael Morris. Researchers at MSK have helped pioneer major advances that will enable doctors to pinpoint the location of prostate cancer cells more precisely than ever before so they can be targeted with personalized treatments. The researchers also have begun to solve an enduring mystery about how some metastatic prostate cancers escape powerful drugs.

The most immediate breakthrough involves a new form of imaging.

"This is the biggest diagnostic advance for prostate cancer since the 1980s, when the PSA [prostate specific antigen] test was introduced," Dr. Morris says. "Imaging has been the Achilles heel of prostate cancer because the disease is hard to detect after it has spread, forcing many treatment choices to be based on estimation and probabilities. Now, we can be much more confident that we are correctly identifying the location of the disease to make an accurate treatment plan."

The new technology uses a radioactive substance that selectively seeks out and attaches to a specific protein on the cancer cell surface. The protein, called prostate-specific membrane antigen (PSMA), is not found on most normal cells. When the radioactive tracer binds to the prostate cancer cells, they show up as bright spots on a PET scan.

"With PSMA PET, we can now detect the cancer cells directly and much earlier than we could with standard CT or PET scans," he says. Dr. Morris played a leading role in clinical trials testing a particular tracer that is easy to manufacture and can be used at all institutions. **MSK radiologist Hebert Alberto Vargas** and **interventional radiologist Jeremy Durack** were key collaborators in the development and testing of the tracer.

In May, the FDA approved this tracer — the first for national, widespread use. The PSMA advance is the result of years of work by MSK's Molecular Imaging and Therapy Service, led by **Heiko Schöder**.

This technology has an even more exciting potential: zeroing in on prostate cells to destroy them. A therapy called 177Lu-PSMA-617 selectively binds to PSMA in prostate cancer cells and delivers DNA-damaging radiation, killing the cell. Patients receive this treatment by injection over six sessions, usually spaced six weeks apart, given by nuclear medicine physicians.

"Effective treatments for metastatic prostate cancer have been limited, so this could be a game-changer," Dr. Morris says.

Just ask Michael Rosenblum. In 2019, his prostate cancer had become resistant to treatment and had spread to his bones. His PSA levels — a marker that normally should be in the single-digit range — had soared to more than 100.

Dr. Morris enrolled Michael in a clinical trial led by **nuclear medicine physician Lisa Bodei** testing the benefits of 177Lu-PSMA-617 when used in combination with standard prostate cancer therapy. Since Michael's last treatment in February 2020, the 75-year-old has been free of symptoms. His scans have improved, and his PSA is less than 1. He just celebrated his 50th wedding anniversary.

"I had no side effects, either on the day of the procedures or afterward," Michael says. "My PSA went right down, and my blood tests have been really good. From how I feel today, you would never think I had cancer a few years ago."

Dr. Morris presented results from the trial, involving more than 800 patients with advanced prostate cancer, at the American Society of Clinical Oncology meeting in June. Men who received the drug had a median of 8.7 months of progression-free survival — the period when the disease didn't worsen — compared with 3.4 months for those receiving only standard treatment. Side effects were not serious. Among the most common was dry mouth.

"We hope this therapy will receive FDA approval," says Dr. Morris, whose research has been supported by the philanthropy of the Magnier family.

For Dr. Morris, the recent inroads against this stubborn disease — the second leading cause of cancer death in men — are especially gratifying.

"I have been involved in the PSMA research since the end of my fellowship at MSK in the late 1990s," he says. "The benefits these advances will bring to men with this common disease cannot be overstated."

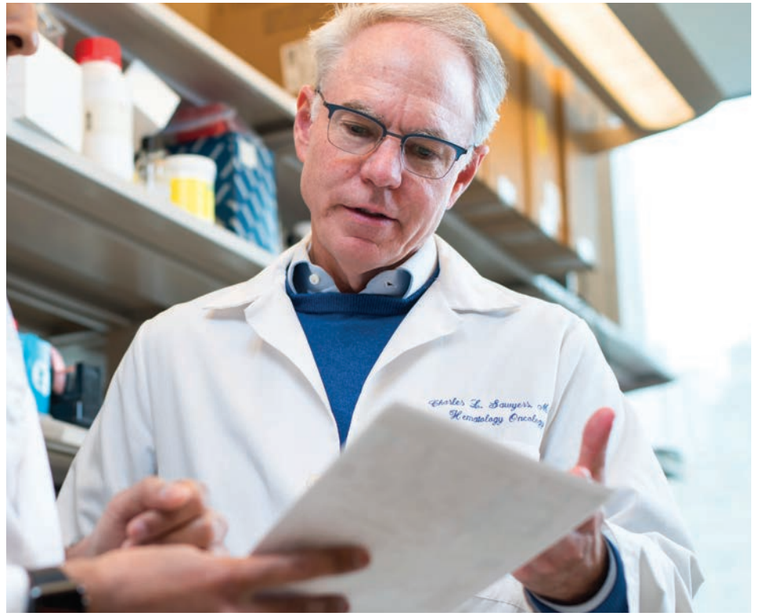
Escape Artists

Another promising effort to help patients with metastatic prostate cancer is being led by **physician-scientist Charles Sawyers, the Marie-Josée Kravis and Henry R. Kravis Chair in Human Oncology and Pathogenesis**. Dr. Sawyers is focused on fighting drug resistance, based on lessons he learned from pioneering the lifesaving treatment imatinib (Gleevec®) to treat chronic myeloid leukemia (CML). Imatinib targets an abnormal protein and essentially cures CML — a landmark in targeted cancer therapy.

But Dr. Sawyers discovered cancer cells could become resistant to imatinib. This raised the question of whether a different mechanism had taken over to promote the cancer. Researchers wondered if they were still focused on the right target. Dr. Sawyers' instincts told him to zero in even more closely on the abnormal protein, believing it was the scene of the crime.

"When you play the game Clue and think the murder happened in a certain room, that's the room you go to," he says. "With CML, we discovered that we had the right target but that the protein was mutating. It didn't completely solve the problem, but it led to important insights into how resistance develops."

Dr. Sawyers says he remembered this lesson when his research shifted to prostate cancer. He put a bullseye on a protein called the androgen receptor (AR), which all prostate cells — prostate cancer cells in particular — need to survive and grow. Staying focused on AR allowed researchers, including Dr. Sawyers, to develop several AR-blocking drugs that have improved survival for advanced prostate cancer.



Physician-scientist Charles Sawyers found that some tumor cells can change their identity to evade treatment and survive.

Identity Theft

But some metastatic prostate cancers still evade destruction. "We make smarter and more potent AR inhibitors, and the tumors still escape," Dr. Sawyers says.

In the last few years, he and MSK colleagues have made a startling discovery: Some metastatic tumor cells actually change their identity to survive. This transformation, known as lineage plasticity, allows prostate cancer cells to no longer depend on the androgen receptor.

To undergo this change, the cancer cells must have certain genetic mutations. Dr. Sawyers says focusing on those mutations should make it possible to know which patients will have cancers that are shape shifters.

"At one level, this is scary because it says that a tumor has the ability to once again outsmart our drugs," Dr. Sawyers says. "But we really understand this at a much better level than we did just a few years ago."

For example, **medical oncologist Charles Rudin** had noticed similar plasticity in lung cancer cells — during treatment, the tumors transformed from adenocarcinoma to small cell lung cancer. When the two researchers realized they had found the same intriguing phenomenon, they decided to collaborate to investigate it further. Dr. Rudin and Dr. Sawyers, along with their lab members, began meeting regularly to trade notes and share insights.

Dr. Sawyers' team is also collaborating with **Sloan Kettering Institute computational biologist Dana Pe'er**, a world-renowned expert in single-cell analysis. This powerful new technology enables researchers to look closely at individual cells to determine which genes are expressed, or "turned on." This makes it possible to get a clearer picture of how the mutations cause cells to change.

"This is similar to the challenges I faced earlier in my career with leukemia in that we're getting to that moment of clarity that will allow us to catch this transition in its earliest stages," Dr. Sawyers says. "That gives us a treatment strategy for these prostate cancer patients when the drugs stop working." •

Dr. Sawyers says he benefits greatly from the expertise of MSK colleagues.

"At one level, this is scary because it says that a tumor has the ability to once again outsmart our drugs. But we really understand this at a much better level than we did just a few years ago."

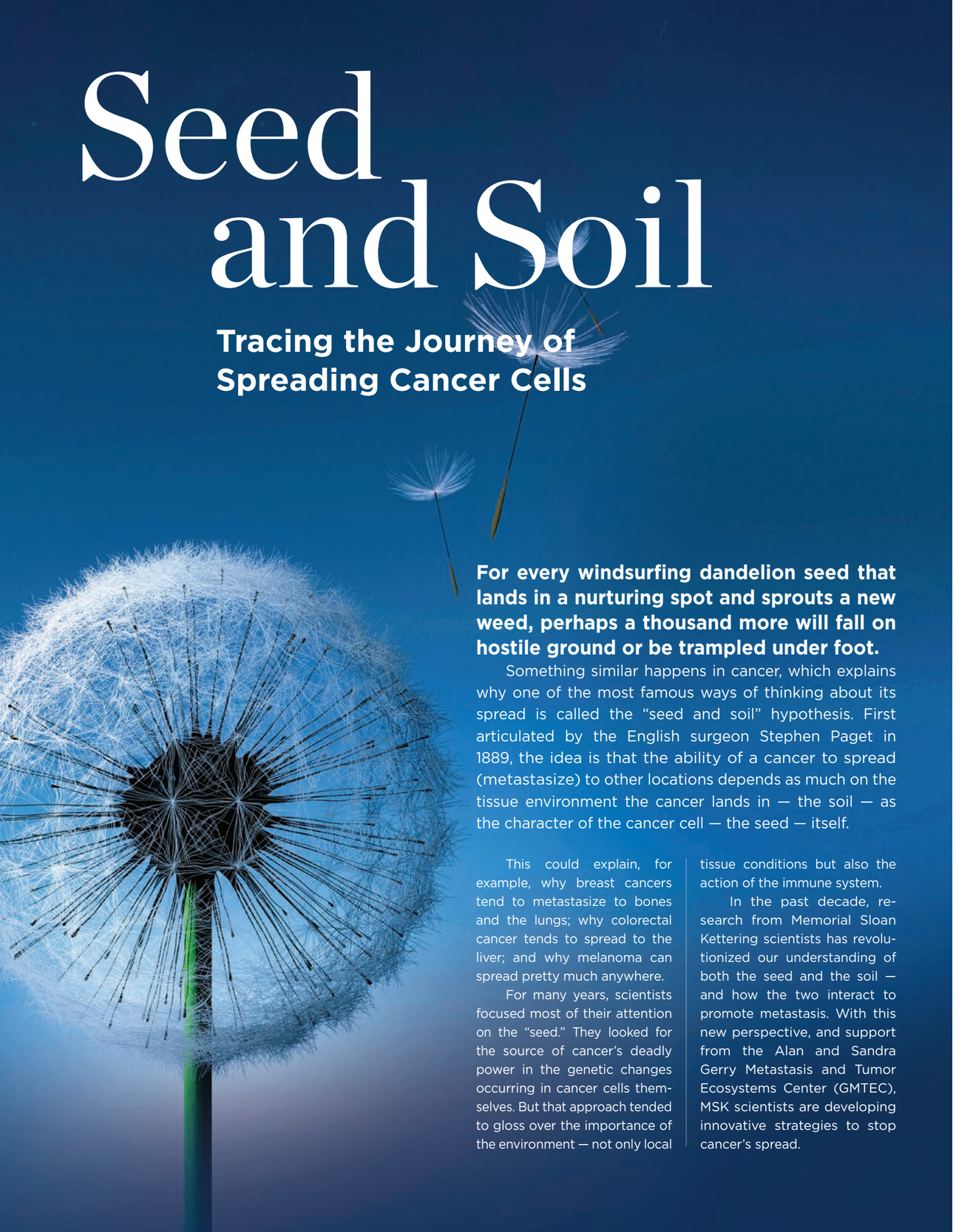
—Charles Sawyers

"The benefits these advances will bring to men with this common disease cannot be overstated."

—Michael Morris

Seed and Soil

Tracing the Journey of Spreading Cancer Cells



For every windsurfing dandelion seed that lands in a nurturing spot and sprouts a new weed, perhaps a thousand more will fall on hostile ground or be trampled under foot.

Something similar happens in cancer, which explains why one of the most famous ways of thinking about its spread is called the "seed and soil" hypothesis. First articulated by the English surgeon Stephen Paget in 1889, the idea is that the ability of a cancer to spread (metastasize) to other locations depends as much on the tissue environment the cancer lands in — the soil — as the character of the cancer cell — the seed — itself.

This could explain, for example, why breast cancers tend to metastasize to bones and the lungs; why colorectal cancer tends to spread to the liver; and why melanoma can spread pretty much anywhere.

For many years, scientists focused most of their attention on the "seed." They looked for the source of cancer's deadly power in the genetic changes occurring in cancer cells themselves. But that approach tended to gloss over the importance of the environment — not only local tissue conditions but also the action of the immune system.

In the past decade, research from Memorial Sloan Kettering scientists has revolutionized our understanding of both the seed and the soil — and how the two interact to promote metastasis. With this new perspective, and support from the Alan and Sandra Gerry Metastasis and Tumor Ecosystems Center (GMTEC), MSK scientists are developing innovative strategies to stop cancer's spread.

A Long and Difficult Road

The need is painfully clear: Metastasis is responsible for 90 percent of cancer deaths. Once a cancer spreads, it's nearly impossible to contain.

Yet this depressing observation obscures a hidden silver lining: For all its deadly power, metastasis is not something that cancer cells can do easily. Much like an individual dandelion seed, the odds of a cancer cell metastasizing are not in its favor.

Between dislodging from a primary tumor and reaching fertile soil are many obstacles that a cancer cell must surmount. First, there is the powerful shear force that comes from hurtling through the bloodstream. Then, there's the challenge of finding an exit from that tumultuous flume ride: a tiny gap in a blood vessel wall through which to crawl to relative safety.

And that's just one leg of the journey. The new environment itself presents unfamiliar conditions. To survive — let alone grow and multiply — the would-be metastatic cell must be capable of adapting to its surroundings. That includes finding ways to dodge the searching sensors of the immune system.

Of course, considering the many millions of cancer cells that break off from a primary tumor every day, it's not surprising that some do manage to clear all the hurdles. But to scientists seeking solutions, each of those hurdles represents an opportunity.

Laying Low

MSK researchers are especially keen to understand what is, perhaps, the most confounding and frightening aspect of metastasis — how lone cancer cells can sometimes survive undetected in the body for months and even years at a time without being killed, before eventually sprouting new tumors. Scientists call this period dormancy.

Dormancy is difficult to study in people, but there's no question it occurs. The most dramatic evidence comes from people who once had cancer, were cured, and then donated an organ. The organ recipient then develops cancer — the very kind of which the donor was cured. The only possible explanation is that the donated organ contained metastatic cancer seeds that were lying dormant — perhaps kept in check by the donor's immune system.

> Like a dandelion seed, the odds of a cancer cell metastasizing are not in its favor.

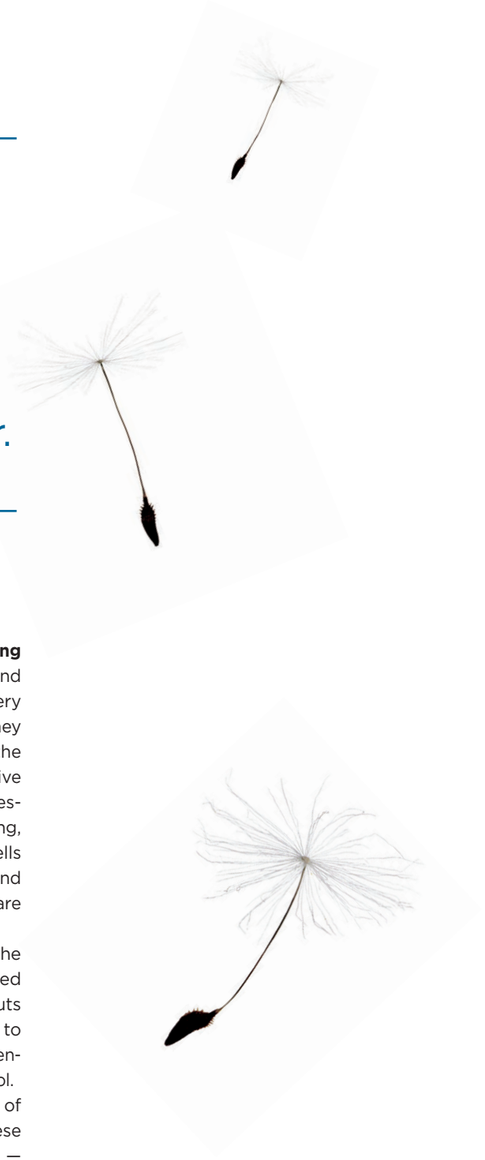
Several years ago, **Sloan Kettering Institute Director Joan Massagué** and his colleagues made a startling discovery that explains how this could happen. They found that dormant cancer cells have the ability to cycle between periods of active division and a sleep-like state called quiescence. When the cells are actively dividing, they grab the attention of immune cells called natural killer cells, which surround and kill them. But when cancer cells are sleeping, they go undetected.

The periodic cycling means that the lurking cancer cells are never killed completely, and the immune system puts pressure on the surviving cancer cells to evolve new survival traits — including, eventually, the ability to escape immune control.

In alternating between periods of active division and dormancy, these rogue cancer cells resemble stem cells — a population of cells that lives in and helps repair tissues.

"Dormancy is a normal state for the stems cells in our body," says Dr. Massagué, who holds the **Marie-Josée and Henry R. Kravis Foundation Chair and is Executive Director of GMTEC**. "They stay dormant until there is a need for their activity to replace lost or damaged cells."

When cancer cells go dormant, they not only escape detection by the immune system, they also evade being killed by treatments like chemotherapy, which work only against dividing cells. It's a surprisingly effective survival trait.



Turning Back the Clock

Just this past year, Dr. Massagué's lab — this time in collaboration with the labs of **computational biologist Dana Pe'er** and **physician-scientist Charles Rudin** — discovered another trick that cancer cells employ to spread. By studying lung cancer in mice and in human tissue samples, they found that lung cancer cells switch on genes that are usually active only during lung development. The cells in a sense "go back in time" to an earlier stage of development as they spread from a primary location to a distant site.

Anna-Katerina "Kat" Hadjantonakis, Chair of the Developmental Biology Program in SKI and Alfred P. Sloan Chair, remembers hearing about these discoveries for the first time. "Joan called me and said, 'We see this sequence of gene expression — does it mean anything to you?' And I said, 'Oh my gosh, this is the same sequence we see in an embryo as a lung forms.'"

The tumors, in effect, "reenact the developmental program for making a lung, but out of time and out of place," Dr. Hadjantonakis says.

A key technology for making this discovery is called single-cell RNA seq (an abbreviation for sequencing pronounced "seek"). It allows researchers to measure precisely which genes are turned on or off in individual cells among thousands of cells all at once.

Dr. Pe'er, a single-cell RNA seq expert who collaborated on the study, thinks the lung cancer findings are likely to apply across different cancer types. In fact, the study, which was published in *Nature Medicine* in 2020, served as the basis for a large grant awarded to MSK from the Human Tumor Cancer Atlas Network, a National Cancer Institute-funded Cancer Moonshot initiative. Dr. Pe'er and **physician-scientist Christine Iacobuzio-Donahue, the David M. Rubenstein Chair**, are the principal investigators. They are studying the transition from primary cancer to metastasis in lung, pancreatic, and colon cancers.

These organs share something in common: They are all derived from the same layer of the embryo called the endoderm.

"Some of the nastiest cancers are those involving endoderm-derived organs," says Dr. Pe'er, who is **Chair of the Computational and Systems Biology Program in SKI, holds the Alan and Sandra Gerry Endowed Chair, and is Scientific Director of GMTEC**. "For combating tumors derived from these organs, understanding normal development is going to be critical."

That's why she and Dr. Hadjantonakis are collaborating on a project to understand the development of endoderm-derived tissues.

Dr. Pe'er and her colleagues are also looking at metastasis to the brain, which is dramatically different than other organs. "The brain is as foreign an environment as a pancreas or lung cancer cell could possibly find itself in," Dr. Pe'er says. "The degree of adaptation that these cells must undergo is extreme."

With **physician-scientist Adrienne Boire**, Dr. Pe'er is using single-cell analysis to explore these adaptations. They've already identified several that could be potential therapeutic targets.

Switching Tracks

The shape-shifting quality that metastatic cancer cells exhibit may also explain some cases of drug resistance. Several years ago, **lung cancer specialists Helena Yu** and Dr. Rudin began to notice that some of their patients, when treated with drugs called epidermal growth factor receptor (EGFR) inhibitors, eventually developed resistance to these targeted drugs. But the way the tumors became resistant was unlike anything they had ever seen. The cells transformed into an entirely different type of lung cell that is not dependent on the growth receptor at all.

"It's as if the cell gets off one set of train tracks and jumps to a completely different set," says Dr. Rudin, the **Sylvia Hassenfeld Chair in Lung Cancer Research at MSK**. "In order to make that switch, the cells have to first go backward toward a less differentiated state. And to do that, they resort to some of the same developmental genes that we also see being turned on in the context of metastasis."

Physician-scientist Charles Rudin

As Dr. Rudin and other MSK scientists are coming to learn, this identity switching is not restricted to lung cancer. Almost exactly the same switching is seen in prostate cancer that is being treated with antiandrogen therapy and in breast cancer that is treated with antiestrogen therapy.

The findings have already changed clinical practice. Now, when someone relapses, doctors routinely re-biopsy the tumor to find out if it has changed. If it has, then they know to switch the treatment to match the new type of cancer. Clinical trials are underway to test drug combinations to prevent drug resistance.

Outbreak

After dislodging from a tumor, after going dormant, after trying on different identities, cancer cells must surmount one final hurdle to spread: They must acquire properties that allow them to grow in a new territory.

Tracking this last step has been the focus of **physician-scientist Karuna Ganesh, a Josie Robertson Investigator**. In the past year, her lab found a particular molecule, called L1CAM, appears to be required for metastatic cells to grow in a new location. L1CAM was originally identified in the context of brain development. But Dr. Ganesh's research has shown that it also plays a crucial role in both colon repair and in colon cancer.

In a normal colon, activating L1CAM in tissue stem cells is part of the way that the colon repairs itself after an injury such as colitis. Stem cells making L1CAM can separate from their neighbors, migrate into the gap of a wound, and then start to fill it in with healthy new cells.

But L1CAM also permits metastatic cancer cells to repair the tumor — and regenerate it in a new location. In fact, cancer cells can't grow without it. The researchers can see this when they knock out L1CAM in tumor cells growing in mice. The cells are able to seed new areas, but they do not germinate. With L1CAM, however, the cells begin to crawl along blood vessels and make themselves at home in their new location, eventually forming a new tumor. Based on this insight, Dr. Ganesh's lab is actively looking for drugs that could block L1CAM.

The fact that metastatic cancer cells co-opt the body's wound-healing system is devilish but also makes a kind of twisted sense. A wound is essentially a hole in a tissue, which is very dangerous for an organism. To repair this hole, tissues rely on stem cells that turn on a wound-healing program. Because cancer creates a wound where it grows, it causes malignant cells to adopt this same wound-healing behavior. It is these cells that will regenerate the tumor.

Karuna Ganesh, a Josie Robertson Investigator, in her SKI lab.

"Metastasis is wound healing gone wrong," Dr. Ganesh says.

By learning more about the ways that cancer cells repurpose these and other properties of stem cells, researchers hope to throw up barriers to metastasis.

"My dream is that the research being done now on dormancy and outbreak will lead to therapeutic breakthroughs," Dr. Massagué says. "One possible approach might be to trick the dormant cells into expressing those genes that alert the immune system so they are eliminated the same way that 99 percent of their comrades were eliminated."

He hopes that learning more about the steps that lead to metastasis in the first place will also help physicians understand what happens when cancers relapse.

Over the next decade, with the help of sophisticated new technologies, MSK researchers plan to mount a concerted attack on the problem from all sides. Their goal is to turn metastatic cancer into a manageable chronic condition and, perhaps one day, uproot cancer for good. •

> The goal of MSK researchers is to turn metastatic cancer into a manageable chronic condition and, perhaps one day, uproot cancer for good.

Metastasis: A Roadmap

Metastasis — the spreading of cancer from its original location to a new location — can be broken down into three main stages: dissemination, dormancy, and outbreak. Memorial Sloan Kettering researchers at the Alan and Sandra Gerry Metastasis and Tumor Ecosystems Center are making advances in understanding each of these three stages.

To learn more and see an animation, scan here

1 Dissemination

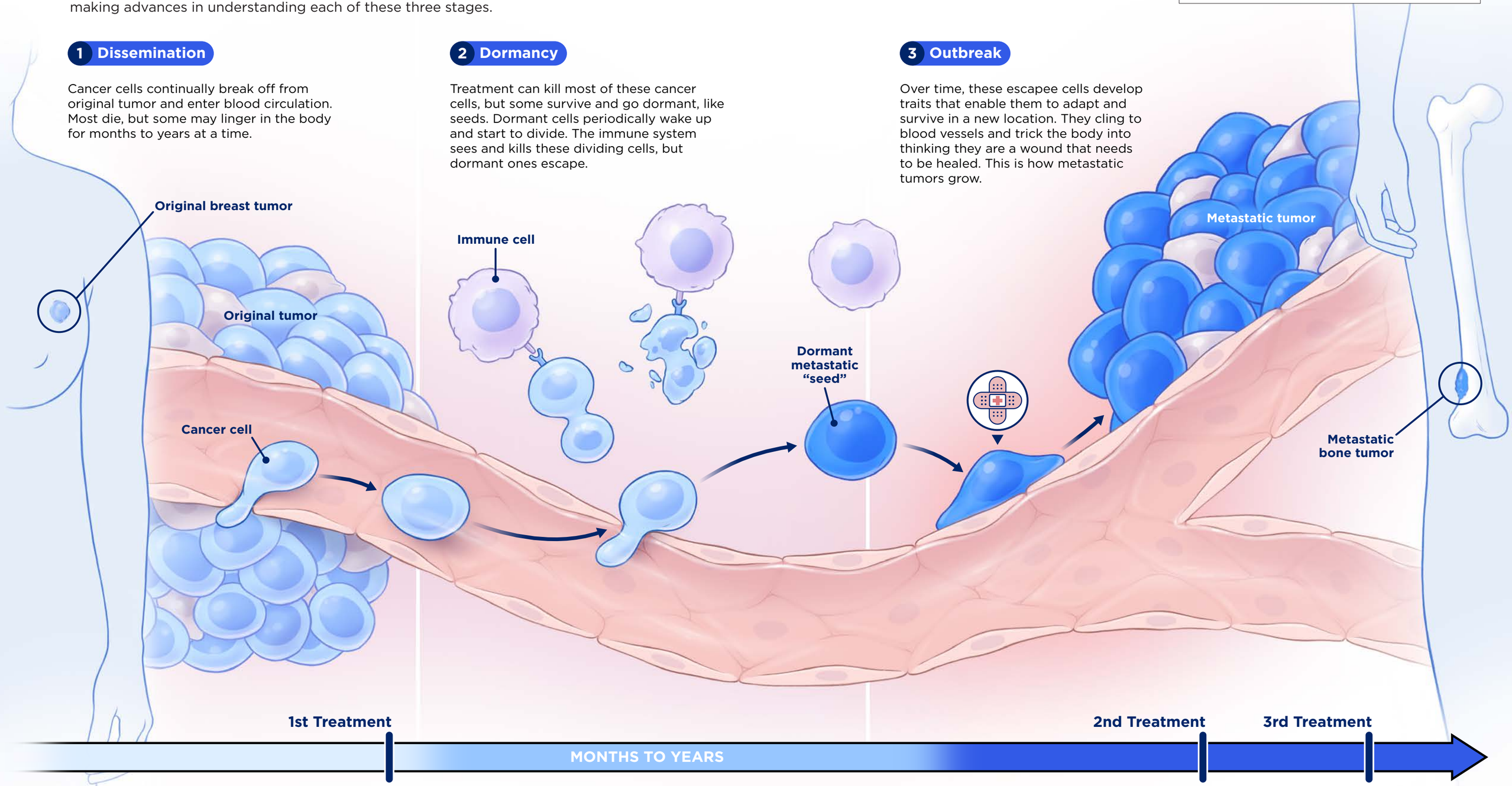
Cancer cells continually break off from original tumor and enter blood circulation. Most die, but some may linger in the body for months to years at a time.

2 Dormancy

Treatment can kill most of these cancer cells, but some survive and go dormant, like seeds. Dormant cells periodically wake up and start to divide. The immune system sees and kills these dividing cells, but dormant ones escape.

3 Outbreak

Over time, these escapee cells develop traits that enable them to adapt and survive in a new location. They cling to blood vessels and trick the body into thinking they are a wound that needs to be healed. This is how metastatic tumors grow.



His Cancer Has Spread Three Times, but It's Not Stopping Garth Atchley

Since being diagnosed with metastatic lung cancer, Garth Atchley has run three ultramarathons, two marathons, and several other races. He raises money for Fred's Team, which supports research at MSK. This photo was taken in front of MSK during the New York Road Runners NYC Half Marathon in March 2019. Photo: Fred's Team

Garth Atchley had just returned from a vacation to Yellowstone National Park with his wife and two teenage daughters when he realized something wasn't right. The 47-year-old ultramarathoner didn't have the energy to go running. He also felt unsteady on his feet, almost like he had vertigo.

He tried new glasses and saw a doctor for his allergies, but there was no improvement. So, he made an appointment with a neurologist near his home in Jersey City, New Jersey. An MRI revealed devastating news: He had a brain tumor, and it was metastatic — the result of an undiagnosed cancer that had started in his lungs. Just two days later, he had brain surgery at a local hospital.

"When I look back now to that time, it feels like a blur," Garth says. "My wife, Judy, and my sister-in-law, Mary, who is a nurse, stepped in and made sure that I was getting the best care possible. They decided I needed to go to Memorial Sloan Kettering."

On his first visit to MSK, he met **thoracic medical oncologist Helena Yu** and immediately felt a rapport. She explained that she would send a sample of his brain tumor for molecular testing with MSK-IMPACT™. This test looks for changes in more than 500 genes linked to cancer so patients can be treated with precisely the right drug.

Nearly four years later, Garth is a testament to how far cancer science has advanced to keep ahead of cells that are constantly changing to outsmart treatment.

Targeted Therapies Lead to New Treatment Options

"Garth's story illustrates the fact that we're always trying to offer more for our patients — to go beyond what's considered standard therapy," Dr. Yu says. "Molecular testing is a crucial part of figuring out those next steps."

Shortly after Garth's tumor samples were submitted for testing, he was walking near his office in Midtown Manhattan, where he works for a global shipping and logistics company, when Dr. Yu called with the first good news in weeks. His MSK-IMPACT results were not back yet, but another preliminary molecular test had revealed his cancer had a mutation in a gene called *EGFR*. "She told me that having this mutation was like winning the lottery," he says.

It meant he wouldn't need chemotherapy. Instead, he immediately began treatment with a targeted therapy aimed at his mutation, a daily pill called osimertinib (Tagrisso®).

It also meant the radiation for his brain tumors could be scaled back to just a few treatments. (Later, to destroy cancer that had spread to his liver, Garth also received selective internal radiation therapy. **MSK interventional radiologist Etay Ziv** inserted small radioactive seeds through a catheter placed near the site of Garth's tumor.)

Staying Ahead of Cancer's Evolution

Molecular testing of tumors has made a monumental difference for people like Garth. MSK-IMPACT and other genetic tests enable patients to be matched with targeted therapies that counteract the mutations driving the growth of their tumors. Unfortunately, though, tumors often find ways to stop responding to medication.

"Tumors learn from the very beginning that the way to survive is by increasing their genetic diversity. We call this intratumor heterogeneity, and it is one of the main drivers of resistance to therapies," says **MSK physician-scientist Pedram Razavi**, who specializes in breast cancer. "The tumor's ability to evolve is the main challenge we have in treating metastatic cancers."

Unfortunately, that's what happened to Garth. After 16 months on osimertinib, when he was feeling almost back to his normal life, his cancer began spreading again. A biopsy of lymph node tumors revealed an additional mutation.

"When you learn your disease has progressed, it's scary," Garth says. "Although I have stage IV cancer, Dr. Yu has never talked to me about prognosis. She has always been so reassuring, letting me know if something happens, there are more options that we can try."

Dr. Yu enrolled him in a trial for a drug called dacomitinib (Vizimpro®), which targeted the new mutation. It worked for an additional six months. But once more,

> "Although I have stage IV cancer, Dr. Yu has never talked to me about prognosis. She has always been so reassuring, letting me know if something happens, there are more options that we can try."
>
> *—Garth Atchley, MSK Patient*

Medical oncologist Helena Yu specializes in finding the best targeted therapy treatments for people with lung cancer.

his cancer stopped responding. Doctors then prescribed chemotherapy. Another biopsy of the lymph nodes in his armpit uncovered more molecular changes. The results were astonishing. He had lost the mutation that caused resistance to the first drug — osimertinib — and picked up another mutation that would make his "miracle drug" work again. He's has been taking his second course of osimertinib since January 2020. His tumors have shown no signs of further growth.

"I'm a big advocate of getting genetic testing more than once, especially if you have tumor progression or something else changes," Garth says. "What I've learned is that the mutations in your tumors are not always fixed."

The Next Frontier of Molecular Testing

Although Garth was able to have multiple tissue biopsies, that's not the case for many patients due to the location or number of metastases. Liquid biopsies, which can detect tumor DNA shed into the bloodstream, are a promising new advancement for addressing that need. MSK has developed its own liquid biopsy test, called MSK-ACCESS, which looks for more than 100 mutations in tumor DNA in the blood.

"Developing liquid biopsies is an important part of our efforts in treating metastatic cancer," Dr. Razavi says. "Being able to learn about cancer mutations from a simple blood draw is easier for patients. Additionally, because tumors that spread to different sites may undergo different evolutionary pathways, liquid biopsies can often help us to get a more complete picture and to more easily monitor the evolution of the disease."

In addition to taking osimertinib, Garth, who will turn 51 in July, now gets a low dose of chemotherapy every three weeks. "I'm not totally used to it, but you get into a rhythm," he says. "You know you won't feel great for a few days after chemo, so you just plan around it."

Garth has resumed running and now raises money for MSK through Fred's Team. His family also goes camping several times a year and hiking whenever they get the chance.

MSK's liquid biopsy test looks for more than

100

mutations in tumor DNA in the blood.

"Treatment has given me the opportunity to enjoy so many important things in my life," he says. "Since we got married, my wife and I have gone to Long Beach Island, New Jersey, for two weeks every summer. But for the past three years, we've rented a place there for the whole season. My daughters have summer jobs on the island, and they get to spend time with their friends. It's really our happy place." •

Garth Atchley with his wife, Judy, and his daughters, Jude (left) and Mary (right), on vacation in Wyoming in July 2017, just before he was diagnosed with cancer. Photo: Garth Atchley

Multiplying the Army of Cancer-Fighting Immune Cells

Physician-scientist Allison Betof Warner is leading a trial of a new immunotherapy for melanoma that has spread to the brain.

Using patients' own immune systems to fight cancer has been one of the most exciting advances in cancer treatment over the past decade. Now, a new immunotherapy could take this approach to the next level.

The treatment, called tumor infiltrating lymphocyte (TIL) therapy, harnesses and expands the power of immune cells that have already been fighting the cancer. The patient's immune cells are removed from their tumor after surgery, given a treatment that makes them multiply, and then infused back into the body where they can seek out and destroy remaining metastases anywhere in the body.

The concept of TIL therapy is not new, but it's only been feasible in the past few years, thanks to advances in biotechnology that allow immune cells that are harvested from tumors to be grown outside the body in large numbers.

Investigators at Memorial Sloan Kettering are conducting clinical trials for TIL therapy, which is being considered for approval by the US Food and Drug Administration later in 2021.

Physician-scientist Allison Betof Warner is leading the development of TIL therapy for metastatic melanoma at MSK, including an upcoming study that will be the only trial to specifically evaluate this approach in melanoma that has spread to the brain. "When melanoma spreads, it often goes to the brain, but patients with brain metastases are usually disqualified from participating in clinical trials of new treatments," she says. "To understand all of the potential benefits of TIL therapy, it's important to include these patients in our studies."

Medical oncologist Adam Schoenfeld is leading another trial for TIL therapy at MSK, which includes patients with several types of metastatic disease, including lung and head and neck cancers and melanoma.

"We are in early-phase trials in lung cancer, but I believe this treatment could be a potential breakthrough for patients — especially those who have disease that's resistant to immunotherapy — when treatment options can be limited," Dr. Schoenfeld says. "While there are several different steps required for TIL therapy, which can be challenging for patients to go through at times, the side effects tend to be short-lived, and after that there is a real possibility that they will have their disease controlled for a long time." •

Radiation Reimagined

How MSK Experts in Radiation Oncology Are Transforming Care for Metastatic Cancer

With potent, knifelike beams that can sear cancer cells yet spare healthy tissue, there's a growing arsenal of weapons pioneered by Memorial Sloan Kettering's radiation oncologists to reach tumors that have recurred deep inside delicate regions of the body.

Radiation oncologist Josh Yamada and his colleagues are helping people with two particularly important advances developed at MSK: high-dose radiation and computer software called ECHO. This algorithm exquisitely fine-tunes radiation doses, resulting in a level of precision that Dr. Yamada says reduces possible side effects and produces better outcomes. It's used on about 8 percent of MSK patients now, but it's expected to treat 80 percent of them in the next decade, says Dr. Yamada.

Higher Doses Also Mean Fewer Treatments

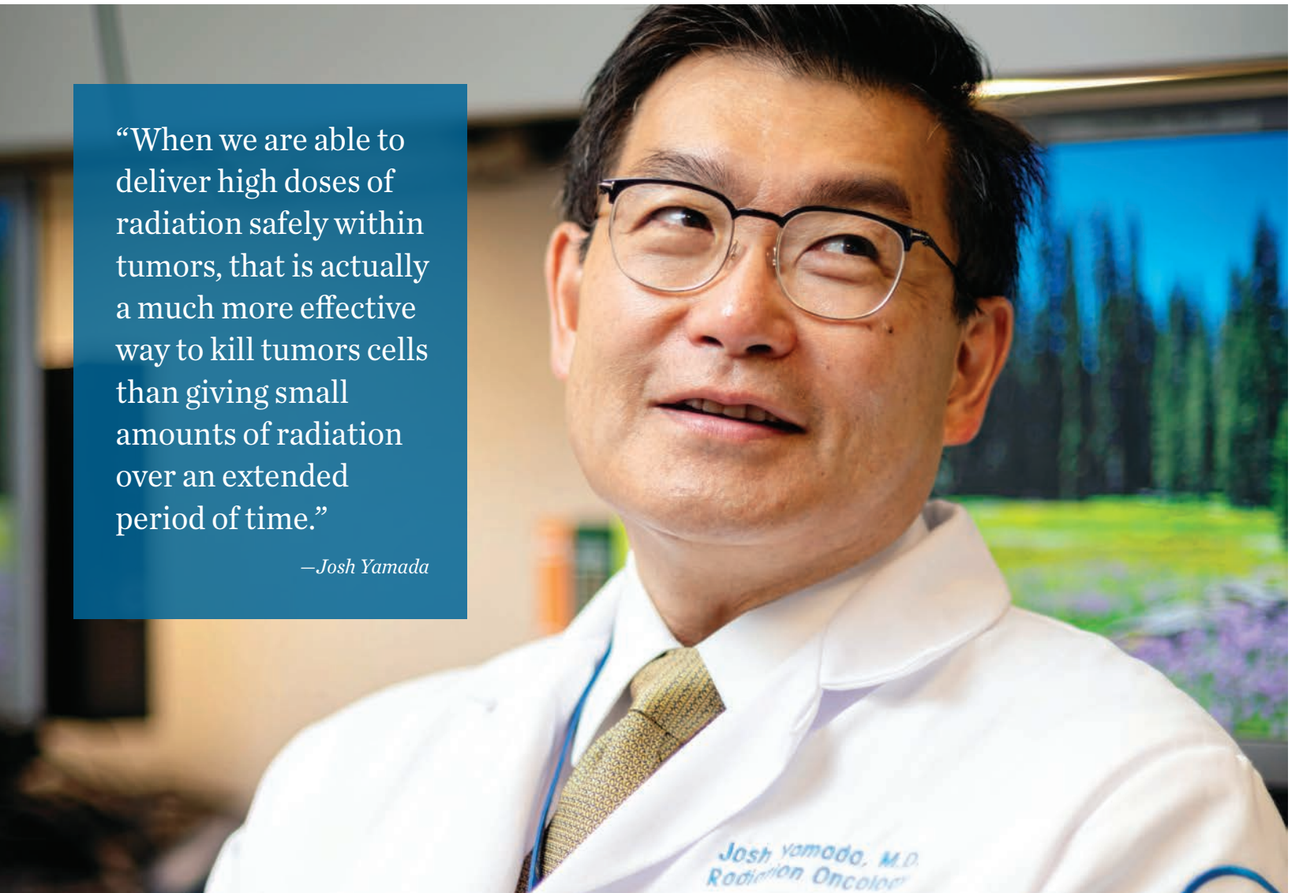
"When we are able to deliver high doses of radiation safely within tumors, it is actually a much more effective way to kill tumor cells than giving small amounts of radiation over an extended period of time," says Dr. Yamada.

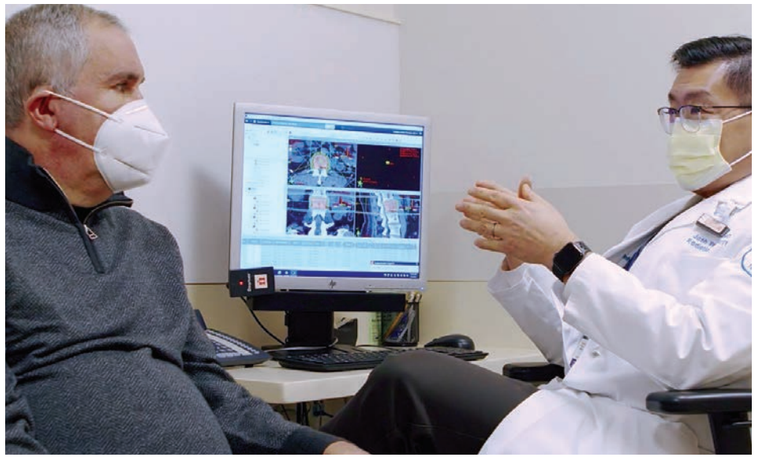
'I've Got This'

MSK patient Tim Willis is a strong example. He came to Dr. Yamada in the fall of 2017 because cancer that started in his kidney had spread, causing tumors on his spine.

Tim was deeply worried about pain and paralysis but remembers, "Once Dr. Yamada gave me his medical assessment, he actually put his hand on my knee and said, 'Just so you know, I've got this,' which still gives me shivers."

Six months later there was no evidence of disease in Tim's spine. "I reclaimed my life," he says. "I feared being debilitated after this treatment. But it was the exact opposite. The quality of life has been absolutely outstanding."





Tim Willis (left) and radiation oncologist Josh Yamada at an appointment in March 2021.

New Tech for Best Treatment

So far, about 1,000 spine tumors have been treated at MSK with the help of ECHO. Creating this high-precision software took seven years, with a team lead by **MSK's Linda Hong and Masoud Zarepisheh. Joseph Deasy, Chair of MSK's Department of Medical Physics and Enid A. Haupt Chair in Medical Oncology**, compares the technology to switching to a self-driving car to navigate tricky paths.

"ECHO is much more like an automated process that drives the car for you. The limitation with radiotherapy treatment up until now was that there was no way to tell that you actually had the best plan. ECHO gives us the best plan."

And because ECHO automates so much of the planning process, Dr. Yamada believes it can help people far outside MSK. "In American hospitals, and especially in lower-resource countries, ECHO can reduce costs and allow medical teams with lower skill levels to give very precise radiation."

Life-Changing Pain Relief

At MSK, new approaches to using radiation therapy can also relieve the physical pain that can make day-to-day living uncomfortable and continuing therapy more difficult — especially when cancer spreads to the bones.

That's an area of intense focus for **MSK radiation oncologist Jonathan Yang**. He explains, "Cancers that spread to the bone are about 100 times more common than cancers that originate in the bone. They often cause acute pain and fractures and can be very frightening and disabling for patients already dealing with their primary cancer."

That was the situation facing Jacqueline Hickey. She had repeatedly fought off lung cancer since she was first diagnosed at age 40 in 2007. When the cancer returned in 2018, her personal physician suggested Memorial Sloan Kettering.

A combination of chemotherapy and radiation helped. But eventually the cancer spread to her left rib. Jacqueline recalls, "It just hurt so bad, especially lying down at night. I got so sleep deprived." During the day, her activities were also severely hampered by pain.

Jacqueline was leery of pain medications. As a mother of four, she explains, "I want to be able to focus. I have one child still at home and my firefighter husband often has to work 24-hour shifts. I don't want to be conked out."

Bone Metastasis Clinic Makes Life Easier

Jacqueline found help at **MSK's Multidisciplinary Bone Metastasis Clinic**, established in 2019, where patients can see all the specialists they need on the same day.

Led by Dr. Yang, **interventional radiologist Ernesto Santos**, and **orthopedic surgeon Max Vaynrub**, the clinic also includes specialists in rehabilitation medicine and pain management.

To help Jacqueline, the clinic team decided to use cryoablation and stereotactic body radiotherapy (SBRT) — the same treatment used on the spinal tumors of Tim Willis — which uses targeted, focused external beam radiation to maximize the radiation dose to the tumor while minimizing damage to the normal tissue. Cryoablation involves inserting small needles into the bone metastases, freezing and killing the bits of tumor.

New Outlook

"It's unbelievable the difference it has made," says Jaqueline. "Now, I'm back to sleeping, going out walking, and being able to function and run a family."

And she has a message for other people with bone metastases. "There are so many new things coming out, and it's exciting — if one thing doesn't work, there's always something else they can try," says Jacqueline. "Even with stage IV lung cancer, I'm never giving up."

Although Tim Willis recently needed another round of treatment for more spine tumors, he shares Jacqueline's attitude. "When people hear that I'm a stage IV patient," he says, "they kind of step back and say, 'Oh, I'm sorry.' And I say, 'No, I feel so much better than I look on paper.'" •

Approximately **1,000** spine tumors have been treated at MSK with the help of ECHO.

A New Frame of Mind

MSK Experts Join Forces When Cancer Spreads to the Brain

A busy real estate broker and married mother of three, Susan van der Griend is an optimist by nature, used to making things happen and moving on. When she was diagnosed with melanoma in 2017, she decided to be treated near her home in Connecticut. But a positive outlook didn't stop the cancer. The disease recurred in four places. She went straight to Memorial Sloan Kettering.

"There's always somebody working on a new approach to cancer treatment there," says the 64-year-old.

Susan was given immunotherapy under the care of **MSK melanoma medical oncologist Parisa Momtaz**. Her cancer seemed to clear. But in 2020, a CT scan showed three new lesions in her brain. "I felt betrayed by my body," she recalls. "I thought, 'How could this happen when the cancer had cleared up in the rest of my body?' My glass is always half full, but this was a setback."

In the past, news like this was assumed to be the beginning of the end for a patient. But MSK doctors are treating metastatic brain cancer aggressively — and getting good results.

Viviane Tabar, who is the Theresa Feng Chair in Neurosurgery, helped found MSK's new Brain Metastasis Clinic.

Storming the Fortress

The brain is like a fortress, surrounded by a barrier that protects it from dangerous pathogens. But that same barrier is also what prevents cancer medicines from reaching their target. What's more, cancer cells can sneak inside, like tiny Trojan horses, by following the cells that are allowed into the brain. The cancer can also express molecules that latch onto the brain's gatekeeper — like talking their way past security.

But efforts are underway to find the leaks in this barrier, says **Adrienne Boire, physician-scientist in MSK's Human Oncology and Pathogenesis Program**. With the help of a liquid biopsy, which is a blood test that can detect DNA from a brain tumor, her lab is also gaining new insight into how brain tumors evolve.

Having this precious DNA gives clinicians the ability to detect hundreds of genes that drive tumor growth. The goal is for doctors to determine the best targeted therapy for a tumor without having to obtain a tissue biopsy from the brain.

These discoveries offer great promise for future therapies, but there is also progress right now. Susan's cancer has been kept in check by immunotherapy, radiation, and surgery.

Care for the Whole Person

"When a cancer spreads to the brain, it creates enormous challenges, clinically and scientifically, but also psychologically for the patient," says **Viviane Tabar, Chair of the Department of Neurosurgery and Theresa Feng Chair in Neurosurgery**.

Susan van der Griend was stunned when melanoma recurred in her brain. But MSK's Brain Metastasis Tumor Board created a multifaceted plan that has kept Susan healthy.
Photo: Susan van der Griend

Dr. Tabar helped establish a new **Brain Metastasis Clinic** that applies a highly efficient team approach for patients like Susan. Experts from many fields study a patient's case and recommend next steps. To make the experience as easy as possible, they organize appointments — including radiation, if needed — to be done all in one day. This collaborative approach is also offered to patients whose primary oncologist is outside MSK.

Great Minds

Like detectives mining a crime scene, MSK specialists from neurosurgery, radiation oncology, neuroradiology, medical oncology, physical therapy, and more pored over Susan's case in 2020. They discussed her case at their **Brain Metastasis Tumor Board**, a newly assembled group of specialists who are focused on treating cancers that spread to the brain.

"She's in a growing population of patients who have done incredibly well on cancer therapies but have tenacious metastases in the brain," says **neurosurgeon Nelson Moss**, the center's surgical lead.

Kathryn Beal, the tumor board's lead radiation oncologist, recommended stereotactic radiosurgery for Susan. This high-dose form of radiation was pioneered at MSK. Administered close to Susan's home at MSK Westchester, the radiation shrunk each tumor, eliminating the activity in two of them.

The third mass was about the size of a walnut, in the part of the brain controlling perception and walking. It was harder to treat and had started to affect her leg function. But Dr. Moss and his colleagues came up with a surgical plan. They also told Susan she could choose to have the tumor monitored over time. The decision was up to her.

"He was very balanced in his approach and clearly pointed out each option. He wasn't pushing me either way," she recalls. "He said, 'This is why I think this is a good idea, but I can understand why you might want to wait.' But I didn't want the problem with my leg to persist or get worse."

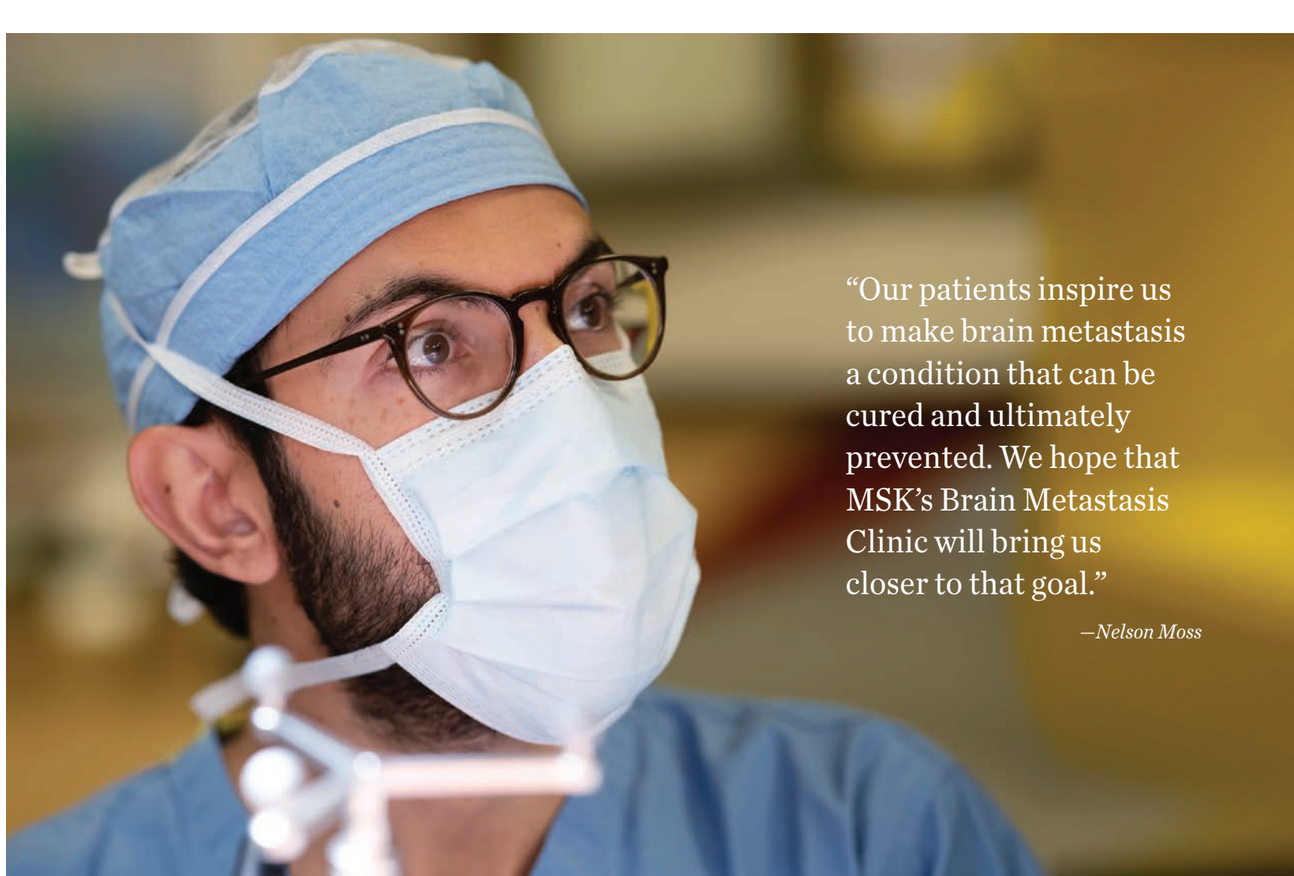
Moving Forward

In a three-hour procedure, Dr. Moss was able to remove all of the tumor. Susan returned home the very next day. A few weeks later, she had another round of radiation to kill any lingering cancer cells. She has otherwise needed no additional treatment and has regained function in her leg. She checks in with Dr. Moss every three months.

Susan is back at work, with her sunny attitude and sense of humor, despite all she's endured. When asked if she'd ever considered that melanoma could one day spread to her brain, she replied, "It didn't even enter my head. Well, I guess it did!"

Dr. Moss is optimistic about Susan's prognosis and hopeful for other patients like her.

"She and all our patients inspire us to make brain metastasis a condition that can be cured and ultimately prevented," says Dr. Moss. "We hope that MSK's Brain Metastasis Clinic will bring us closer to that goal." ●



Always by Your Side

How MSK Helps People Facing Metastatic Breast Cancer

Reilly Starr (left) with her husband, Sean Mohammed, and their son. Photo: Courtney Bowles

For Reilly Starr, the relationships inside her support group are nearly impossible to describe — or for people outside to comprehend. "It's hard to say that these people are just friends," she says. "The relationships are so deep. They are really like another treatment for your cancer."

Reilly is talking about the Metastatic Breast Cancer Support Group at Memorial Sloan Kettering. She joined after coming to MSK in 2019 seeking treatment for stage IV breast cancer that was diagnosed when she was 40 years old.

Every other week, she joins a group of around eight to 12 people who are also facing metastatic breast cancer. Many have young children, like Reilly, who has a 3-year-old. In this group, everything is on the table, says Reilly. "This is a safe place to cry and to share things your family and friends don't understand or can't handle. It's okay to be raw."

The group is one of two at MSK. Reilly's group focuses on the needs of younger people, who often are in the middle of careers and raising a family. The other group is geared toward people facing metastatic breast cancer at a later stage in life.

Roz Kleban, a senior manager in the Department of Social Work and a 30-year veteran at MSK, helps lead both groups along with **social worker Susan Glaser**. Ms. Kleban explains, "Some people with metastatic breast cancer are afraid of these groups because you might witness someone you get close to who is dying." She continues, "But the people who participate see that as part of it. They think, 'I need to be there for you because I know you'll be there for me.'"

Turning Down the Radio

According to the American Cancer Society, more than 150,000 survivors of breast cancer are living with metastatic disease, which is far and away the most lethal form of breast cancer.

Still, says Ms. Kleban, until 15 or 20 years ago, metastatic breast cancer was "almost never mentioned, and a huge population of people was mostly ignored." This distressed some patients with metastatic breast cancer at MSK, who started a group that raised awareness. "For many years," says Ms. Kleban, "MSK was the only facility that had support groups for people with metastatic breast cancer."

Today, one of the big aims of these MSK support groups is what Ms. Kleban calls "turning down the radio." She explains that for people with metastatic breast cancer, "there's a radio on in your head, 24/7, banging at you about the illness, the treatments."

She tells patients, "It's the doctor's job to keep the illness at bay. But it's your job to keep that radio low. The volume is always on, and sometimes it's screaming, like when you're waiting for the results of a scan." But, she stresses, "it's within your power to try to keep it as low as possible to live as well as possible."

A Godsend

Ilene Thompson was looking to lower the volume when she came to MSK in 2018 after her breast cancer recurred and was diagnosed at stage IV.

Ilene Thompson with her grandsons. Photo: Ilene Thompson

After a career in healthcare, she recognized that she could use help, beyond her two grown daughters and a "supportive group of friends in Brooklyn." She explains, "I knew the group members would understand my issues. Sometimes family and friends just can't, and I have to explain the same thing over and over. That can be frustrating and tiring."

In the support group, she says, "we bounce off each other, and find out about new treatments and little home remedies to make yourself more comfortable." There are also subgroups, including a writing group and "one coming together that will do meditation — these really help on a daily basis."

Just as important is the emotional support. Ilene explains, "We have each other's phone numbers and emails so we can just call if we want between meetings." Before COVID-19, members also visited those who had taken a turn for the worse. However, she stresses that joy also plays a part in the group. "We know many of us are living day to day, so we try to enjoy it. We encourage laughter and fun."

Roz Kleban tells patients it's within their power to live as well as possible.

She concludes, "I'm really happy I sought out this group. I know emotionally this has been a godsend for me." That's a message echoed by Reilly, who says, "I'd recommend this 1,000 percent. The group is a necessity for me."

Ms. Kleban says these women help each other stay positive. While stopping cancer's spread does not depend on keeping a positive attitude, having hope helps patients find joy and human connection every day. ●

More than
150,000 survivors
of breast cancer are living with metastatic disease.

How Two Visionary Donors Are Changing the Way Metastasis Is Studied at MSK

Alan Gerry has always recognized an opportunity when he sees one. His parents both emigrated from Russia to New York City in their youth so their families could build better lives.

By the time he was 12, Alan had built his first radio receiver. By the time he was 27, he had founded Liberty Video, which would become Cablevision Industries, the largest privately owned cable television company in the United States. His ambition to build a brighter future led him to Memorial Sloan Kettering.

In 2007, Alan and his wife, Sandra, met Joan Massagué of the Sloan Kettering Institute, one of the world's leading researchers in metastasis. "As soon as I heard Joan Massagué speak about his work and goals for saving so many lives in the future through research, I knew we had to help move the needle," recalls Alan.

The results of that meeting revolutionized how metastasis is understood and treated, not just at MSK but around the world. After Alan and Sandra gave their first gift in 2007, ten years of unwavering support followed, and in 2017, the Alan and Sandra Gerry Metastasis and Tumor Ecosystems Center was named in their honor.

"The progress we've made at MSK has opened the door for massive discoveries in the coming decade," says Dr. Massagué. "Alan and Sandra have helped create the current environment of optimism, and they are essential partners in this work."

Read more about how Alan and Sandra Gerry's support is helping transform our understanding and treatment of metastasis at the Alan and Sandra Gerry Metastasis and Tumor Ecosystems Center at **mskcc.org/summer-2021.** •

Memorial Sloan Kettering Cancer Center

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MIX Paper FSC® C012441