

THE SIDNEY KIMMEL
COMPREHENSIVE
CANCER CENTER AT
JOHNS HOPKINS

PROMISE & PROGRESS

SPECIAL ISSUE

BLOOMBERG~KIMMEL INSTITUTE *for* CANCER IMMUNOTHERAPY

“Immune therapy is a game changer. We need more research to take us the rest of the distance, but we don’t think there is a single cancer that the patient’s own immune system ultimately can’t beat.”

—Cancer Immunologist **Drew Pardoll, M.D., Ph.D.**



Our Time Harnessing the Power of the Immune System

WE HAVE ALWAYS believed that if we could harness the power of the immune system, no cancer could survive. For more than three decades, the Kimmel Cancer Center has played a key role in advancing the science of cancer immunology with world-renowned immunology experts like Drew Pardoll, Elizabeth Jaffee, Charles Drake, Jonathan Powell, and Suzanne Topalian leading the way. Much like the cancer cell, the immune cell and system have proven to be extraordinarily complex, but our experts have demonstrated that they are up to the challenge.

Our expertise in cancer immunology, genetics, and epigenetics, which thrives in an environment of collaboration, has been key to making progress. It has resulted in new findings that have been transferred to patient care with unprecedented speed. Checkpoint blockades—which block signals cancer cells use to neutralize the immune system—have resulted in remarkable and lasting responses in patients with melanoma and lung cancer, and are now being explored in other cancers.

Cancer vaccines that recruit large numbers of immune cells have made our center the leader in the research and treatment of pancreatic cancer, one of the most lethal forms of cancer.

Epigenetic-targeted therapies that prime immune responses to cancer and

a genetic biomarker are also among some of our innovative approaches.

Many of these findings are the product of investigator-initiated research and so clearly demonstrate the value of collaborative, integrative science. I would argue that no place does it better than the Johns Hopkins Kimmel Cancer Center, and it is evidenced by our success.

Helping us identify which patients' cancers are wired to react to immune therapies and which ones need help to respond makes it possible to get immune therapies to the right patients sooner. As important, it advances the science that will allow us to convert many of the cancers that currently do not respond to cancers that do respond.

Many of these breakthroughs were funded entirely, and all of them relied at least in part, on private support. At this critical time, when the Kimmel Cancer Center's cancer immune therapies are having unprecedented success, two Johns Hopkins champions have once more answered the challenge and are providing essential funding to help ensure we realize the full potential of the immune system's ability to fight cancer. **Sidney Kimmel**, who helped lay the foundation upon which our success is built, and three-term New York City Mayor, and a leading Johns Hopkins supporter, **Michael Bloomberg** are each contributing \$50 million over

the next five years to establish the Bloomberg-Kimmel Institute for Cancer Immunotherapy.

Of course, there are many others that have helped pave the way for this latest endeavor. The Commonwealth Foundation, the Skip Viragh Foundation, Stand Up To Cancer, Swim Across America, and so many other organizations and individuals, as you will read, have gotten us here.

This support comes at a vital time. Laboratory and clinical research ensures that we will unravel the intertwined biology of the cancer cell, the immune cell, and the cells that surround the tumor so that we can begin to harness the power of the immune system for all cancer patients. For decades cancer experts have sought this moment—when the immune system could precisely and predictably be recruited to fight cancer universally across all cancer types. The success of immune therapies is real, but the full promise cannot be realized without continued research. We have the talent and the technology, and I believe this is our time.

William G. Nelson, M.D., Ph.D.
Marion I. Knott Professor and Director
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins



02

Promise & Progress
is published by
*The Sidney Kimmel
Comprehensive Cancer Center
at Johns Hopkins*
Office of Public Affairs
901 South Bond Street
Suite 573
Baltimore, Maryland 21231
(410) 955-1287

William G. Nelson, M.D., Ph.D.
Director

Amy Mone
Director of Public Affairs

Valerie Matthews Mehl
Editor and Sr. Writer
mehlva@jhmi.edu

Michelle Potter
*Production Manager,
Editorial Assistant,
and Web Exclusives*

Flynn Larson
Feature Photography

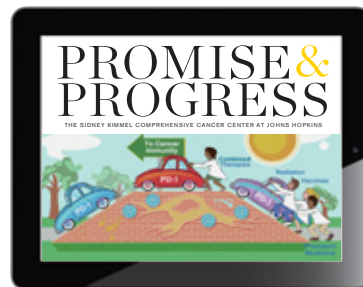
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JOHN RYAN IS AMONG THE MANY PATIENTS WHO HAVE BENEFITTED FROM A PROMISING NEW IMMUNE THERAPY CALLED ANTI-PD1.



The Final Frontier?

Immune Therapies Break Through Cancer's Protective Barriers

Immune therapy is recognizably different from all conventional cancer therapies. Imagine a cancer treatment that works without making patients sick or causing their hair to fall out. Doctors and nurses agree it is unlike anything they have ever witnessed in the world of cancer medicine. Gone are the iconic bald heads that immediately identified a person—inside or outside of the hospital—as a cancer patient. Like no other disease, cancer has traumatized the human population with its lethality and toxic treatments. That's all changing now, as therapies that empower the body's own natural defenses are at last becoming a reality and providing unparalleled, long-lasting responses across many cancer types, and even in the most advanced and treatment-resistant cancers.

PATIENTS ARE SAYING they don't feel like they have cancer. Knowing what cancer treatment is "supposed" to be like—many having already experienced it—they worry that they feel too well. Many ask: "If I feel this healthy, could the treatment really be working?"

The answer, experts say, is a resounding "yes," and the Kimmel Cancer Center is leading the way with its unprecedented findings echoing through the laboratories and waiting rooms of medical institutions, community hospitals, and cancer clinics all over the world.

"This is oncology of the future," says **William Nelson**, Kimmel Cancer Center Director, "and the future is now."

A Game Changer

As long as cancer has been a recognized disease, doctors have believed the power to eliminate it existed within the immune system, but attempt after attempt to unlock this potential has largely failed. The potential always existed, but the key information needed to turn this promise into real treatments was locked away inside the DNA of tumor and immune

cells. Researchers and clinicians at the Kimmel Cancer Center have worked together with experts throughout Johns Hopkins, using science to follow the clues and bring the world what may be a universal treatment for cancer. Cancer immunology and melanoma expert **Suzanne Topalian** calls immunotherapy "the common denominator."



DREW PARDOLL AND ELIZABETH JAFFEE, CIRCA 1999.

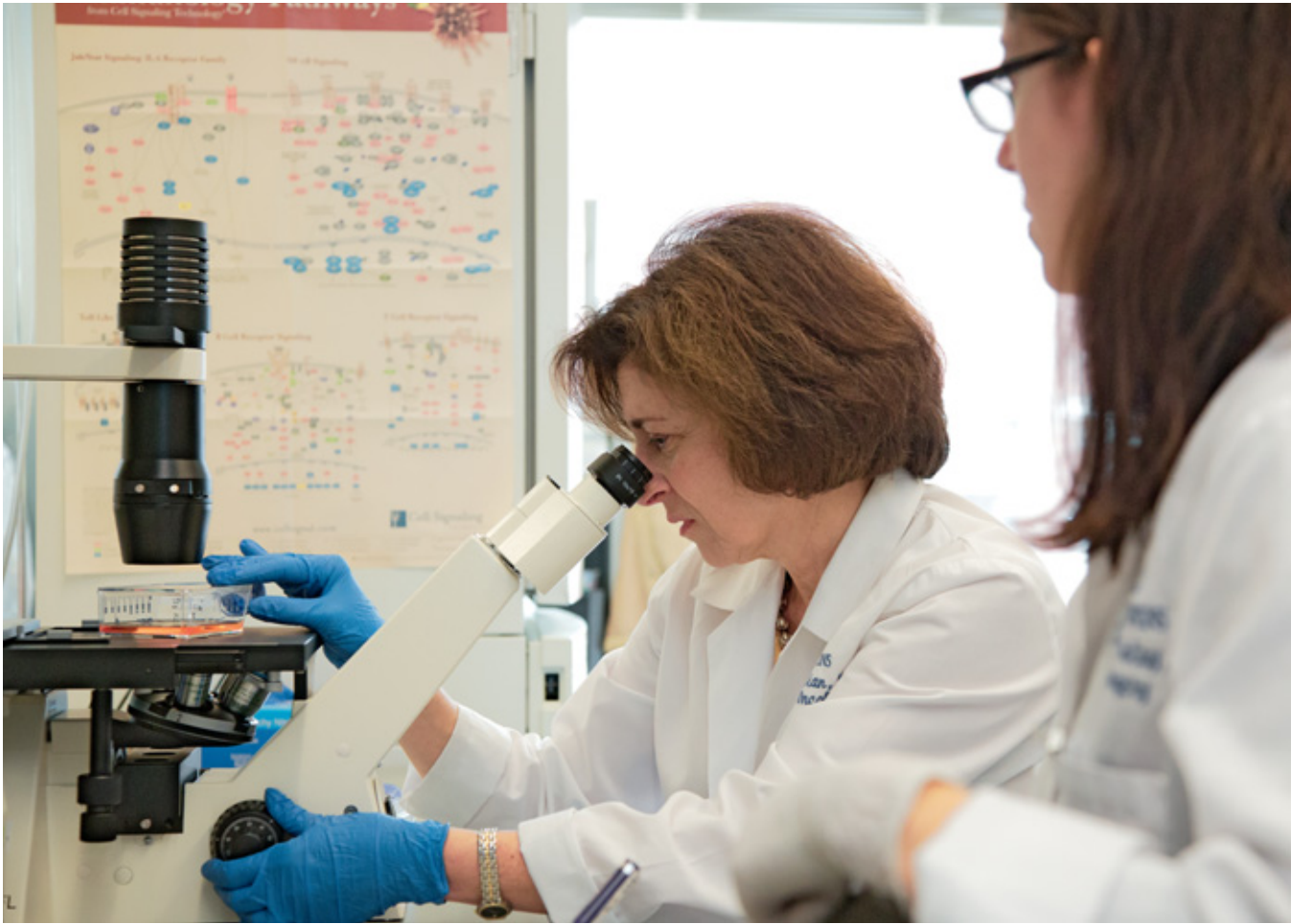
Immune-based therapies reflect a different approach to treatment. Instead of targeting cancer cells, the new therapies target immune cells in and around cancers. Some treatments increase the number of immune cells summoned to the tumor,

and others unleash the commands that send the immune cells to work against it. These types of immune therapies have had success alone, but perhaps their greatest power will come in combining them and, through precision medicine, using the biological clues within each patient's cancer to guide treatment.

Leading the way are scientists, like **Drew Pardoll** and **Elizabeth Jaffee**, who have been at work for more than 30 years deciphering the mechanisms of the immune system, how it works and why it all too often does not work against cancer. As students of the immune system, Pardoll, Jaffee, and others understood that the characteristics of the immune system should make it the perfect anti-cancer weapon, but if the cancer cell was complex in its molecular construction, the intricacies of the immune system were equally complicated.

Unlike viruses and bacteria that are easily recognized by our immune system because they are so different, cancer originates from our own cells. As a result, it has all of the cellular mechanisms that are used by normal cells at its disposal.

RESEARCHERS AND CLINICIANS AT THE KIMMEL CANCER CENTER HAVE WORKED TOGETHER WITH EXPERTS THROUGHOUT JOHNS HOPKINS, USING SCIENCE TO FOLLOW THE CLUES AND BRING THE WORLD WHAT MAY BE A UNIVERSAL TREATMENT FOR CANCER. CANCER IMMUNOLOGY AND MELANOMA EXPERT **SUZANNE TOPALIAN** CALLS IMMUNOTHERAPY "THE COMMON DENOMINATOR."



Cancer co-opts them selectively, using them like superpowers to grow, spread, and cloak themselves from the immune system.

It took time for the technology to catch up with the scientific ideas, but the invincible cancer cell may have finally met its match. This Kimmel Cancer Center team of multispecialty collaborators—seasoned investigators and young clinician-scientists—has figured out how to reset the cellular controls hijacked by the cancer cell and restore power to the immune system. In a convergence of immunology, genetic, and epigenetic findings, the secrets of the cancer cell's

ability to dodge an immune attack are being revealed, and the results, though admittedly early, are like nothing that has ever been seen in cancer medicine. Utter destruction of the most resistant, lethal tumors is occurring across many cancer types and with few side effects. Patients who were months, even weeks, from dying are alive and well, some five years or more after treatment.

It was what Pardoll and Jaffee imagined three decades ago when they first began studying the immune system—perhaps even better.

Immune Checkpoint Blockades

More than 8000 practicing oncologists and clinical cancer scientists from all over the world filled the lecture hall at the 2015 annual meeting of the American Society of Clinical Oncology (ASCO). It's not the first time a standing-room-only crowd has come there to hear a Kimmel Cancer Center cancer expert discuss one of the most promising new cancer therapies in decades—immune checkpoint blockade. This time, cancer immunology expert Suzanne Topalian was there as the David A. Karnofsky Memorial

The secrets of the cancer cell's ability to dodge an immune attack are being revealed, and the results, though admittedly early, are like nothing that has ever been seen in cancer medicine.

“Cancer cells take control of a valuable immune response regulator and turn it on its head. The anti-PD-1 therapy allows us to seize that power back.”

Award and Lecture recipient for “outstanding contributions to the research, diagnosis, and treatment of cancer.” In 2012, Thoracic Oncology Program Director **Julie Brahmer** presented findings on an immune checkpoint blockade study in lung cancer. It marks a changing tide in clinical cancer research. Immunology studies had never before received this level of attention at ASCO meetings.

With remarkable and lasting results in about 20 to 40 percent of patients with advanced cancers that resisted all other

types of therapy, oncologists wanted to know more. Scholarly journals and the news media alike were reporting on drugs that caused lethal melanoma skin cancers, kidney cancers, and lung cancers to melt away and stay away.

The therapies are so new—first tested in patients in 2006—that the Kimmel Cancer Center immunology team readily admits there is much left to learn. “We don’t know yet what the ultimate survival benefit will be, but for some patients in these first trials, the responses are still

ongoing after many years,” says Pardoll. These long-lasting responses that continued even after therapy was stopped and caused few side effects are the reason the auditorium was filled to capacity with doctors anxious to learn how and when they could get this new therapy for their patients.

The source of the excitement is an immune target called PD-1 and a related partner protein on tumor cells called PD-L1. PD-1 is what immunology experts call an immune checkpoint. Pardoll stops short of calling it an immune system master switch, but the results in laboratory research and these early clinical trials point to it as one of the strongest influencers of an immune response to cancer identified so far. It—and likely some other similar proteins—is responsible for cancer’s ability to avert an immune attack.

There are two main actions at play in an immune reaction. The first is a “go” signal. “Our cells are constantly presenting our own proteins to our own immune system,” explains pathologist **Bob Anders**. One can think of DNA as the blueprint of a cell, and the proteins its genes encode are its building blocks. A protein from a mutated gene looks different than its normal counterpart. In the same way it recognizes bacteria and viruses, the patrolling immune system can recognize abnormal cells that don’t belong. “When immune cells come upon something that shouldn’t be there, they generate an immune reaction,” says Anders. This is the

AMONG NORMAL CELLS, PD-1 IS NOT A BAD ACTOR, EXPLAINS BLOOD AND BONE MARROW CANCER EXPERT AND IMMUNOLOGY COLLABORATOR **JONATHAN POWELL**. “IT’S ACTUALLY A GOOD THING. IT’S THE MEANS BY WHICH THE IMMUNE SYSTEM REGULATES ITSELF. IT MAKES SURE THE IMMUNE SYSTEM DOESN’T OVERDO ITS JOB.”



Lessons from the First Immune Therapy

SOME OF THE earliest research at the Kimmel Cancer Center that focused on the immune system was in blood and bone marrow cancers and bone marrow transplantation. Cancers of the blood and bone marrow, such as leukemia, lymphoma, and multiple myeloma, provided a unique perspective of normal immune cells, malignant ones, and the magnitude of the immune system's power

In most cancers, the goal is to engage the immune system, but in bone marrow transplant, where the patient's cancer-filled bone marrow is replaced with healthy marrow from a donor, the goal is to disengage—well, at least a little. The reason is a serious complication of bone marrow transplant known as graft versus host disease (GVHD), a destructive immune attack against the patient's organs and tissue. The transplanted marrow sees its new host as foreign and wages an assault that can be as lethal as cancer.

Veteran cancer immunology leader **Drew Pardoll** first observed its wrath as an oncology trainee treating a young girl dying from severe GVHD. It was a defining moment for the young physician-scientist. "I realized that the immune system was probably the most powerful anticancer weapon we have," says Pardoll. "If we learned how it worked and could focus it more precisely against cancer, I believe it could be more powerful than any drug."

Pardoll decided to focus on deciphering how the immune system worked, while Kimmel Cancer Center bone marrow transplant experts began solving the problem of GVHD in what could be considered one of the first immune success stories in cancer treatment.

Making Bone Marrow Transplant Safe and Available to All

FOR DECADES GVHD prevented bone marrow transplants from being performed on patients who did not have a donor with a nearly identically matching immune



system, usually found in a brother or sister. A large national registry matched some of these patients with unrelated donors, but most grew sicker and many died waiting for a match to be found. As a result, only about one-half of patients were candidates for the potentially curative therapy. Minorities suffered the most. African-American patients who did not have a match in their family had less than a 10 percent chance of finding a donor in the unrelated registry.

Pioneering discoveries led by Kimmel Cancer Center investigators **Richard Jones, Ephraim Fuchs** and **Leo Luznik** have now made it possible for almost any patient to receive a transplant. The research that led to this breakthrough focused on immune cells known as T cells and technologies to remove these cells from the donor marrow. Clinical studies showed that when the T cells were removed, patients did not get GVHD but their cancers sometimes came back. It was one of the first observations of the immune system's ability to kill cancer cells. The challenge was to remove a precise amount of T cells—small enough to avoid the most severe cases of GVHD, yet a large enough number to allow the immune system to keep the cancer from returning.

It turns out that the same drug used to treat patients before bone marrow transplant could be given post-transplant to limit GVHD without hampering the T cells' ability to mop up any surviving cancer cells. This discovery led Kimmel Cancer Center experts to develop a new type of bone marrow transplant, known as a haploidentical or half-identical transplant.


In this breakthrough approach developed at the Kimmel Cancer Center,



almost all parents, siblings, and children of patients—and sometimes even aunts and uncles, nieces and nephews, half-siblings, and grandparents or grandchildren—can safely serve as donors. Now, almost every patient who needs a bone marrow transplant can find a matching donor. Since developing the treatment more than a decade ago, Kimmel Cancer Center experts have performed more than 600 half-matched transplants for adult and pediatric leukemia and lymphoma.

These clinical studies have proven so successful, with safety and toxicity comparable to matched transplants, that the therapy is now used to treat chronic but debilitating noncancerous diseases of the blood in adults and children, such as sickle cell disease and severe autoimmune disorders.

More recently, a revolutionary study using half-matched transplants to improve the effectiveness and safety of solid organ transplants with living donors has begun. Kimmel Cancer Center researchers are collaborating with transplant surgeons to begin a combined kidney/half-identical bone marrow transplant. Since the patient and donor would have the same immune system, it could essentially eliminate organ rejection and a lifetime of antirejection drugs.

If successful, this important work will conquer the transplantation barrier—rejection—and what is learned could be applied to all solid organ transplants. It also facilitates the research being done in regenerative medicine, where work to grow transplantable tissue and organs would ultimately be of no clinical use without the means to successfully and safely transplant them into humans. 

go signal. When the job is done and the invading cells are taken care of, the immune system issues a “stop” signal.

These stop signals are controlled by immune checkpoints like PD-1. In cancer, malignant cells hijack the “stop” signal to maintain their own survival. They send a deceptive message to cancer-killing immune cells that there is no problem. Immune cells arrive at the tumor, but they are duped with a false message that everything is OK. “Essentially, they’re told to go home. There is nothing to see here,” says pathologist **Janis Taube**.

Taube and Anders describe a scenario in which a tumor is spreading, and as immune cells come in to try to remove the cancer, the cancer turns up the volume on PD-1, a signal that turns the immune cells off. “The tumor cells use our own physiology against us,” says Anders.

The “volume” of the PD-1 stop signal is controlled in the cancer cell by the expression of one or both of two partner proteins called PD-L1 and PD-L2. In solid tumors, like melanoma and lung cancer, PD-L1 has received the most attention today, but PD-L2 appears to play an important role in cancers that start in the blood and lymph nodes, such as leukemia and lymphoma. “We see PD-L1 frequently in melanoma,” says Taube. “PD-L1 is expressed on the surface of the tumor cell. When you see it through the microscope, it looks like someone outlined the cells with a marker. It forms an armor that protects the cancer cell from the immune system.”

Giving patients a drug, known as an anti-PD-1 checkpoint blocker, for its ability to interrupt PD-1 signaling as well as the communication between PD-1 and PD-L1 and PD-L2, removes the stop signal and re-engages the immune system.

Among normal cells, PD-1 is not a bad actor, explains blood and bone

marrow cancer expert and immunology collaborator **Jonathan Powell**. “It’s actually a good thing. It’s the means by which the immune system regulates itself. It makes sure the immune system doesn’t overdo its job,” he says. It’s the cancer cell that once again assumes the role of villain. PD-1 is an immune mechanism that has been usurped by the cancer cell. “Cancer cells take control of a valuable immune response regulator and turn it on its head,” he says. “Anti-PD-1 therapy allows us to seize that power back.”

Unbelievable Patient Responses

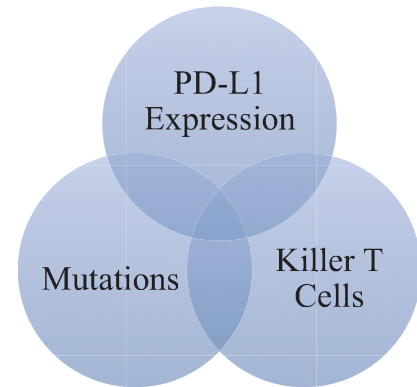
John Ryan is among the many patients who have benefited from the anti-PD-1 therapy being discussed at ASCO.

Ryan, 71, began experiencing symptoms in 2013 when he coughed up a small amount of blood. The husband and father of eight thought it was strange, but with no pain or other symptoms he was stunned to learn he had the most advanced stage of a common form of lung cancer known as non-small cell lung cancer. The cancer had already spread to a rib.

There are few diagnoses worse than late stage lung cancer. The cancer kills more people than any other type of cancer, and few patients survive once it has spread. At this stage, the cancer is treatment resistant, responding for a brief time to chemotherapy or cancer-gene-targeted therapies, but almost

always resurging even stronger.

Medically speaking, Ryan’s diagnosis was Stage 4 non small cell adenocarcinoma of the lung. “One of my sons was graduating from college, and my daughter was about to leave for a study abroad. I wondered if I would live long enough to see my son graduate or to welcome my daughter back home,” Ryan recalls.



PATHOLOGIST **JANIS TAUBE** SAYS THERE ARE BIOMARKERS THAT CAN BE USED TO PREDICT RESPONSE TO IMMUNE THERAPY WITH ANTI-PD-1 CHECKPOINT INHIBITORS. TUMOR CELLS THAT EXPRESS PD-L1, HAVE MANY GENE MUTATIONS, AND ALREADY HAVE KILLER IMMUNE CELLS PRESENT ARE MOST LIKELY TO RESPOND. THE CANCER IMMUNOLOGY TEAM IS WORKING TO IDENTIFY OTHER CHARACTERISTICS, LIKE MISMATCH REPAIR ALTERATIONS, THAT WILL MAKE CANCER CELLS MORE VULNERABLE TO IMMUNE THERAPY.

For a time the chemotherapy worked, but the treatment came at great physical cost, and these side effects were worsening. The simplest tasks became difficult. His body was weakening, and worse, he learned his cancer was no longer responding. Genetic testing of his tumor did not reveal any mutations that would make him a candidate for targeted therapies. It seemed he was out of options until his doctor suggested he go to the Kimmel Cancer Center and meet with lung cancer expert **Julie Brahmer**.

Brahmer was one of the lead investigators on an experimental clinical study of the anti-PD-1 therapy in a variety of advanced cancers. Ryan’s form of lung cancer was among the cancers that showed unprecedented responses.

“Before I began treatment, I struggled to sit at my kitchen table. After just four treatments, the tumor shrunk by 65 percent, and I felt like a human being again,” says Ryan. A few more treatments and Ryan’s rapidly growing lung cancer was nearly gone, and the cancer that spread to his rib was eliminated. His only side effect was some minor skin irritations he compared to a mosquito bite.



Anti-PD-1 is not the first checkpoint blockade therapy, but it is the first to work beyond melanoma in as many as 14 other cancer types, and that’s the pivotal difference that has excited the cancer world.

Ryan is not an isolated case. Topalian and Brahmer say about one-quarter of the lung cancer patients in their studies responded to the treatment. The numbers are even higher for melanoma and kidney cancer patients.

Anti-PD-1 is not the first checkpoint blockade therapy, but it is the first to work beyond melanoma in as many as 14 other cancer types, and that's the pivotal difference that has excited the cancer world.

The Lung Cancer Difference

The first clinical reports of checkpoint inhibitors in melanoma were exciting and peaked interest, but excitement was tempered because the few successes in immune therapy over the last three decades had also been primarily in melanoma and kidney cancer. There have been documented cases of these cancers occasionally going into spontaneous remission, so experts long maintained that, by nature, these types of cancers had a way of engaging the immune system. No other type of cancer was considered to be responsive to immune interventions. The new therapy was greeted with guarded optimism.

That all changed in 2012 when the Kimmel Cancer Center group published the results of anti-PD-1 therapy in lung cancer patients. Lung cancer had never

before responded to an immune therapy, and the remarkable activity of anti-PD-1 in a small number of lung cancer patients proved what Pardoll and other cancer immunologists long believed—if understood, the immune system could be used to fight any cancer. “Anti-PD-1 has become a cancer juggernaut,” says Pardoll.

Pardoll first became interested in the protein in 2000, when he came upon PD-1's second partner, PD-L2. Lieping Chen, a collaborator of Pardoll's at the Kimmel Cancer Center who is now at Yale, had just discovered PD-L1 and showed that it's expression in human lung cancer cells was highly elevated compared to normal cells. Although lung cancers had not responded to other past immune therapy attempts, this discovery provided new evidence that it had the potential to work and was the reason the Kimmel Cancer Center team included lung cancer patients in the first anti-PD-1 trial.

Powell is excited about the success of PD-1 in patients, but he is also enthusiastic about what he sees as a triumph of science. “What we have learned is so encouraging,” he says. “The mere fact that we can block a checkpoint and make a tumor go away is an incredibly important finding because it tells us that the human body—even without help from

immunologists—has an immune response to cancer. The problem is that the response is being blocked. That concept, and the fact that it is true in people, is exceedingly important.”

“This is yet more evidence that well-thought-out, consistent and collaborative research pays off,” says William Nelson, the Kimmel Cancer Center Director. “Anti-PD-1 is a triumph of team science.” It is this willingness to follow leads and seek out other experts that can inform the process that continues to position Johns Hopkins as a leader in transitioning laboratory science into pioneering cancer therapies, he says.

“We developed this one from scratch at the Kimmel Cancer Center,” says Pardoll. As soon as the components of the PD-1 pathway were discovered in 2000, Pardoll, Topalian, Brahmer, and immunology and genitourinary cancer expert **Chuck Drake** saw the potential of blocking it. They began working with the small biotech company Medarex to develop the first anti-PD-1 antibody in the laboratory and took it to patients. They too found strong responses in melanoma, but it was Brahmer's lung cancer patients that were game changers.

This was the moment Pardoll and Topalian, who are not only research partners but also husband and wife, were waiting for. It was a belief Pardoll had staked his career on, and one that caused Topalian to change course from a career as surgical oncologist to immunology. She worked as a National Cancer Institute scientist alongside cancer immunology pioneer Steven Rosenberg for 20 years before coming to the Kimmel Cancer Center.

Rosenberg's research of interferons and interleukins, cellular messengers critical to immune responses, garnered similar excitement in the 1980s as a potential broad-based immune treatment for cancer. The cover of *Time* magazine boasted the headline “Interferon: The Cure for Cancer.” When the celebrated treatment failed to live up to expectations—most of which had been generated by an eager news media desperately waiting for the grand-slam victory that had been promised when the “war against cancer”

JULIE BRAHMER WAS ONE OF THE LEAD INVESTIGATORS ON AN EXPERIMENTAL CLINICAL STUDY OF THE ANTI-PD-1 THERAPY IN A VARIETY OF ADVANCED CANCERS.



Personalized Cell Therapy



Kimmel Cancer Center immunology and bone marrow transplant expert **Ivan Borrello** has developed a novel personalized cancer treatment approach called adoptive T cell therapy using the patients' own immune cells to fight their cancer. This approach uses cells from the bone marrow known as marrow infiltrating lymphocytes, or MILs.

T CELLS ARE THE foot soldiers of the immune system, and MILs are a type of tumor-specific T cell, a small subset of immune cells that recognize cancer cells. In cancers of the blood, MILs are found in the bone marrow where the cancer originates. In this new approach, our scientists retrieve patients' own MILs from their bone marrow, expand their numbers and coat the cells with immune-activating antibodies in a special Cell Therapy Lab at Johns Hopkins, and then infuse them back into the patient's bloodstream where they seek out and destroy cancer cells.

Borrello is using MILs therapy to treat patients with an incurable cancer of the blood plasma cells known as multiple


myeloma. In a first-of-its-kind clinical trial of the therapy, 22 patients with newly diagnosed or recurrent multiple myeloma received the therapy. Following standard treatment for multiple myeloma—high-dose chemotherapy to destroy the diseased bone marrow—and a stem cell transplant to repopulate the marrow with normal blood and immune cells, patients were given their own MILs.

One year after MILs therapy, 13 patients had at least a 50 percent reduction in their cancer. Their cancer remained stable for nearly a year, and overall survival was close to three years. Seven patients saw a 90 percent reduction, and their cancer has remained in check for more than six years. There were no

serious side effects to the therapy. "This was a small trial, but we learned that large numbers of activated MILs can selectively target and kill myeloma cells," says Borrello.

There is currently an ongoing clinical trial targeting myeloma patients with high risk features. Borrello and team hope to determine if the approach can impact patients where standard approaches are ineffective. The trial will soon be extended to other cancer centers.

Borrello and collaborator Kimberly Noonan, a research associate in the school of medicine, say the studies shed light on better ways to grown MILs. "In most of these trials, you see that the more cells you get, the better response you get in patients. Learning how to improve cell growth may improve the outcomes of therapy," says Noonan.

The research indicates that MILs could also be beneficial in the treatment of a variety of other cancers, so Borrello has involved a team of heavy hitters to help advance the science and clinical reach beyond myeloma. Other plans include administering MILs in patients that have relapsed following an allogeneic bone marrow transplant, using MILs from the patient grown and expanded in the laboratory, rather than immune cells from the bone marrow donor. MILs are being developed to treat lung, esophageal, gastric, and prostate cancer in adults and neuroblastoma and Ewing's sarcoma in pediatric patients. The team includes of some of the Kimmel Cancer Center's leading experts in immunology, blood and bone marrow cancer, and experts in specific cancers, including **Drew Pardoll, Carol Ann Huff, Leo Luznik, William Matsui, Jonathan Powell, Ephraim Fuchs, Richard Ambinder, Richard Jones, Ronan Kelly, Nate Brennan,** and **Brian Ladle.** 

“Pancreatic cancer is notorious for being in areas outside of the pancreas, and the vaccine allows us to get ahead of the disease and get microscopic cancer cells that surgery might miss.”

was announced in 1971—the field of cancer immunology was nearly crushed. To be fair, interleukin-2 treatment, while a difficult treatment for patients, continues to be used occasionally today and is highly effective in some patients with melanoma and kidney cancer. However, instead of being the blockbuster immune therapy people had hoped for, it was a start. “It was the first evidence that a drug that acted only through the immune system could fight very advanced cancer,” says Topalian. “That was important because it told us we were on the right track with immunotherapy and needed to keep working on this.”

In fact, many outside the field of cancer immunology had begun to doubt the promise of immune treatments in cancer. Immunotherapy discussions at the large national cancer meetings were sparsely attended, and research funding was hard to come by. The Kimmel Cancer Center immunology team remained undeterred. They knew the power of the immune system and their convictions were cemented in this truth. The challenge was channeling this power into real therapies.

The promise of immune therapy is

changing the way new therapies are studied and evaluated. Chemotherapy poisons cells dividing quickly, including immune cells. This toxic effect is the cause of the common side effects, like hair loss, nausea, and infection risk due to a compromised immune system. Immune therapies appear to work more slowly over time, and it’s looking now like they work better for longer. Some of this was learned almost serendipitously, as cancers that initially looked like they were not responding to immune treatments, with more time, began to shrink. “The immune system has been living with cancer for years. To make it not be so happy living with the cancer takes some time,” says Drake.

Eventually, it all rested upon what was learned with science and technology—powerful new ways to look inside the DNA of cancer cells and computerized data mining that measures and quantifies the subtlest of changes and differences among seemingly similar cancers.

The mechanisms that make therapy work in one patient and not in another are now being teased out. Treatments that worked only in a small subset of patients

were once deemed failures. Now, in an era of precision medicine that uses molecular markers to identify the right treatment for each patient, the options are much broader and the outlook is significantly brighter.

First, There Were Cancer Vaccines

Cancer vaccines were one of the first immune treatments studied by Kimmel Cancer Center investigators. Early research on cancer vaccines by immunologist and pancreatic cancer expert **Elizabeth Jaffee** proved the ability to successfully recruit immune cells to tumors, and even had some therapeutic benefit. All too often, however, the immune cells—called to the tumor by the vaccine in large numbers—did not fully attack the cancer.

Vaccines can peak the immune response in days, calling immune cells to the tumor site. To reverse tolerance of the cancer—characterized by immune cells flooding to the tumor site but not taking action—can take time. It may also require additional kinds of immune therapies. Some patients’ immune systems are on the edge, requiring just a vaccine to make them respond. Others need more.

Jaffee and **Daniel Laheru**, co-directors of the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care, are leading the way in cancer vaccine therapy, and their target is one of the deadliest of cancers.

Jaffee began working on a pancreatic cancer vaccine more than two decades ago. To make vaccine therapy a reality, she became an expert in FDA regulations and vaccine manufacturing, and she opened a GMP (good manufacturing practices) facility at the Kimmel Cancer Center to make vaccines for clinical studies.

Jaffee, Laheru, and young investigators **Dung Le, Lei Zheng, Erik Lutz** and others are testing various versions of



IMMUNOLOGY AND GENITOURINARY CANCER EXPERT **CHUCK DRAKE** HELPED DEVELOP THE FIRST ANTI-PD1 ANTIBODY IN THE LABORATORY.



EARLY RESEARCH ON CANCER VACCINES BY IMMUNOLOGIST AND PANCREATIC CANCER EXPERT **ELIZABETH JAFFEE** PROVED THE ABILITY TO SUCCESSFULLY RECRUIT IMMUNE CELLS TO TUMORS AND EVEN HAD SOME THERAPEUTIC BENEFIT.



the vaccine. It is built from pancreatic cancer cells that have been rendered dormant with radiation and engineered to recruit immune cells to track and attack malignant cells anywhere in the body and to continue to do it indefinitely.

In some patients, the original iteration of the vaccine has worked remarkably. Patients like nearly 20-year survivor Kathleen Dowell, 12-year survivor Donna Bender, and eight-year survivor Nancy Amato were given months to live when their pancreatic cancers persisted after surgery, chemotherapy, and radiation therapy. Jaffee's vaccine continues to keep their cancers in check.

Because it is perhaps one of the only treatments that make any real difference in long-term survival for this most aggressive of cancers, the vaccine has attracted worldwide attention. Clinic

coordinator and research nurse Barbara Biedrzycki receives more than 60 calls per month from patients who want to get the vaccine. Once after an appearance by Jaffee on *The Dr. Oz Show*, the clinic was flooded with more than 1,000 inquiries from patients all over the country. "There is no other cancer center doing this kind of work," say Zheng.

With funding from the Skip Viragh Foundation, Laheru, Zheng, Lutz, and Le are working with Jaffee to optimize the effects of her pioneering vaccine. They are making tweaks in timing of vaccination and changes to its composition and delivery that they hope will boost its cancer-killing capabilities and make the vaccine a treatment option for many more patients.

One of their new approaches is to give the vaccine before surgery. "Pancreatic cancer is notorious for being in areas

outside of the pancreas, and the vaccine allows us to get ahead of the disease and get microscopic cancer cells that surgery might miss," says Laheru.

Other variations include combined treatments. In some patients, giving the immune-modulating drug cyclophosphamide before the vaccine causes immune structures to form inside tumors that help regulate immune cell activation. "These organized immune structures do not naturally appear in pancreatic cancers," says Zheng. "This suggests that there has been significant reprogramming of immune cells within the tumor." There is evidence that adding a checkpoint blockade like anti-PD-1 treatment to the mix could further enhance immune activity.

Another combined approach adds a second kind of vaccine, a weakened version of the bacterium *listeria*. The

DANIEL LAHERU, CO-DIRECTOR OF THE SKIP VIRAGH CENTER FOR PANCREAS CANCER CLINICAL RESEARCH AND PATIENT CARE, IS HELPING LEAD THE WAY IN CANCER VACCINE THERAPY. HIS TARGET IS ONE OF THE DEADLIEST OF CANCERS.



listeria is genetically modified to be safe for humans but stimulates an immune response against the protein mesothelin. **Ralph Hruban**, pathologist and Director of the Sol Goldman Pancreatic Cancer Research Center, found mesothelin in high levels on the surface of pancreatic cancer cells, and Jaffee and Le believe the protein helps pancreatic cancer cells to grow and spread. “The combination essentially trains the body to recognize and attack pancreatic tumors,” says Le.

Ongoing research has revealed that mesothelin is over-expressed in many cancers, including about one-half of lung

cancers, mesotheliomas, ovarian cancers, and stomach cancers. As a result, the vaccine is now being tested in lung cancer and mesothelioma, and Kimmel Cancer Center immunology expert **Leisha Emens** will lead a trial testing it in ovarian cancer.

Patient Perspective

Sarasota internist Jonathan Greco, 58, is among 90 patients enrolled in a clinical trial to test the effectiveness of a cyclophosphamide, GVAX, listeria, and anti-PD-1 quadruple combination.

After nine weeks of chemotherapy at a cancer clinic near his home, Greco



IMMUNOLOGY EXPERT **LEISHA EMENS** IS STUDYING VACCINES FOR BREAST CANCER AND OVARIAN CANCER.

says he felt worse than he ever had his life. He told himself it was worth it because, as bad as he felt, his doctors told him it was causing his pancreatic cancer to shrink enough that it could be cut out with surgery.

As a physician, Greco knew of Johns Hopkins expertise in the Whipple procedure, the primary surgical treatment for pancreatic cancer. Johns Hopkins surgeons perfected the procedure, perform more of them, and train more new surgeons how to do the procedure than any other institution in the world. With this in mind, Greco scheduled a consultation at the Kimmel Cancer Center’s Skip Viragh Center.

At his consultation, he learned the chemotherapy hadn’t worked. In fact, his cancer was quite advanced, and a Whipple procedure would not help him. “I’m so thankful I came to Johns Hopkins,” says Greco. “If I had listened to the doctors in Florida and went ahead with the surgery, I’m certain I would have died.”

Greco continued to do his research. He was familiar with immune therapy and went to the National Cancer Institute’s clinicaltrials.gov website to search for experimental treatments and information. “Johns Hopkins clearly had the most immunotherapy experience. It was evident they had been doing this longer than anybody,” says Greco.

He enrolled in a clinical trial

designed and led by Elizabeth Jaffee and Dung Le that is the centerpiece of a *Stand Up To Cancer* pancreatic cancer dream team directed by Jaffee. It combines treatments with the vaccine-enhancing drug cyclophosphamide, the immune-activating GVAX vaccine, mesothelin-targeting listeria, and the immune checkpoint blockade with anti-PD-1. The pancreatic cancer GVAX vaccine was developed by Jaffee with Viragh funding and is manufactured at a GMP facility in the Kimmel Cancer Center that she opened and directs.

The combined therapy represents a culmination of immunology laboratory and clinical science, joining the strength of several immune-targeted therapies in an attempt to topple one of the most lethal cancers. Jaffee and Le hope the combination will pack the immune punch needed to break the resistance of pancreatic cancer.

“I feel fortunate to be one of the 90 patients participating in this trial,” says Greco. Le says it’s too early in his treatment to measure the effect the treatment is having on his cancer or to know what the long-term impact will be. After his experience with chemotherapy, Greco says he is grateful for a treatment that doesn’t make him sick. “I feel like myself again. I feel great. I swim every day, and I’m still seeing patients. I feel like I’m cured.”

Then Came PD-1

The first patients were treated with anti-PD-1 in 2006 as part of a small clinical trial led by Brahmer and funded by Medarex, now part of pharmaceutical giant Bristol-Myers Squibb. The scientific studies to better understand how anti-PD-1 was working were supported by the Melanoma Research Alliance, the National Cancer Institute, and faculty support Susan Topalian received from the Kimmel Cancer Center and the Department of Surgery when she came to Johns Hopkins.

Fast forward to 2015, and people were getting very excited again about immunotherapy when the attention of the cancer world—some 30,000 people

Immune Therapy Shows Promise for Breast Cancer



PRELIMINARY results of an early, multi-center study showed an experimental immune therapy drug was safe in patients with metastatic, triple-negative breast cancer. These early findings offer new hope in the fight against this particularly aggressive and difficult-to-treat disease.

The study involved 54 patients with advanced triple-negative breast cancer from the Kimmel Cancer Center and other cancer centers. The patients received an experimental drug, known as a PD-1 blockade, designed to disrupt a pathway that hides tumor cells from the immune system.


“Early data in this trial show that the drug is generally safe and well-tolerated, and it appears to be able to control disease in some of these patients,” says study leader Leisha Emens, M.D., Ph.D. “Now we’ll need to test it further in more patients and compare it with standard therapies to establish its therapeutic value.”

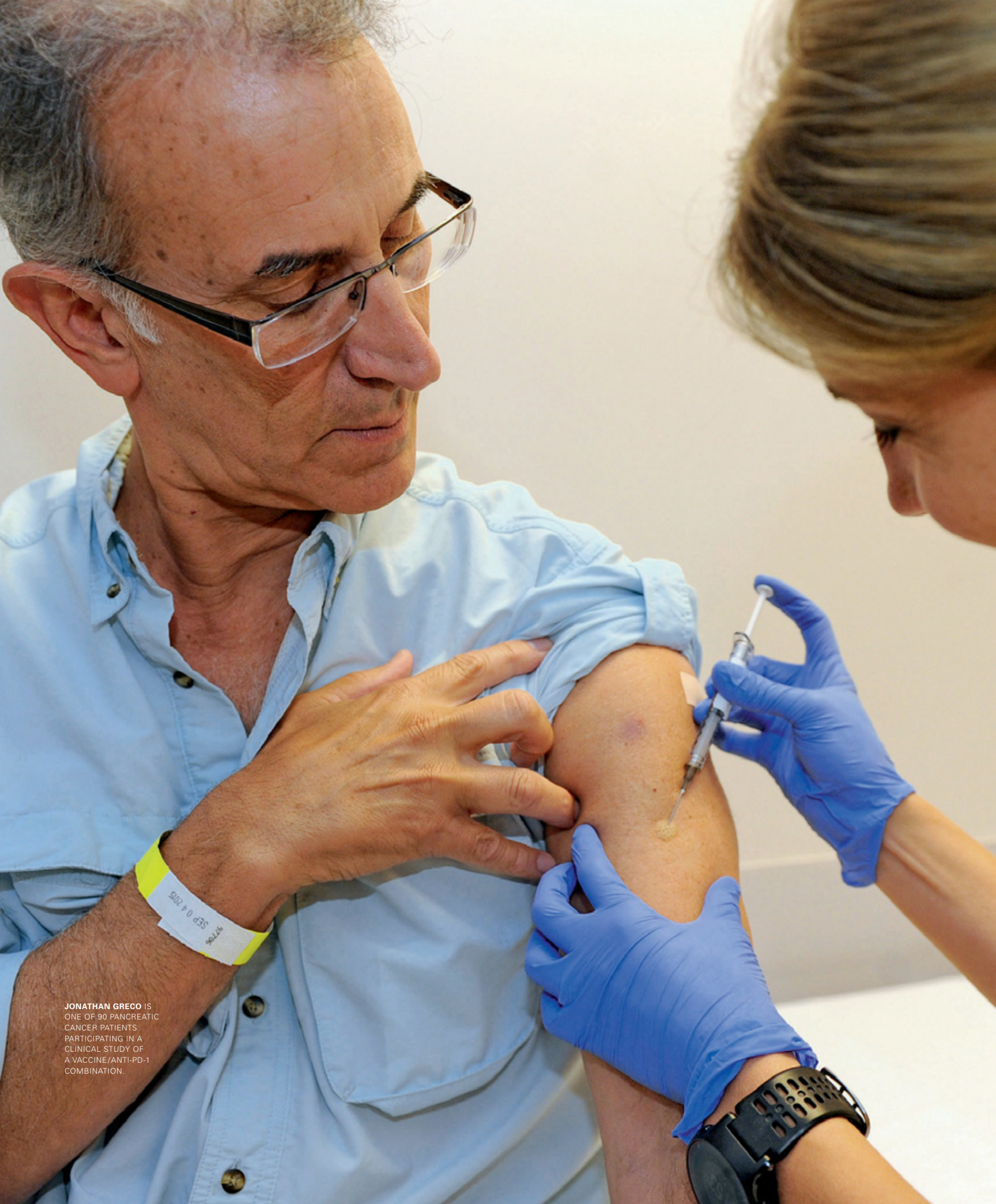
The drug binds to an immune-regulating protein known as PD-L1, disrupting an interaction between it and a related protein known as PD-1, enabling an immune response against the cancer cells. The researchers determined that 37 of the 54 patients expressed the PD-L1 protein in some immune cells within their tumors, and 21 of these patients

ROISIN CONNOLLY, M.B.B.CH., WAS AWARDED A YOUNG INVESTIGATOR AWARD FROM THE NATIONAL COMPREHENSIVE CANCER NETWORK TO INVESTIGATE WHETHER THE IMMUNE SYSTEM CAN BE HARNESSSED IN THE TREATMENT OF TRIPLE-NEGATIVE BREAST CANCER. TUMOR BIOPSIES AND BLOOD SAMPLES OBTAINED FROM PATIENTS WILL BE USED TO LEARN MORE ABOUT HOW THE IMMUNE SYSTEM ACTS IN PATIENTS WITH TRIPLE-NEGATIVE BREAST CANCER AND TO IDENTIFY BIOMARKERS THAT WILL HELP DISTINGUISH PATIENTS WHO WILL RESPOND BEST TO THESE TREATMENTS.

were evaluated to assess the impact of the drug. Six patients survived at least 24 weeks without disease progression, an unusual result among patients with this type of advanced and resistant cancer. Two patients saw their cancers disappear, and tumors shrunk in another two patients.

Next steps include testing the drug’s benefit in groups of patients and comparing it with standard treatments to determine its therapeutic value. A large global study to evaluate it as a possible standard therapy is underway.

“Engaging the immune system to fight breast cancer is a game changer,” says Emens. “This is especially true for triple-negative breast cancer, for which chemotherapy is currently the only standard treatment option outside of a clinical trial. Identifying a way to predict ahead of treatment which patients are more likely to respond is critically important, and there are ongoing efforts to identify biomarkers for patients who are more likely to respond to this therapy.” 



JONATHAN GRECO IS ONE OF 90 PANCREATIC CANCER PATIENTS PARTICIPATING IN A CLINICAL STUDY OF A VACCINE/ANTI-PD-1 COMBINATION.



NURSE ANGELA VAN TASSEL ADMINISTERS THE SECOND OF NINE VACCINATIONS TO PANCREATIC CANCER PATIENT JONATHAN GRECO.

attending the ASCO meeting—was fixed on the findings from the Kimmel Cancer Center cancer immunology team as Topalian explained this immune checkpoint that could be reset with a drug. In addition to igniting an immune response against cancer, the anti-PD-1 drug could be given in the outpatient clinic and caused very few side effects. The media, including *Science*, one of the world's leading scientific journals, dubbed it a breakthrough. "The attention it was receiving and the number of people who wanted to learn about our work

were signs that immune therapy was now part of mainstream oncology," says Topalian.

Topalian, who has been there through many of the ups and downs in cancer immunology, prefers to call it an evolution. To the public and even scientists outside of cancer immunology, it may seem like an overnight sensation. In reality, it was the product of research that occurred over decades with many contributors, when all but the immunology diehards weren't looking. "It's been a long process," she says. "Today, it's cele-

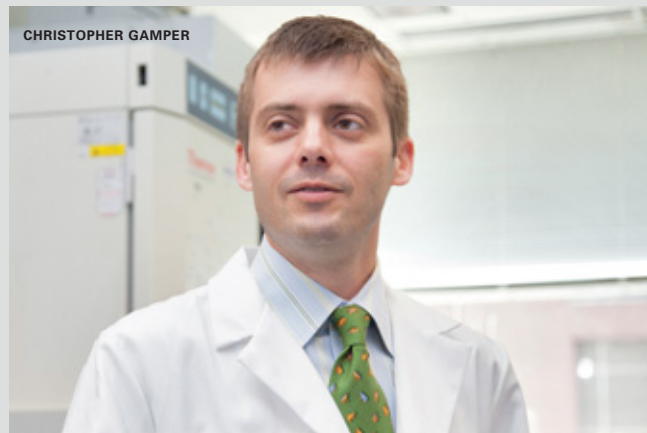
brated, but over the last 30 years there have been many things that looked great in the laboratory that did not translate into patients." Although cancer immunology experts had held steadfast to their convictions that they could figure out a way to make the immune system work against cancer, outside of the field there were whispers of defeat. "In 2012, with our publication in the *New England Journal of Medicine* on a 300-patient clinical trial of anti-PD-1, everything came together. It was our moment," she says.

"The notion of doing clinical trials with experimental drug combinations, even where none of the drugs have FDA approval, is becoming the norm. These drugs are turning clinical therapeutics on its head. This is a game changer."

Immune Therapy for Childhood Cancers



BRIAN LADLE



CHRISTOPHER GAMPER

WITH THEIR LOW toxicities, immune therapies seem tailor-made for pediatric cancer patients where long-term effects caused by conventional therapies are of great concern. Childhood cancer patients can suffer the consequences of chemotherapy throughout their lifetime, including fertility issues, cardiac toxicities, learning impairment and more. In fact, many cancer immunology experts believe immune therapies may be a paradigm changer, eventually replacing chemotherapy as the first-line treatment in many pediatric cancers because of its ability to spare patients from these dangerous toxicities.

Take, for example, Hodgkin's lymphoma. It is a common childhood cancer that responds well to chemotherapy, but treatment is long and toxic, and the growing brains and bodies of children and adolescents are particularly susceptible to the damaging effects of chemotherapy. New research shows Hodgkin's lymphoma may be one of the best responders so far to anti-PD-1 immune checkpoint blockade therapy, with response rates approaching 90 percent. There have been excellent responses and low toxicities even in patients whose cancer resisted standard drug treatment.

Researchers like pediatric oncologists and cancer immunology experts **Brian Ladle** and **Christopher Gamper**

say there is emerging evidence that immune therapies may be more effective against chemotherapy-resistant cancer. They offer new hope for pediatric patients with cancers that currently cannot be cured with standard treatments.

Ladle is excited about this less toxic approach to destroying cancers. "It's a privilege to be able to cure kids of cancer, but right now, what we have to put them through to get them there is unacceptable," he says. "We have to do better for them."

While he doesn't think immune therapy will completely replace the need for surgery and chemotherapy, he believes it has great potential to reduce the amount and duration of treatment. More importantly, since immune cells can travel anywhere throughout the body—inside bones and to organs and tissue—they have a unique ability to find and destroy lingering cancer cells that often result in the recurrence and spread of cancers.

Ladle and Gamper are discovering crucial links between T cell behavior, the main cells activated in an immune response, and the epigenetic or chemical environment of T cell DNA. Although the DNA code of a T cell that has never been activated is identical to that of T cells engaged in an immune attack, significant changes occur in the chemicals

that surround the DNA that help signal it to remain dormant or go into action. As a result, Ladle and Gamper are deciphering the normal epigenetic activity of immune T cells and exploring whether existing epigenetic-targeted treatments might be able to improve immune responses to cancer.

Ladle and Gamper believe epigenetic drugs may augment the effectiveness of other immune treatments, such as cancer vaccines and immune checkpoint blockers. They are also looking for other proteins expressed by tumor cells that work like PD-1 to shut down an immune response to cancer. In addition, new pediatric oncology physician-scientist **Nico Lloso** is working on ways to use PD-1 blockade and other similar immune agents to fight pediatric cancers.

While there have been significant advances in cancer immune therapies in adults over the last few years, translating these findings to pediatric cancers lags far behind. "This is the main reason I wanted to work in pediatric oncology," says Ladle. "There is so much promise. We know that children's immune systems are much more responsive than adults.'" What Ladle envisions are treatments that harness and deploy the body's own natural ability to fight cancer and decrease the need for invasive surgeries and toxic, cell-poisoning drugs. **P.P.**

Pioneering Patients



“I Don’t Feel Like I Have Cancer”

Thomas Kotula, a patient with melanoma being treated by **Evan Lipson**, is receiving a combination of two immune checkpoint inhibitors, anti-PD-1 and anti-CTLA-4. He comes to the Kimmel Cancer Center every two weeks for the hourlong infusion.

“He was in pretty rough shape the first time I saw him,” says Lipson. Kotula’s melanoma had spread, including a softball-size tumor in his thigh that made it difficult to walk. By his third treatment, the tumors began to get smaller. A year later they have shrunk by more than half. The clinical trial he is on, headed by melanoma expert **William Sharfman**, calls for two years of treatment.


“A major focus of our research involves understanding how to safely and effectively use these new immune-based medications in as many patients as possible,” says Lipson. “One of the potential advantages of immune therapy is that once the immune system is activated, it can keep cancer at bay for long periods of time.”

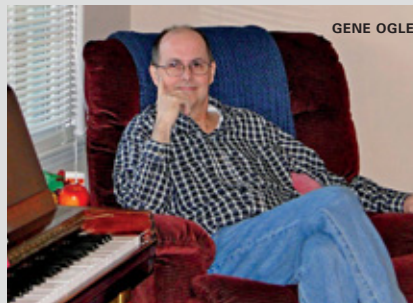
Kotula, a husband, father of six, and grandfather of nine, says he came to the Kimmel Cancer Center for a second opinion at the encouragement of his children. His doctor at a community hospital near his home recommended surgery. Lipson had to deliver the bad news to Kotula that surgery would be of little value because the cancer had spread, but he offered him an opportunity to participate in Sharfman’s immune therapy trial.

Kotula has experienced relatively mild side effects from treatment, including a rash and some thyroid issues, says Lipson. He and his cancer immunology

collaborators are working to better understand how to encourage the immune system to attack only tumors and leave other parts of the body alone.

“He’s living his life,” says cancer immunology nurse **Trish Brothers**. “Immune therapy has offered real hope to Mr. Kotula, both in terms of combating his cancer and allowing him to avoid some of the debilitating side effects often associated with traditional cancer treatments.”

“I’m so glad I came here. I can’t say enough about these doctors and nurses. They are like family,” says Kotula. “What a difference from a year ago. I don’t even feel like I have cancer.” 



“I Beat Pancreatic Cancer”

When Gene Ogle’s doctor told him he had pancreatic cancer, his first question was: “How long do I have to live?” Ogle was just 54 years old when he got the news, and his thoughts immediately turned to his father, who died of the same disease 30 years earlier at 63. Although many years had passed, his memory was clear. “My father died two months after he was diagnosed. My knowledge was that it was incurable and killed quickly.”

Ogle’s doctor told him that there had been many advances since his father’s diagnosis, and specifically referred to discoveries at the Johns Hopkins Kimmel Cancer Center. He decided to make an appointment at its Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care.

Despite the diagnosis, there was some good news. His cancer was not as advanced as his father’s, and he was a candidate for a Whipple procedure, a complex pancreatic cancer surgery perfected at Johns Hopkins. At the appointment research nurse **Carol Judkins** also


talked to him about a clinical trial testing the benefits of giving a pancreatic cancer vaccine before surgery.

The pancreatic vaccine, developed by Elizabeth Jaffee, supercharged the immune system, drawing cancer-attacking killer T cells to pancreatic tumors. Jaffee had laboratory evidence that giving the vaccine before surgery gave the immune system a step up on the cancer and might help it get at microscopic cancer cells that could cause the cancer to spread. She was working with two young clinical investigators, Dung Le and Lei Zheng, to explore whether earlier use of the vaccine would provide a clinical advantage.

Ogle was well aware of the high rate of pancreatic cancer spread and recurrence. As an engineer, he is a numbers guy. He recalled a survival chart he saw around the time of his surgery. “It peaked at one year and went down after that. Less than 5 percent of people survived past five years,” says Ogle.

“Enrolling in the vaccine trial was an easy decision for me,” says Ogle. “I still had no hope that I would survive, but I thought if I participated in the vaccine study, I might be able to help doctors move that survival curve far beyond five percent.”

That was nearly six years go, and contrary to the statistics and his own personal predictions, Ogle is alive and doing well. It’s been almost four years since his final vaccination. His cancer isn’t gone, but it’s not growing. With the boost from the vaccine, his immune system appears to be keeping it in check. “I’m still here, and I want to be a message of hope to others,” he says.

Ogle fully expected to become a pancreatic statistic, but not a positive one. “My perspective is changing,” he says. He is certain the wonderful care he received, including surgery, chemotherapy, radiation therapy, and particularly the pancreatic cancer vaccine, allowed him to beat the odds. “I’m so proud to be a part of these studies. It’s a huge honor,” says Ogle. “Everyone who took care of me—from the receptionist to the nurses and doctors—was top-notch. They all had so much compassion.” 

A Milestone in Cancer Medicine

Remarkable responses were occurring in a significant number of patients, putting the framework for a potentially broad-based treatment for cancer in place. This glimmer quickly ignited into a spark and continues to gain momentum as collaborations across many specialties at Johns Hopkins are expanding its benefit to other cancers.

This success revealed that the immune system could be employed against cancers beyond melanoma and kidney cancer. As important, it provided definitive proof that there was a common force at work to shut down an immune response to cancer.

The most recent clinical study provides clear evidence that for lung cancer patients whose immune cells express PD-1 or whose tumor cells express PD-L1, immune therapy works better than the best chemotherapy drugs and with far fewer side effects. In addition, patients with late-stage lung cancers frequently become resistant to chemotherapy, but Brahmer says that patients who respond to immune therapy tend to continue responding. “In my 20 years in practice, I have never seen anything like this. We’re reporting three-year and more survival rates in lung cancer patients who honestly would not typically be around,” says Brahmer. “This is truly a milestone in cancer medicine.”

As for how long patients will continue to respond off treatment and whether there are any long-term effects of this type of immune therapy, it’s too soon to know. Pardoll, Topalian and collaborators are working to answer these questions. They also want to make sense of the varied responses. In some patients, tumors were held in check, neither growing nor shrinking. Other patients, like Ryan, experienced huge reductions in the size of their tumors, but they didn’t go away completely. Pardoll and Topalian have gone back to the laboratory to better understand the biology of these responses. In virtually all patients, however, the responses appear to be long lasting. Some patients from the original clinical studies

continue to do well. Such responses are virtually unheard of in advanced cancers. “We don’t know yet what the ultimate survival benefit will be, but for these early trials and these patients, the responses are lasting a long time,” says Pardoll. “We don’t have to intervene anymore with therapy. The patients’ own immune systems have taken over the battle.”

“It is a cyclical process,” says Topalian. “We need to continue working between the laboratory and the clinic to advance the science and understand more about responses, how long the drugs need to be given, and how to make the treatment work in more patients.” To help gather these answers, she is turning to pathologists Anders, Taube, and **Ed Gabrielson**, who are uncovering the biomarkers, the unique cellular characteristics and signals that differentiate cancers that respond to anti-PD-1 from those that do not.

The list of responding cancers continues to grow. Bladder cancer, Hodgkin’s lymphoma and a few difficult-to-treat cancers, like triple-negative breast cancer and mesothelioma, are on it, with others, like certain ovarian, endometrial, colon, head and neck, stomach, liver, and esophageal cancers, expected to soon be added.

Drake tells of a patient referred to him from fellow Greenberg Bladder Cancer Institute physician-scientist **Trinity Bivalacqua**. The patient was getting chemotherapy to shrink the size of his bladder cancer so that it could be removed with surgery. When Bivalacqua operated, he found the cancer had already spread. Surgery would not cure him, so he left his bladder intact and referred the patient to Drake.

The patient had lost his hair and was underweight from the chemotherapy, and now it was no longer working. “He was not looking well when he came to see me in 2013,” says Drake. He recommended immune therapy with anti-PD-1. Almost immediately, the patient regained his appetite and put some weight back on and reported just generally feeling better. Over time, his cancer shrank by 80 percent. His only side effect was a small, itchy rash on his shoulder. “He has three children and was able to witness impor-

tant events in their lives that he honestly might not have otherwise lived to see,” says Drake.

On the other hand, there are cancers, including prostate and pancreatic cancers, that remain largely resistant. “We need to address that on the research side,” says Topalian. Drake does not get a good response in all bladder cancer patients either. “In some patients, it works quite well, but in others, the cancer continues to grow,” he says. Understanding why some tumors do not respond is as important as learning why others do, he says. “If we can figure out when it works and how it works—what kinds of cells are involved and what is happening from an immunological standpoint—maybe we can take non-responders and make them responders,” Drake says.

There are currently about eight different types of antibodies that block PD-1 or PD-L1 on the market. The treatment is now FDA-approved for melanoma and lung cancers, and Pardoll says approvals for kidney cancer, bladder cancer, and Hodgkin’s lymphoma are anticipated by the end of 2015 or early 2016. They aren’t cheap, costing about \$100,000 or more per year for each patient treated.

Although there have been many news reports about the pricing of the drugs, immunology research nurse **Alice Pons**



and colleagues say patients have not seemed concerned about the cost. That could be because some insurance companies are covering

them even before final FDA approval. Nurse practitioner and immunology expert **Barbara Biedrzycki** says other insurance companies may resist approving immune therapy, requiring patients to first try less expensive drug therapies. To help ease the cost burden, the pharmaceutical companies making anti-PD-1 drugs say they have programs to provide free drugs for patients who cannot afford them.

Immune therapies are outpatient treatments, and although there have been some serious side effects, in most patients they have so far proven to be very safe. When hospitalizations, management of side effects, and the

cost of drugs, are taken into consideration, Biedrzycki suspects the costs of chemotherapy and immune therapy will become much more comparable.

With improved responses and lower toxicities, which are clearly documented in common cancers, such as non small cell lung cancer, withholding immune therapies from patients could intensify public ire aimed at the already battered reputations of the pharmaceutical and insurance industries.

“This research has completely changed the slow, conservative approval process for drugs,” says Pardoll. “Typically you would have phase I and II clinical trials and then a big phase III trial, and if a drug makes it all the way through, it gets approval.” Some of the anti-PD-1 drugs are getting approved right out of the gate in phase I trials. “They have such remarkable therapeutic effects and little toxicity that we don’t need phase III studies. There is an obligation to get the therapy to patients quickly,” he says.

Nelson says this is where Johns Hopkins leadership in precision medicine

will play a leading role. The first anti-PD-1 trials were open to all patients with advanced cancers that were resistant to standard treatments, but as our scientists learn more about what cancers respond and what cancers do not, they can begin to use biomarkers to identify the cancers and patients most likely to benefit from immune therapy. Pharmaceutical companies have already begun developing biomarker tests for PD-L1 based on the work of Anders and Taube that demonstrated PD-L1 expression was the best predictor of response to anti-PD-1 treatment.

“PD-L1 on tumor cells is the cloak that shields cancer from the immune system,” says Anders. “If the tumor is not expressing PD-L1, it is not likely to respond to anti-PD-1 therapy.” Some clinical trials already require the biomarker test for PD-L1 before treatment, says Topalian.

At the same time, the cancer immunology team continues to work in the laboratory to find other immune “stop” signals and learn how to transform immune therapy-resistant cancers into responsive cancers.

Expanding Responses

One of the ways cancer immunology experts are improving response is by combining immune drugs. “The notion of doing clinical trials with experimental drug combinations, even where none of the drugs have FDA approval, is becoming the norm,” says Pardoll. “These drugs are turning clinical therapeutics on its head,” he says. “This is a game changer.”

One of these combinations is anti-LAG-3 and anti-PD-1. LAG-3 was shown by Drake, Powell and others to shut down immune responses to cancer cells, similar to PD-1. Unlike PD-1, however, inhibiting LAG-3 did not create the same robust response that occurred with anti-PD-1 therapies. However, Drake found that combining two drugs—one that targets PD-1 and another targeting LAG-3—works in synergy to boost the immune response against cancers. Combined approaches using another checkpoint inhibitor known as anti-CTLA-4 and anti-PD-1 drugs also have been studied, and Drake believes that as more immune regulatory genes are identified, more combinations will be revealed.

CANCER IMMUNOLOGY NURSING TEAM (LEFT TO RIGHT), **BARB BIEDRZYCKI, ANGELA SCARDINA, BETH ONNERS, HOLLY KEMBERLING, MAUREEN BERG, SUSAN SARTORIUS-MERGENTHALER, KATRINA PURTELL, TIANNA DAUSES, ANGIE VAN TASSEL, DENISE GALLAGHER, GALINA MELANCON, KATHY ELZA-BROWN**



Micromanaging Colon Cancer

THERE IS A microscopic society living within us. Our bodies are home to more than 100 trillion microorganisms, more than 10 times the number of human cells in the body. Many of them reside in our gut. Most of the time, this microcommunity—which includes hundreds of species of bacteria—and its human host coexist harmoniously. The “bugs” we live with aid in digestion, metabolism and immunity.

With such an overwhelming numbers advantage, it may only take the activity of a single organism to shift this harmonious relationship in a way that can promote cancer, says infectious disease expert **Cynthia Sears**.

Of the trillions of possibilities, Sears has zeroed in on a population that appears to be related to colon cancer development.

The entire colon is lined with a thick protective layer of mucus, and, under normal conditions, bacteria are excluded. In some colon cancers, however, Sears, researcher **Christine Dejea**, and team have found biofilms made up of a subset of bacteria that has managed to invade the mucus. “They invade the layer of mucus that protects the epithelial cells lining the colon and upend the whole biology of the system,” says Sears.

With so many different forms of bacteria colonized within the human body, it is a difficult task differentiating those that keep us healthy from those that contribute to disease. In this case, the association seems clear. The risk of colon cancer may be as much as five times greater in patients who have biofilms in their colons compared to those who have none.

Sears doesn’t yet know how these biofilms develop, but she has a hunch about their link to cancer. She speculates that they cause inflammation in the colon, which spurs genetic mutations that lead to cancer. “When we look at people who undergo screening colonoscopy, we find a subset of people who have biofilms.

What happens in that tissue and cells right under the biofilm, are the same processes we see in cancer.” Another mystery was related to the location of the biofilms. In her team’s study of 178 surgery or colonoscopy patients treated at either The Johns Hopkins Hospital or the University of Malaya Medical Centre in Malaysia, the vast majority of biofilms were located in the right colon. “It’s virtually a universal feature of tumors that appear in that section of the colon, although we don’t understand why,” says Sears.


To help answer some of these questions, Sears is working with cancer prevention and control expert **Elizabeth Platz**, cancer immunology expert **Drew Pardoll**, and gastroenterologist **Francis Giardiello** to establish a large multicenter colonoscopy study to define the natural history of biofilms and their association to changes in tissue. “When we detect biofilms, where are they? How long do they last, and what do they do? This is what we want to figure out,” says Sears.

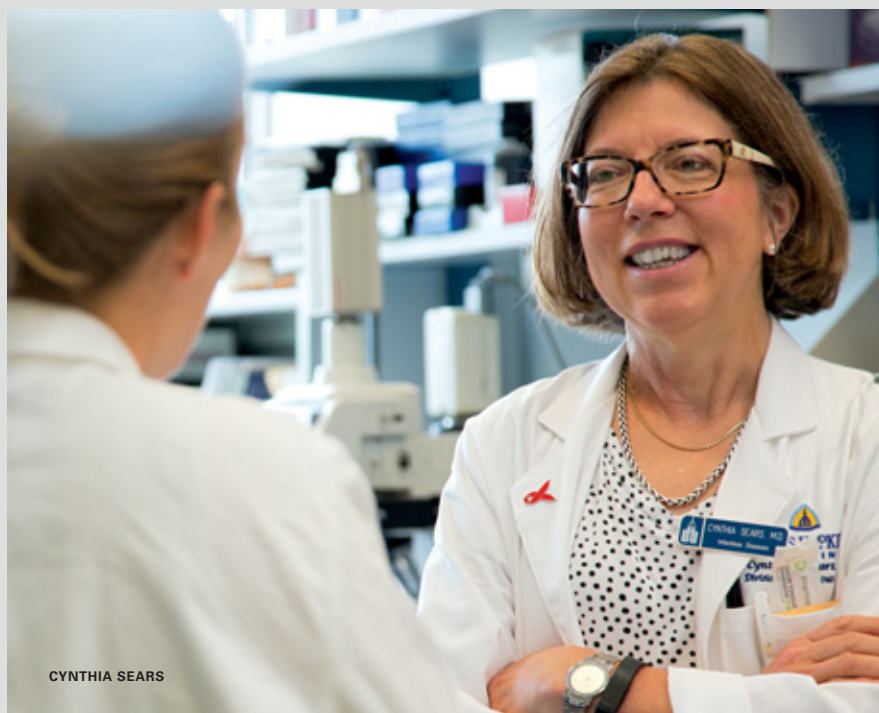
The study will also establish a large bank of biofilm samples to integrate complex microbial and immune analyses. “We want to understand how the immune

system responds to biofilms as well as the gene expression of these bacterial communities and how they interact with other bacteria inside of the biofilm,” she says.

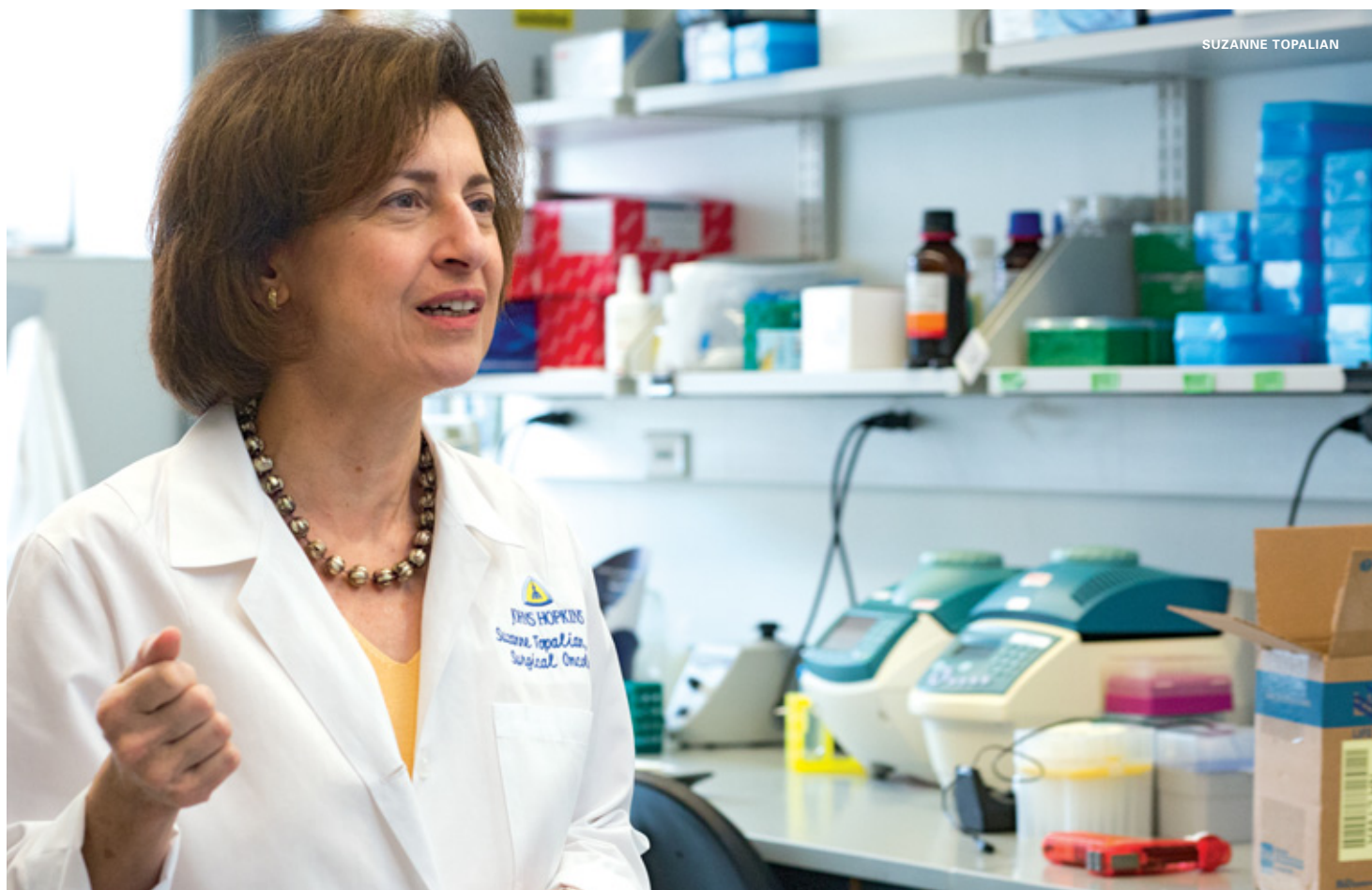
Biofilms are a new discovery, and Sears and team are the first to systematically explore them in colon cancer.

Patients with an inherited form of colon cancer, known as familial adenomatous polyposis (FAP), may provide some early answers. The disease is characterized by large numbers of polyps in the colon. Sears says FAP sufferers also develop many biofilms, but instead of being made up of many types of microorganisms, they primarily consist of two types of bacteria. “This is the best evidence so far that particular organisms may be relevant, and it may help us zero in on the bacteria that could be pushing this process,” says Sears.

Among her long-term goals, Sears hopes to use her findings to develop a non-invasive test to detect biofilms and predict a person’s risk of developing cancer. “Most colon cancers are known to develop slowly over time,” she says. “It’s a disease that’s curable if diagnosed early, and maybe biofilms are an early warning sign.” 



CYNTHIA SEARS



“We know there are more checkpoints and that, in some cancers, we might have to block more than one,” says Powell. “Maybe in some patients, PD-1 is not the relevant checkpoint, and we’ll have to find the one that is. In other cancers, we may have to block more than one checkpoint because both are relevant.”

Powell and colleagues are also having success using anti-PD-1 in combination with a drug that interferes with metabolism of cancer cells. Tumors kill by growing, and they require nutrients—lots of them—to sustain this growth. Blocking cell pathways that enable this growth

by providing amino acids, glucose, and lipids that nourish tumor cells can have an antitumor effect.

“We think tumor cell metabolism can be considered a kind of immune checkpoint because it creates an environment that turns off the immune response,” says Powell. Surprisingly, blocking these nutrients is cancer specific. All cells need nutrients, but normal cells don’t require the extraordinarily high levels demanded by rapidly dividing cancer cells. “To be a really good cancer cell, it needs a huge amount of these nutrients,” he says. Cutting off the biological supply line of

these nutrients slows the growth of cancer cells without harming normal cells. Adding a checkpoint blocker like anti-PD-1 allows the immune system to sweep in and finish the job on the weakened cancer cells.

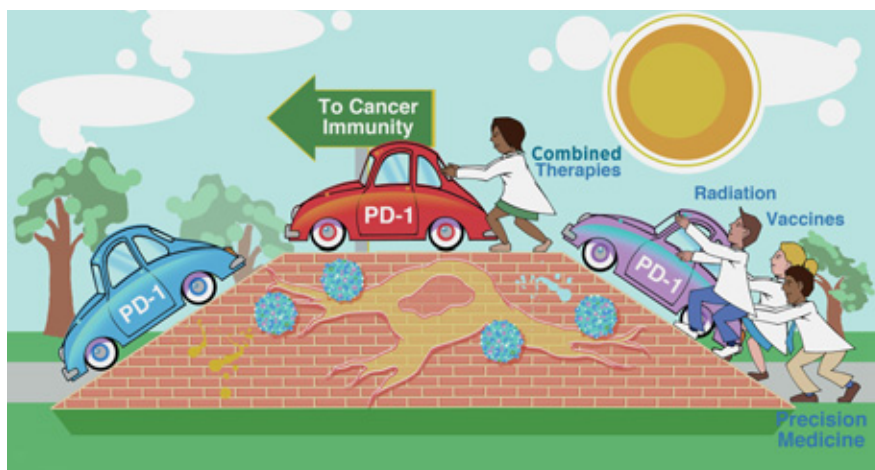
Powell is also studying a group of failed Parkinson’s disease drugs that target a pathway known as adenosine that acts as an on/off switch for immune T cells. Studies in Powell’s laboratory found that the drugs were remarkably proficient at instigating an immune response against cancer cells. The drugs have already been studied in patients

“I have never seen anything like this. We’re reporting three-year and more survival rates in lung cancer patients who honestly would not typically be around. **This is truly a milestone in cancer medicine.**”

with Parkinson's disease and proved safe, so with funding, he hopes to be able to bring them to clinical trials for patients with cancer in less than a year.

These new combinations will not be limited to immune agents. Animal research by radiation oncology fellow **Andrew Sharabi** and Drake found that focused radiation treatment, like that used in radiosurgery, stimulates an immune response against the cancer. Sharabi says cell damage caused by radiation deploys immune cells to the tumor site, and combining anti-PD-1 with radiosurgery unleashes an immune assault on the cancer. "Radiation opens the door, and anti-PD-1 therapy allows the immune cells to get to work," says Sharabi.

Radiation oncologist **Joseph Herman**, Anders, and Taube find evidence that radiosurgery may be activating immune cells in pancreatic cancer as well, a cancer that currently does not respond well to anti-PD-1 treatment. Combining radiosurgery with the right immune-targeted drugs may increase responses in a variety of cancers. Anders is examining tumors that are traditionally treated with radiation, including head and neck cancers and esophageal cancers to look for expression of PD-L1 in tumor cells, an indicator that they might respond to an anti-PD-1 checkpoint blockade/radiation therapy combination.



THE ROAD TO CANCER IMMUNITY "IF A CAR IS SITTING AT THE TOP OF A HILL WITH THE FRONT POINTING DOWNHILL, IT MAY ONLY NEED THE PARKING BRAKE RELEASED TO START MOVING. ANOTHER CAR SITTING ON A FLAT ROAD MAY NEED THE BRAKE RELEASED AND A PUSH TO GET GOING. A CAR SITTING AT THE BOTTOM OF A HILL AND FACING UPHILL WILL NEED THE BRAKE RELEASED AND A LOT OF GAS TO GET MOVING," SAYS **DREW PARDOLL**.

Pardoll and Topalian are hopeful that combination therapies may be the key to converting currently nonresponding cancers like prostate cancer into responders. Similar to Sharabi and Drake's work, Topalian believes that giving another kind of therapy up front, including radiation, chemotherapy or targeted therapies, and following with anti-PD-1 could provoke an immune response in currently resistant cancers.

She is working in her laboratory to see what therapies incite an inflammatory response in the tumor, because inflammation draws the attention of immune

cells. These are the situations where adding anti-PD-1 has the potential to cause a synergistic immune response. She and others are compiling this laboratory evidence. This component is critical, she says. "There are endless possibilities of potential treatment combinations. We can't test them all, and we can't simply do combinations of convenience," says Topalian. "We have to let the research lead us, and then move to the clinic only with combinations supported by scientific evidence."

Some cancers will respond to anti-PD-1, but others will need more to get the immune system working. Pardoll is confident that working together over time Johns Hopkins experts will be able to figure out the right combinations to get the immune therapy moving against almost any cancer.

The Learning Curve

With Ryan's cancer stable—no longer shrinking, but not growing either—Brahmer has decided to stop anti-PD-1 treatment. "We think that over time the immune system creates a memory. The T-cell remembers how to attack the cancer and stop the cancer from shielding itself from the immune cells. We think the immune system can keep the cancer under control now, even without treatment," says Brahmer.



If Ryan's cancer begins to grow, she will start therapy again. Other patients whose tumors began to grow again after anti-PD-1 treatment was stopped have responded with treatment that was reinitiated. It's all part of the learning curve. Ryan continues his regular trips from his home near Middleburg, Virginia, to the Kimmel Cancer Center to have his cancer monitored. He also participates in a Stand Up To Cancer-funded study providing blood samples that help researchers understand more about how immune checkpoint blockade therapy works against cancer. Not every patient whose immune cells express PD-1 or whose tumor cells express PD-L1 respond to immune therapy. Patients like Ryan are helping investigators solve those mysteries and leading them to ways to help more patients.

"I feel like this is about more than just me," says Ryan. "Immune therapy saved my life, and I want to bring this message of hope to others. I know how fortunate I was to have this wonderful team of doctors and nurses at Johns Hopkins. They are my heroes," he says. "Two years ago, in a very short period of time, I went from feeling fine to being in serious trouble. I thought I might have only months to live and that I would miss so many important moments in my children's lives. Time was critical, and I was fortunate to get in the right hands quickly."

Today, Ryan says, he feels better than he has in years. He recently provided around-the-clock logistical support as a crew chief to his son as he participated in a grueling 100-mile ultra-marathon through the Vermont mountains. "My friends and family were worried when I told them I planned to do this. They were shocked by how much energy I had."



Pardoll sees the therapy as a true breakthrough in cancer medicine. This is not just hyperbole; he actually did the math. With 14 different cancer types responding at rates of between 15 and 40 percent, early studies in Hodgkin's lymphoma reporting response rates of nearly 90 percent, and enduring cancer remissions, immune checkpoint blockade therapy has distinguished itself from chemotherapy and gene-targeted therapies. "By a factor of 30," he says, "anti-PD-1 is the most powerful single agent in the history of cancer therapeutics."

Another Road Leads to PD-1

Forty years ago as efforts to decipher the causes and cures for cancer intensified, many began looking to the laboratories of the fledgling cancer center at Johns Hopkins. From the beginning, the National Cancer Institute had named it a center of excellence. Among the main areas of research were laboratories focused on immunology, genetics, and epigenetics. One of them, experts hoped, would lead to a discovery that would

"I feel like this is about more than just me. Immune therapy saved my life, and I want to bring this message of hope to others. I know how fortunate I was to have this wonderful team of doctors and nurses at Johns Hopkins. **They are my heroes.**"



DREW PARDOLL

conquer cancer. No one, including Pardoll, ever imagined the interconnection of these three areas of research or that it would result in some of the most significant cancer discoveries of our time.

In 1977, **Bert Vogelstein**, a young scientist concentrating on the nearly impossible task of cracking cancer's genetic code, and Pardoll, his graduate student at the time, met monthly with senior cancer researcher **Donald Coffey** to toss around ideas about how to cure cancer. Ideas were about all anyone had at that time. Coffey remains an iconic figure at the Kimmel Cancer Center. The consummate teacher with an enthralling Southern drawl challenged talented young investigators then—as he continues to do today—to work together and look for creative solutions to a tough problem. Usually, they would talk casually over tea. Even then, the immune system was on their short list of ideas. Vogelstein continued to pursue genetics, convinced it would yield greater insights into the cellular processes that result in cancer.

Vogelstein, the Clayton Professor of Oncology and co-director of the Kimmel Cancer Center's Ludwig Center, went on to define cancer as a genetic disease. Starting with colon cancer, he, **Kenneth Kinzler**, and their Ludwig Center team

developed a model for cancer initiation and progression that became the paradigm for much of modern cancer research.

Pardoll continued to pursue cancer immunology, in part inspired by the monthly meetings with Coffey. With his and Vogelstein's encouragement, he soon joined the faculty and started his own cancer immunology laboratory. But that was not the end of the Vogelstein/Pardoll collaboration. As Vogelstein focused on the cancer genome, Pardoll began to explore the genetic mechanisms of immune cells. Neither anticipated an intersection of the two laboratories that would lead to an unusual discovery.

"This kind of collaboration is what makes us Hopkins," says Vogelstein. "People share their ideas and results here. Drew [Pardoll] and Suzanne [Topalian] showed us what they found and asked for our ideas."

Pardoll and Topalian were trying to figure out why one of the first colon cancer patients ever treated with anti-PD-1 had a complete response—with no detectable tumor six years later—but another 32 colon cancer patients did not respond. They hoped that the Vogelstein team's expertise in colon cancer could shed light on what was unique about that patient and maybe what they learned

TOP: IN 1977, **BERT VOGELSTEIN**, (RIGHT) A YOUNG SCIENTIST CONCENTRATING ON THE NEARLY IMPOSSIBLE TASK OF CRACKING CANCER'S GENETIC CODE, AND **DREW PARDOLL**, (CENTER) HIS GRADUATE STUDENT AT THE TIME, MET MONTHLY WITH SENIOR CANCER RESEARCHER **DONALD COFFEY** (LEFT) TO TOSS AROUND IDEAS ABOUT HOW TO CURE CANCER. BOTTOM: SOME 35 YEARS LATER, THE RESEARCH TRIO IS STILL COLLABORATING.



could be used to turn the tide of strikingly poor responses for that disease. "We were happy to share any of our research that could help," says Vogelstein. "It's all done in the service of patients. There is no discussion of the usual academic kinds of things. We don't do that in the Kimmel Cancer Center."

The Mystery of the Single Responder

Cancer is a disease of genetic mistakes, so for all intents and purposes, the signals sent out by mutated genes should be an announcement to the immune system that they don't belong. "Ironically, this very mechanism that the tumor uses to accelerate its genetic diversity creates an Achilles heel for immunotherapy," says **Luis Diaz**, investigator in the Kimmel Cancer Center's Ludwig Center. The more mutations that exist in the cancer, the louder the signal and the more likely it is that the immune system will take notice.

Healing Cancer



BIOMEDICAL ENGINEER **Jennifer Elisseeff** was working on a way to promote healing in trauma patients when a friend of a cancer patient visiting Elisseeff's lab told her that similar approaches were reported to fight cancer.

A few years later, Elisseeff began research that promised to bridge the fields of immunology and biomedical engineering. She called the emerging field regenerative immunology. It led her to a new use for her trauma-targeted therapy.

Elisseeff works with biologically engineered animal and tumor tissues that are implanted locally at the site of an injury. "The immune system is a first responder when trauma to tissue and cells occur," says Elisseeff, the Jules Stein Professor in the Translational Tissue Engineering Center. Her engineered biologic materials give it an extra nudge. "They trigger immune cells, particularly T cells, to direct other immune cells to heal the injury," she says.

Elisseeff and team are collaborating with the U.S. military to study in people, including servicemen and women injured in combat, the safety and activity of her biomaterials. The engineered materials are made in the Kimmel Cancer Center's GMP facility. If human studies are successful, it creates a framework for eventually transferring the technology to an experimental clinical trial for cancer patients.

The first step was to test the ostensible cancer fighting potential in her laboratory. Elisseeff injected her biomaterials in mice engrafted with human melanoma skin cancer cells, and it hampered the growth of the cancer. "We've looked at the lymph nodes near the injection site and lymph nodes in other parts of the body and have identified immune changes directly related to the biomaterials," she says. These observations indicated that the treatment has the ability to chase down cancer cells that have broken off from the primary tumor and spread to other parts of the body.

Just as important, Elisseeff and team's findings challenge the common perception that regenerative medicine is cancer promoting. "This has been a nagging concern in our field, but we've never actually seen it occur," she says. "Our research provides evidence that this may not be a concern."

The promising anticancer activity in animal models occurred using biomaterials alone. Elisseeff says adding immune therapies, such as anti-PD1 blockades, may make it work even better. To find out she is collaborating with cancer immunology experts **Drew Pardoll** and **Jonathan Powell**, who have worked with her to establish this fledgling field of regenerative immunology.

Elisseeff met Pardoll when they worked together on Johns Hopkins University President Ronald Daniels' innovation hub committee aimed at promoting innovation translation to bring life-changing technologies to market. It led to the current collaboration focused on combined biomaterials/immune therapy animal and clinical studies, and Powell is helping decipher the biologic mechanisms. He has provided laboratory models that reveal the specific immune T cells essential to the healing immune response.

"This is the first therapeutic model," says Elisseeff. "No one has ever before bridged the fields of immune-engineering and regeneration."

She says they have only begun to scratch the surface of this new type of therapy and admits there is much they need to learn. Still, early findings point to the therapy she has created as a way to heal both wounds and disease. A patient undergoing cancer surgery could have the biologic material injected during the operation to promote healing of the surgical wound and to simultaneously generate a cancer-fighting immune response.

Nanoparticle Therapy

Gene therapy may be an effective treatment option for the deadly brain cancer glioma, but getting the right genes to cancer cells in the brain has proven difficult. Now, for the first time, Johns Hopkins researchers used biodegradable nanoparticles filled with genes to turn an inactive prodrug into a potent brain cancer cell killer. The nanoparticles, encoding a special gene, were injected into brain tumors in rats and followed by treatment with the drug ganciclovir. The treatment successfully killed cancer cells and extended survival in this animal model.

"Our nanoparticles penetrated completely throughout the tumor following a single injection," says biomedical engineer **Jordan Green**. "When combined with systematic administration of ganciclovir, rats with malignant glioma lived significantly longer than rats that did not receive treatment."

Nanoparticles are ultra tiny structures that are about 20 times larger than a molecule but 100 times smaller than a cell, so they can be loaded with genes and small molecules, including immune therapies, and guide and deploy these therapeutics inside cells. These nanoparticles are able to penetrate tumors and deliver immune-system-activating drugs and antibodies that cause immune cells to specifically attack cancer cells. This type of therapy kills cancer cells more effectively and with far few side effects.





LUIS DIAZ (LEFT), AND **DUNG LE** (RIGHT) ARE TWO OF THE YOUNG RISING STARS OF THE KIMMEL CANCER CENTER. LE IS A VIRAGH SCHOLAR FOCUSED ON IMMUNOLOGY AND PANCREATIC CANCER VACCINES, AND DIAZ IS A GI CANCER AND GENETICS EXPERT AND DIRECTOR OF THE SWIM ACROSS AMERICA LABORATORY.

So it was not surprising when Kimmel Cancer Center investigators, including Diaz, had an idea. “It’s mutations,” they suggested, suspecting that the single patient who responded to anti-PD-1 treatment had Lynch Syndrome, an inherited form of colon cancer characterized by abnormally large numbers of mutations.

The research that formed the basis for their conclusion occurred some 20 years earlier, remarkably from the same Ludwig Center laboratory. In 1993, Vogelstein, Kinzler, and **Nickolas Papadopoulos** of the Kimmel Cancer Center and Albert de la Chapelle from The Ohio State University identified a genetic alteration linked to Lynch syndrome, a hereditary form of colon cancer that is caused by mistakes in mismatch repair genes.

The job of mismatch repair is to correct copying errors that occur when DNA replicates and cells divide. People who inherit a defective copy of the gene experience high rates of mutations and are at increased risk of developing colon cancer. Colon cancers in patients with mismatch repair deficiency have more than 1,000 mutations while those without typically have less than 100. Vogelstein,

Kinzler, and Papadopoulos developed a test for mismatch repair gene mutations, so that families with a history of Lynch syndrome could be screened and their colon cancers detected in an early and curable stage.

They could have never envisioned the clinical application that Diaz and another young immunology investigator, **Dung Le**, would have for the test. It would prove instrumental. “What is the patient’s mismatch repair status?” Diaz asked Pardoll and Topalian about the single colon cancer responder. Using the test Vogelstein, Kinzler, and Papadopoulos developed two decades earlier, they proved their suspicion was spot on. The patient’s tumor was positive for mismatch repair alterations. The large number of mutations common to mismatch repair served as an alert to immune cells because they make the tumor look much more different from normal colon cells that don’t have this large number of mutations.

Imagine a crowd of people in a room. If one person is speaking a language different from the rest, it might go unnoticed. If many of them are speaking a different language, it will likely garner attention. In principle, this is the way the

immune system should work, ignoring those things that are “self” and noticing those things that are different. This is called immune recognition; the next step is action. That’s the role of anti-PD-1, which works by shutting down the cancer cell’s ability to send false signals to commandeer and divert immune cells from reacting. With anti-PD-1, the immune cells alerted by the high number of gene mutations were put into action to kill cancer cells.

“For other treatments, including chemotherapy, the changing tumor biology due to accumulating mutations causes treatments to stop working, but it seems to make immune therapies work better,” says Le. It’s likely more about the quantity of mutations than the specific type of mutation. The investigators believe the good responses to anti-PD-1 that occur in a subset of melanoma and lung cancers are also related to the accumulating gene mutations caused by sun exposure in melanoma and smoking in lung cancer. “In theory, you only need one mutation to get the immune system’s attention, but larger numbers of mutations, shift the odds in your favor,” he says.

The only way to prove the hypothesis

“Immune therapy is a game changer. We need more research to take us the rest of the distance, but we don’t think there is a single cancer that the patient’s own immune system ultimately can’t beat.”

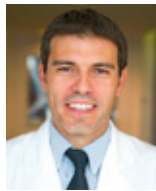
was to test it in patients, but these trials are expensive and a huge undertaking for young investigators. Diaz and Le were undeterred. Merck agreed to donate the drug, but it was the generosity of private funders—Swim Across America, the Lustgarten Foundation, the Skip Viragh Foundation, the Banyan Gate Foundation, the Commonwealth Fund, and the Sol Goldman Pancreatic Cancer Research Center—that allowed Diaz and Le to make it happen.

Le and Diaz are two of the young rising stars of the Kimmel Cancer Center. Le is a Viragh Scholar focused on immunology and pancreatic cancer vaccines, and Diaz is a GI cancer and genetics expert and director of the Swim Across America Laboratory. The balance of cancer genetics/cancer immunology expertise each brought to the table was perfectly suited to this study.

“The success of the Kimmel Cancer Center is inextricably tied to our ability to attract the best and brightest talent,” says Nelson. “This trial is an example of the depth of talent we have in our young investigators. Unfortunately, as this study illustrates, it can be a challenge for them to find funding for their science because they may not yet have a large body of work or the notoriety of more senior investigators. It is one of the greatest shortcomings in research but a priority at the Kimmel Cancer Center. It was our benefactor Sidney Kimmel’s vision—a vision he brought to life through the Kimmel Scholars Program—and vitally important to the future of cancer medicine.”

With funding in place and the drug acquired, Le and Diaz began a clinical trial in 48 patients. Le, the more subdued of the research duo, speaks calmly and

straightforwardly about the significance of their findings. Even before accrual to the study was completed, the results



NICO LLOSA

were so dramatic that they were viewed as a major finding, warranting publication in the prestigious *New England Journal of Medicine* in 2015, featured at the American Society of Clinical Oncology, and setting the stage for FDA breakthrough status for anti-PD-1 immune therapy in patients with mismatch repair deficiency.

Roughly 60 percent of patients with mismatch repair deficiencies responded to treatment, pointing to the presence of other checkpoint blockades that work similarly to PD-1. This will be the focus of additional laboratory research. As critical of a finding, however, was that none of the 25 patients with normal mismatch repair responded to treatment. The investigators will need to replicate their findings in a larger number of patients, but it provides clear evidence that mismatch repair alterations in tumors predicts which patients are good candidates for immune therapy with anti-PD-1.

Additional laboratory research at the Kimmel Cancer Center has pointed to other immune checkpoints in these tumors, which could be targeted in combination with anti-PD-1. **Frank Housseau** and pediatric cancer expert **Nico Llosa** found high expression of LAG-3 in mismatch repair deficient tumors.


Beyond colon cancer, the clinical study demonstrated that mismatch repair deficiency is a universal biomarker of response to immune therapy. They tested the treatment in a small number of other cancers marked by mismatch repair

mistakes—including some rare, difficult-to-treat cancers—and the treatment worked. “If you have the mismatch repair signature, you should be treated with a checkpoint inhibitor,” says Diaz. “Defects in mismatch repair genes are found in a small percentage of many cancer types,” says Le. Vogelstein estimates that 2 to 4 percent of all cancers have mismatch repair mistakes, and when that is calculated across every cancer type, the potential to help a lot of people is very real. Le believes that similar biomarkers for immunotherapy response could be applied to cancers with errors in other DNA repair genes.

“There is a tsunami coming,” says Anders, who believes the mismatch repair test is the first of many that will be used to predict response to immune therapy.

This is what excites Diaz and Le. They witnessed it firsthand, and Diaz brims with enthusiasm when he speaks particularly of two young patients who were part of the clinical study.

Stephanie Joho, who has Lynch syndrome, had just graduated from college when she was diagnosed with colon cancer. Surgery and two different types of chemotherapy did nothing to avert the aggressive cancer. Out of options and in excruciating pain, Joho searched desperately for other treatments and had reached out to Diaz, who until the mismatch repair discovery had tried everything available. Recognizing Joho would be a perfect candidate for his new study, he called her. She was distraught, sitting in a waiting room at another comprehensive cancer center after one more failed search for an experimental therapy, when she got Diaz’s call. “Come down here. We’ll cure you,” he told her. After treatment with anti-PD-1, Joho’s tumor

A close-up, profile view of a middle-aged man with graying hair, looking thoughtfully to the left. He is wearing a dark blue suit jacket, a light blue dress shirt, and a patterned tie. The background is softly blurred, suggesting an outdoor setting with warm lighting.

“Throughout my career as a clinician and scientist and now as cancer center director, I cannot recall another time when so many opportunities were within our grasp.”

—William Nelson, Director
*Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins*

shrank, and her pain subsided. “I haven’t felt this well in four years,” says Joho, now 25.

Another patient was weeks from dying and being encouraged to enter hospice care when Diaz and Le learned his tumor was positive for mismatch repair. He was so sick that they had to get a special exception to get him enrolled in the trial. “Without any doubt, this young man’s life was saved by this treatment,” says Diaz.

Diaz recalls more patients. “We could fill this room with people who have benefited,” says Diaz. The two recognize their study was small, and in science, numbers matter. Still, they have met every one of the patients in their study, and they also recognize that medicine is more than numbers. Behind every statistic is a human being.

“It is rare to get a response in colon cancer patients who have not responded to other standard therapies, and most of them had just months to live,” says Le. She is hopeful this discovery will very soon benefit thousands, but nonetheless, at this moment, they celebrate Joho and the 20 other lives that were saved.

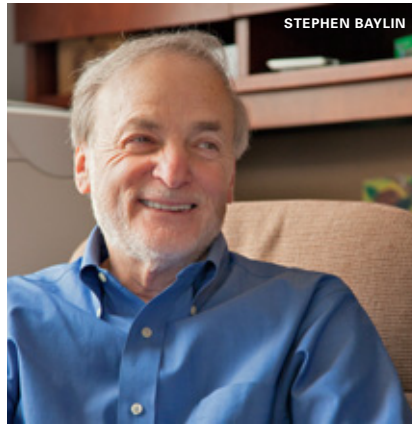
“One of the things that put us at the forefront of clinical breakthroughs in cancer immunology is that we never forgot the science,” says Pardoll. “Having the leading epigenetics and genetics researchers here gives us an edge. At most institutions, the different laboratories don’t interact at all. At Johns Hopkins, interaction among different disciplines is the norm, and these types of collaborations have led to some exciting immunology advances. There is no other place I know of with these deep, intellectual roots in genetics and immunology and the support of the institution to carry out investigator-initiated trials,” says Vogelstein. “You can’t create that environment from scratch. It has to be built in from

the ground up, and we’re very fortunate to have it here.”

“Dung and I are standing on the shoulders of many giants,” says Diaz.

The Epigenetic Connection

A number of the controls that turn the immune system on and off are epigenetic in nature. These chemically mediated on and off switches alter the function of genes without mutating the DNA, usually by adding chemical groups to the signaling portion of genes or by tightening or relaxing how the DNA is packaged within the cell. Epigenetic therapies that target these control mechanisms, can reactivate genes that have been turned off.



Stephen Baylin is one of the world’s foremost epigenetics experts. He, Vogelstein, and Pardoll have independently informed some of the most vexing problems of cancer initiation, spread, and treatment resistance. Their combined knowledge is the cancer world’s triple threat. By deciphering the inter-related complexities of genetics, epigenetics, and immunology, they are bringing forth some of the most encouraging cancer treatment strategies of our time.

As Baylin explored the effects of epigenetic-targeted drugs on lung cancer

cells in his laboratory, he found that some of the genes that were being reactivated were connected to immune responses. Among them was PD-L1 which interacts with a key molecule on immune cells, PD-1.



Baylin and young investigator **Cynthia Zahnow**, working with him as part of the *Stand Up To Cancer* Epigenetics Dream Team, shared their findings with Pardoll. In some lung cancer cells, the PD-L1 gene was already active, and epigenetic therapy made its signal even stronger. Pardoll believed that adding anti-PD-1 therapy in conjunction with epigenetic therapy could activate an immune response right within the tumor.

Treated with epigenetic drugs, the ability of cancer cells to evade the immune system is broken and they send new signals, beckoning immune cells to come and get them. At the same time, they begin to express PD-L1 to shield against immune attack. Anti-PD-1 breaks off that communication, unleashing the immune system on the cancer cells.

Baylin, Zahnow, and team went back to the laboratory to decipher the immune evasion signature for lung, breast, colon, and ovarian cancers. To do this, they looked at all of the genes in lung, breast, and ovarian cancers that got turned on in cancer cells with epigenetic-targeted therapies. Lots of genes were switched on, they found, but what stood out were the 20 percent or so related to immune regulation. These

By deciphering the inter-related complexities of genetics, epigenetics, and immunology, they are bringing forth some of the most encouraging cancer treatment strategies of our time.

“Kimmel Cancer Center scientists have made seminal contributions to the basic science, and now what is happening is almost magical as we make the unbelievable transformation to harness the immune system to attack tumors. Our latest findings further decipher the mechanisms that lead to this immune reaction and offer a novel way to potentially boost the success of immune therapies in cancer patients.”

genes were studied in depth by post-doctoral fellow **Kate Chiappinelli** and found to be epigenetically programmed to evade detection by the immune system.

They are now looking at tumor samples from patients receiving combined epigenetic and anti-PD-1 immune therapy to see if the epigenetic therapy turned on immune genes that would cause the cancer cells to respond to anti-PD-1 treatment. “Epigenetic therapy does not break immune tolerance, but it has the potential to sensitize cancers to an immune anti-PD-1 checkpoint blockade treatment,” says Baylin. “We think it brings in immune cells, so if we follow it with anti-PD-1, we can cause an immune reaction against cancer cells.” This theory is currently being studied in clinical trials funded by Stand Up To Cancer.

Baylin continued his research of epigenetic controls of immune response, collaborating with another epigenetics research giant, Peter Jones, director of research at the Van Andel Institute. Working together as co-leaders of the Stand Up To Cancer Epigenetics Dream Team, they uncovered a viral defense mechanism in tumors that mimics a viral infection. Epigenetic drugs cause it to simulate an infection and summon immune cells to tumors.

“Epigenetic drugs upregulate the viral defense pathway, activating interferon signaling, and this brings in immune cells,” says Chiappinelli. “When epigenetic therapy is followed by anti-PD-1 checkpoint blockade immune therapy, the immune cells go into action against the cancer.”

The viral defense pathway is an ancient human biological mechanism that allows cells to recognize when they have been infected by a virus and helps activate an immune response to the viral invader. Our DNA retain a record of our viral exposure, creating a history that becomes integrated into the genome. This viral record is rendered dormant through epigenetic signaling, but as Baylin and Chiappinelli found, it can be reactivated when epigenetic-targeted therapies are given. Since it reactivates just a memory of viruses, it only mimics an infection in tumor cells, but fake infection is enough to generate an immune response.

When they examined the DNA of a variety of cancer types, including ovarian cancer, colon cancer, and melanoma, they found that tumors with high expression of the viral defense pathway were more likely to respond to immune therapy with anti-PD-1. Tumors with low viral defense expression could be coaxed into response if epigenetic-targeted drugs were given before immune therapy. The FDA-approved epigenetic drug 5-azacytidine (Aza) converted low viral defense expression to high expression.

“Our research findings are consistent with the previous notion that silencing viral sequences in the human genome is a major function controlled epigenetically,” says Baylin. Using drugs like Aza to remove the epigenetic controls that silence the noninfectious viral memory locked away within tumor cells activates interferon, a signal to the immune system released by cells when they are invaded by bacteria or viruses. In essence,

Aza makes tumor cells think they are infected with a virus and causes them to sound the alarm to alert the immune system. In laboratory experiments where Baylin and Chiappinelli blocked interferon in tumor cells, the Aza-induced immune response stopped.

To further test their theory, the two collaborated with experts at Memorial Sloan Kettering Cancer Center in New York to examine cancer cells from melanoma patients treated with anti-CTLA-4, another checkpoint blockade immune therapy similar to anti-PD-1. They determined the viral defense pathway expression for each tumor and matched it back to the patients. High viral defense expression matched with all of the patients who responded to immune therapy, and low expression matched with those who did not respond.

In a mouse model of melanoma, adding an epigenetic drug to cancers that were not responding to immune checkpoint blockade triggered an immune response. Baylin says the true test will come from clinical studies, but he is energized by these laboratory results.

“This is the most exciting time of my entire career,” says Baylin. “Kimmel Cancer Center scientists have made seminal contributions to the basic science, and now what is happening is almost magical as we make the unbelievable transformation to harness the immune system to attack tumors. Our latest findings further decipher the mechanisms that lead to this immune reaction and offer a novel way to potentially boost the success of immune therapies in cancer patients.”



CYNTHIA ZAHNOW AND STEPHEN BAYLIN

Baylin, like all of the Kimmel Cancer Center researchers and clinicians who held firm to their belief in immune therapy, is most excited by the safe and durable responses it delivers.

“Many people still view cancer as a terminal disease, particularly advanced cancers, and look what we have to put patients through to treat them,” says Baylin. “Immunotherapy promises to change that. It’s already made a huge difference. We have patients now who, against all odds, are alive and living well even when we have not completely eliminated their cancer. I can only imagine what the next 10 years will bring. You have to be excited about this.”

Whispers of a Cure

These combined approaches are the newest adaptation of cancer immunology therapies. Pardoll, Topalian, Drake, Jaffee and their immunology teams are optimistic that the power of immune therapy and the right combinations will continue to expand the numbers of cancer patients who will see their immune systems engaged against their cancers. For the first time in the history of cancer, experts and patients alike are beginning to see in immune therapy, the potential for a universal cure for cancer.

Through the convergence of a wealth of expertise, the advancement of

technology and in an environment where bench-to-bedside research flourishes, Kimmel Cancer Center experts have solved the puzzle of cancer immune resistance, or at least they have identified many of the pieces. The critical component—immune resistance, how the cancer cell escapes an immune attack—was revealed and therapies to undo cancer’s ability to manipulate the immune cells to its own benefit can now be developed.

“The success we have had so far is unlike anything we have ever seen in cancer, and consider that we have only mined about 5 percent of what the immune system can do in cancer. This is just the beginning,” says Pardoll. “As we learn about other immune signals and combined approaches, we think it will only start to look better. In 20 years, possibly less, immune therapy has the promise to completely change the face of cancer and make almost all cancers curable or controllable.”

Patients, even those who are not currently on immune therapy, seem to sense the changing tide, says veteran immunology nurse practitioner **Tianna Daus**. “Every day, we get calls from cancer patients who want to come to the Kimmel Cancer Center for immune therapy. Current patients, including many who are on other types of therapies, express the hopefulness they feel from

being at a cancer center that is engaged in this kind of paradigm-shifting research.” Her immunology nursing colleagues concur. “I’ve worked in oncology for a long time. It’s an exciting time to see these new therapies that work in the worst cancers and don’t cause terrible side effects,” says research nurse **Beth Onners**. “One of the first questions I typically get from patients is, ‘Will it make my hair fall out? It’s so nice to be able to tell them it won’t.’”

The patients who were on chemotherapy before treatments like anti-PD-1 were discovered say they feel like chemotherapy kept them alive, but immune therapy gave them their lives back, says Biedrzycki. “It is so exciting to be a part of this,” she says.

After decades of research, it is the patients that matter most to the Kimmel Cancer Center immunology researchers and clinicians. It is not seeing their scientific theories proven correct that they find most gratifying. The real satisfaction, they say, comes from seeing these scientific theories actually help patients and without the terrible side effects that have defined cancer treatment for decades. “Immune therapy is a game changer,” says Pardoll. “We need more research to take us the rest of the distance, but we don’t think there is a single cancer that the patient’s own immune system ultimately can’t beat.” **P.O.P.**

Headline Makers



A Random Act of Cancer

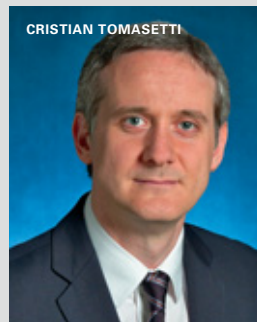
SCIENCE IS ABOUT solving mysteries—figuring out why things happen. The Kimmel Cancer Center laboratory directed by **Bert Vogelstein** and **Kenneth Kinzler** has been focused on figuring out why cancer happens for nearly 35 years. “History shows that once we figure out what causes a disease, it is only a matter of time before we conquer that disease,” says Vogelstein.

The inspiration for his quest to figure out what causes cancer came in 1975, when he was a pediatric resident at Johns Hopkins. Late one Friday night, young parents brought their sick four-year-old daughter into the emergency room. Tests revealed she had leukemia. She was the first cancer patient Vogelstein had ever treated, and it became a defining moment for him.

He had to deliver the devastating news to the girl’s parents. Her father asked him, his voice trembling, “How did my little girl get this?” Vogelstein did not have an answer. At that time, no one did.

“Most of my career has been dedicated to finding the answer to this man’s question,” says Vogelstein.

In fact, it was the work of Vogelstein, Kinzler and their Ludwig Center team of scientists that revealed cancer as disease of genetic mistakes—accumulating errors to our DNA. The group’s work in deciphering the genetic architecture of cancer is universally regarded as the most relevant in the study of the disease. It is



the classic model—the paradigm—for much of modern cancer research.

How precisely do these genetic errors occur? That too had remained somewhat of a mystery until Vogelstein and biomathematician **Cristian Tomasetti** took a deeper look.

Some cancer-related errors are the result of heredity, the shared DNA passed from parent to child, but these are the rare cases, accounting for just five to 10 percent of cancers. The Vogelstein/Kinzler-led group relied heavily upon these familial cancers in their research of the biology of cancer. These inherited cancer syndromes allowed them to zero in on and reveal the genetic errors that caused them and led to the unraveling of the genetic landscape of the much more common cancers that occurred sporadically among the general population. What about the other 90 percent?

The leading groups that study diseases on a population scale report that about one-quarter to one-third of cancers are the result of genetic alterations caused by bad habits and exposure to things in our environment.

The U.S. Centers for Disease Control and Prevention reports that 20 percent of cancers are preventable, mainly through lifestyle and environmental interventions, such as increased exercise, changes in diet, and eliminating smoking. Globally, the World Health Organization states that about 40 percent of cancers are preventable.

Inherent to these statistics is the fact that a significant portion of cancers—

“How did my little girl get cancer?” Vogelstein did not have an answer. At that time, no one did. “Most of my career has been dedicated to finding the answer to this man’s question.”

as many as two-thirds—are not currently preventable through lifestyle and environmental interventions. It's the old “glass half empty/glass half full” dilemma. On one hand, the ability to prevent a substantial number of cancers is a good thing, but the lack of knowledge about what causes the majority nonetheless reveals an existing gap in our understanding of cancer.

Vogelstein is a genetics expert with a background in mathematics. Tomasetti is an expert in applied mathematics and former Harvard biostatistician whose research is focused on cancer. Working together, they set out to precisely figure out how and why cancer develops in the remaining two-thirds of people.

Understanding What Causes Cancer

Keep in mind, their goal was to create a general model of this unknown cancer contributor, not to identify the precise causes of each individual person's cancer development.

No two cancers are exactly the same. Vogelstein and team showed that in their earlier research that revealed a complex genetic landscape that varied from cancer patient to cancer patient. Cancer results from a combination of things, with heredity, lifestyle and environment among the factors. Since the things we know accounted for only about one-third of cancers among the general population, it was clear that another cause or causes remained.

To unmask the other contributing factors, Vogelstein and Tomasetti created a statistical model to measure the proportion of cancer incidence across many cancer types and matched them to the total number of stem cell divisions in those cancers. Stem cells are self-renewing, master cells of sorts. By copying and dividing, they give rise to the specialized cells that make up human organs and tissue.

“It is well-known that cancer arises when cell DNA is mutated during cell

“No single thing causes cancer. Cancer is caused by a combination of environment, inherited gene alterations, and random mistakes that occur during stem cell division.”

copying and division,” says Vogelstein. The full role these mistakes play in cancer overall, however, was not known. In attempt to figure it out, Vogelstein and Tomasetti scoured the scientific literature to compile a catalog of the total number of stem cell divisions that would occur throughout an average lifetime for 31 tissue types. They compared the data with the overall lifetime risks of cancer in the same tissue types. Vogelstein and Tomasetti calculated that two-thirds of variations in cancer incidence likely originated from random mistakes made during these cell divisions.

As human stem cells divide to repair and regenerate the linings of our tissues and organs, random copying errors occur. Over time, these errors begin to fundamentally change cell behavior and lead to cancer. Scientists call these mistakes mutations. They result when the chemical alphabet that makes up our DNA experiences a transposition—one chemical letter is mistakenly swapped for another. As these mistakes, or mutations, accumulate throughout a lifetime, the risk for cancer increases.

Vogelstein, who has been a staunch supporter of cancer prevention and early detection, says the new findings point out that behavior and environmental changes alone may not be enough to stave off cancer. It stresses the need for better ways to detect and treat cancer early.

Picture This

Cancer is a complex, multi-step process. On average, it takes about three genetic missteps occurring sequentially over time for a cancer to form, says Vogelstein. One of these mistakes is likely

caused by heredity or behaviors, but the other two mistakes are probably out of our control, he explains.

We can think of cancer as a cellular accident, say the researchers. To make it clearer, they compare the events leading up to cancer to those involved in a car accident. The risk of having an accident goes up with the length of the trip, just as the risk of developing cancer increases with length of life. Cancer is most common among people over age 65. A longer trip offers greater opportunity for something to go wrong on the road in the same way that longevity provides more chances for cellular mistakes to occur.

Still, there are other variables that come into play. Poor road conditions or texting while driving add to accident risk, just as behavior choices, like smoking or poor diet, add to cancer risk. A car with mechanical issues, such as worn tires or bad brakes, has an increased accident risk, and a person with an inherited gene alteration linked to cancer is predisposed to an increased risk of developing cancer.

How each type of risk colludes to result in a specific accident—or individual cancer—is unknown. “No single thing causes cancer,” says Vogelstein. “Cancer is caused by a combination of environment, inherited gene alterations, and random mistakes that occur during stem cell division.” In some cases, one risk factor may be the driving cause, and in others, another risk dominates.

The purpose of Vogelstein and Tomasetti's research is not to provide a detailed schematic for how each individual's cancer develops. “Our results are about differences in the incidences of different cancer types, not about a

specific cancer type in a particular person,” says Tomasetti. The real value of their study is in pointing to a greatly neglected area of cancer research, and one that has the potential to save more lives than any form of cancer treatment.

Preventing Suffering and Death

Many detractors of the study were quick to assume that Vogelstein and Tomasetti were questioning the benefit of cancer prevention. They added two and two together and came up with 10, concluding that when the researchers identified uncontrollable randomness as a major contributor to cancer, they somehow conveyed a public message that cancer prevention was an exercise in futility.

To the contrary, Vogelstein and Tomasetti contend that prevention is the best way to avert cancer, and they believe their research supports this contention. “Just because we have identified random mutations as a cause of cancer doesn’t mean it can’t be prevented,” says Tomasetti. In fact, Vogelstein and Tomasetti’s model validated—not to any great surprise—that smoking is the leading contributor to lung cancer development. Similarly, their work supported the idea that sun exposure is the leading contributor to basal cell skin cancer; infection with human papillomavirus-16 greatly increases the risk for head and neck cancer, as does hepatitis C infection for liver cancer; and that lifestyle and heredity play a major role in colon cancer development. In these cancers, what experts dub primary prevention—avoiding known causes—could play a significant role in controlling the incidence rates.

On the other hand, many other can-

cers, including brain cancers, lung and esophageal cancers in non-smokers, leukemias, bone cancers, and many pediatric cancers are most likely caused by random mistakes in cell division. For these tumors, it will take more than changes in behavior to stave off cancer development. “Our new research suggests that some cancer types will be much more difficult to prevent by changes in lifestyle than others,” says Vogelstein. “In these cases, we should seek to prevent cancer suffering and deaths by detecting the cancer early when it is still curable with surgery.”

Vogelstein and Tomasetti stress the need for a greater emphasis on new cancer detection methods to augment those already available, such as Pap smears, mammography, and colonoscopy. When performed correctly, Vogelstein says, such tests can detect cancers in an early and curable stage and have saved countless lives.

“Our research does not minimize the importance of healthy living—primary prevention. However, we cannot stop there,” says Vogelstein. “Even the healthiest of lifestyles will not prevent cancer from occurring in many individuals. These cancers will occur simply because of copying mistakes made as cells divide, regardless of lifestyle. Fortunately, suffering and death from these cancers are largely preventable, but from secondary prevention rather than primary prevention.”

A New Model For Cancer Prevention

As one of the scientists whose research defined cancer as a genetic disease, Vogelstein has an unparalleled view of

the complex and varied molecular structure of the cancer cell. He recognized it would be very difficult to develop therapies that could control cancer by correcting or overcoming the genetic alterations rooted in the disease. Advanced cancers, which have the greatest accumulation of genetic mistakes, are engrained for treatment resistance and have, to no surprise, proven to be the most difficult to manage. One of Vogelstein’s goals is to use his research team’s gene discoveries to develop methods that would allow cancers to be eradicated and deaths prevented through early detection. “This is a form of secondary prevention,” says Vogelstein.

With this in mind, Vogelstein and Kinzler’s team are using their genetic discoveries to develop better cancer screening tests. Their tests represent the future of cancer screening and detection. They are simple, noninvasive tests that have the power to detect cancer DNA through a blood test or a test of bodily fluids or excretions. Most importantly, with more research, these tests have the promise to detect cancer in the very earliest stages of development, when they are most curable.

Vogelstein and Tomasetti call for increased funding for cancer prevention research, not less. Despite its potential, prevention gets a small amount of cancer funding when compared to that spent on the research of cancer treatments.

“We consider the development of early diagnostic tests for cancer one of the most important goals in cancer research,” says Vogelstein. “Our statistical model provides further justification for this view. In particular, we believe that prevention—not the therapy of advanced disease—is the best way to reduce cancer deaths in the long-term.” Kinzler

“Our new research suggests that some cancer types will be much more difficult to prevent by changes in lifestyle than others,” says Vogelstein. “In these cases, we should seek to prevent cancer suffering and deaths by detecting the cancer early when it is still curable with surgery.”

“The history of medicine documents that once a disease is understood, it’s only a matter of time before that disease is conquered. We don’t know exactly how long that will take, but eventually it will come. Of that I am certain.”

points out that even cancers that are preventable in principle, such as lung cancer by eliminating smoking, are currently not prevented because many individuals unfortunately do not follow the lifestyle recommendations of groups like the American Cancer Society and the American Association of Cancer Research. “Even for these preventable cancers, early diagnosis—or secondary prevention—can be life-saving,” says Kinzler.

The value of modern medicine—what experts call precision medicine—is knowing what interventions are best for specific situations. Vogelstein and Tomasetti’s model helps shed additional light on the causes of cancer and helps guide prevention strategies.

With this research, Vogelstein’s career has come full circle. In 1975, when his young leukemia patient’s father asked him how his daughter got cancer, he had no answer. “I didn’t even have a good idea for an answer, and no one else did either,” says Vogelstein. “It wasn’t just that I couldn’t answer her parents, it was this feeling of hopelessness. If you don’t understand something, how can you ever hope to do something about it?”

Now, Vogelstein and Tomasetti have done more than provide a better understanding of cancer. They have given closure and healing to those who blamed themselves for their own cancer or the cancer of a loved one, believing there was something they could have done to prevent it. One person, who was burdened by guilt for years thinking he was somehow to blame for his son’s brain cancer, wrote to Vogelstein, “For me, [this research] means that I can stop wondering what, if anything, we did wrong and accept that there was nothing anyone could have done to change it.”

Of course, Vogelstein is determined

to change it—not necessarily the origination of cancer, but the outcome. “The history of medicine documents that once a disease is understood, it’s only a matter of time before that disease is conquered,” he says. “We don’t know exactly how long that will take, but eventually it will come. Of that I am certain.”

We may look for simple solutions to complex problems because they provide us some sense of comfort and assurance. We tell ourselves if we do not do eat certain foods or live a certain way, we will be safe. Of course, we know cancer strikes more than its fair share of innocent victims. Even when we think we have it figured out, it shows us there is more to the story than we recognize. Not everyone who smokes gets lung cancer, and people who never smoked sometimes do. Vogelstein and Tomasetti’s research explains that these seemingly nonsensical events are part of the random nature of cancer. But his research offers the promise of another solution.

For many cancers, the Vogelstein/Kinzler laboratory has uncovered a lengthy timeline—as much as 30 years—for a cancer to develop from a single errant cell into an advanced disease. The deadly spread of cancer, they find, occurs in the last few years of this long process. “Although our findings reveal a large window of time before many cancers turn deadly, too many patients are diagnosed after that window has closed,” says Vogelstein.

Imagine simple tests that can be given during a routine physical exam and with pinpoint precision find the DNA copying errors indicative of cancer. These tests will find cancer-promoting genetic mistakes early enough in the process to provide an opportunity to destroy it before it can cause harm.

Sputum tests that can detect lung cancer, urine tests for bladder cancer, stool tests for colon cancer, or a broad-based blood test that could potentially detect any type of cancer at its beginning—these are cancer tests the Vogelstein/Kinzler laboratory scientists are developing. Such a test is already used to help decipher harmless pancreatic cysts from ones that are likely to develop into the lethal cancer. Their studies also demonstrated that a gene-based test of cervical fluid has the ability to detect ovarian and endometrial cancers, and that blood tests have the capability to detect early cancers.

The researchers are working to improve the sensitivity of their tests so that they may find the minute levels of cancer DNA that foretell an early-stage, surgically curable cancer. Their work could one day rewrite the onerous history of cancer.

The knowledge, technology, and science have converged to make it possible. Through this work, Vogelstein and Tomasetti imagine a day when the diagnosis of cancer will not instill fear or guilt in the minds of people diagnosed with the disease or those who love them. The power of cancer over the mind and body will be diminished by the assurance of a cure.

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Philanthropy

Sidney Kimmel: Helping Others

Sidney Kimmel understands the “You can’t take it with you” philosophy better than most. He made his money late in life, after many years in the women’s apparel business, creating the Jones New York clothing line.

“Someone once told me, don’t give like it’s a pinch; give ’till it hurts. Extend yourself, and give to other people and to good causes.”

This self-made billionaire is now a part of “The Giving Pledge,” a commit-

ment by the world’s wealthiest individuals to dedicate the majority of their wealth to philanthropy.

A child of The Great Depression, Kimmel remembers the struggles his parents endured providing for the family. “My sole motive in life was to earn a living. I wanted to be able to help my family.”

That was just the beginning. Sidney Kimmel’s philanthropy has reached deep into communities to support the Arts and Education, but above all, his efforts in the world of cancer research have changed the face of the disease.

He led the charge at The March on Washington nearly 20 years ago that resulted in a doubling of the National Cancer Institute’s budget. He is the quiet giant behind Stand Up To Cancer,

raising millions of dollars annually to fund cancer researchers who are making a difference in cancer care and treatment.

The Kimmel Scholars Program supports young investigators with distinctive, new ideas on cancer research. The Scholars program is the heart of the Kimmel Foundation.

“Sidney Kimmel is one of the great philanthropists of our age,” says **William G. Nelson**, director of the Johns Hopkins Kimmel Cancer Center. “His impact on the field of cancer research is unparalleled and without equal.”

Sherry Lansing, co-founder of Stand Up To Cancer says, “Sidney is an inspiration to anybody who is engaged in philanthropy. He’s the gold standard we aspire to.”



“Someone once told me, don’t give like it’s a pinch; give ’till it hurts. Extend yourself, and give to other people and to good causes.”



WATCH VIDEOS

Sidney Kimmel - Then & Now
Conversations About Cancer
bit.ly/1Ph7QhS

Bloomberg~Kimmel Institute Cements Progress in Cancer Immunotherapy

TWO FAMILIAR NAMES are cementing the Kimmel Cancer Center's ability to continue its groundbreaking laboratory and clinical advances in cancer immunology. **Sidney Kimmel**, for whom the Kimmel Cancer Center is named, and three-term New York City mayor **Michael Bloomberg** are each contributing \$50 million over five years to establish the **Bloomberg~Kimmel Institute for Cancer Immunotherapy**.

"I could not be more honored to partner with Mike Bloomberg and capture the opportunity to advance immunotherapy research at this critical moment," says Kimmel. "Having been committed to cancer research for more than 20 years, it simply thrills me to know that the scientists at the Hopkins Kimmel Cancer Center see a new light at the end of the tunnel. I know I speak for Mike in recognizing Hopkins' extraordinary capacities. If together we can make a true difference in the well-being of others at the scale possible, it will prove to be one of the most important acts either of us have ever made."

"Sidney and Mike continue to put extraordinary resources exactly where and when they are needed. We are at a pivotal time to change dramatically the way we treat cancers." —William Nelson

"Sidney and Mike continue to put extraordinary resources exactly where and when they are needed. We are at a pivotal time to change dramatically the way we treat cancers. With the new institute, we will go farther faster,"

says **William Nelson**, Kimmel Cancer Center director.

As a result of the two lead gifts from Kimmel and Bloomberg, additional money has been raised toward the goal of \$125 million for the first five years.

Kimmel and Bloomberg have a long history of support for Johns Hopkins. Since 2001, Kimmel has contributed \$157 million, and The Johns Hopkins cancer center is named in his honor. Kimmel has given an additional \$2.4 million to support 12 young cancer scientists at Johns Hopkins as part of the national Kimmel Scholars Program. Bloomberg is a 1964 alumnus of The

Johns Hopkins University and was chairman of its board of trustees from 1996 to 2002. He has given \$1.2 billion to the University and Johns Hopkins Health System since graduating. The Johns Hopkins Bloomberg School of

Public Health and Charlotte R. Bloomberg Children's Center are among the facilities named to honor his contributions.

Cancer immune therapy is one of the most promising areas of cancer research. It makes cancer cells visible to immune cells and causes the immune system to take action against cancer. (Read *The Final Frontier*, page 3 for breakthrough immune therapy discoveries by Kimmel Cancer Center scientists.)

"Sidney Kimmel and Michael Bloomberg are visionaries," says **Ronald Daniels**, Johns Hopkins University President. "Their combined philanthropy has already fostered remarkable innovation throughout Johns Hopkins. The new Bloomberg-Kimmel Institute will go even further, revolutionizing our approach to cancer."

Internationally recognized immunology expert **Drew Pardoll**, will serve as the Institute's director. Pardoll is a veteran scientist whose career in immunology and cancer research spans more than 25 years.

The Bloomberg-Kimmel Institute will support cancer immunology research across many cancer types, including melanoma and colon, pancreatic, urologic, lung, breast, and ovarian cancers.



Construction Begins On New Skip Viragh Outpatient Cancer Building

JOHNS HOPKINS University President **Ronald Daniels** welcomed a standing-room only crowd to the groundbreaking ceremony for the Kimmel Cancer Center's Skip Viragh Outpatient Cancer Building on September 10, 2015. The new \$100 million, 184,000 square-foot outpatient cancer diagnostic and treatment facility is slated to open in late 2017.

The building is named for Albert P. "Skip" Viragh, a Maryland mutual fund investment leader, philanthropist and a Kimmel Cancer Center pancreatic cancer patient who died in 2003 of the cancer. He was 62.

"This building is a state of the art testament to Skip's legacy," says Daniels. He described Viragh as having a pioneering vision and spirit; a trait he says is shared by the Johns Hopkins cancer clinicians and scientists working to develop better ways to manage cancer.

Funding for the building comes entirely from private philanthropy, including a \$65 million gift honoring Skip Viragh, a \$10 million gift from Under Armour, and other donations received through *Rising to the Challenge: the Campaign for Johns Hopkins*.

It will accommodate more than 180 daily patients visits and 60 to 80 new patient appointments each week. It will also be home to the multidisciplinary cancer clinics. The novel clinics are modeled after one established by the Skip Viragh Center for Pancreatic Cancer Clinical Research and Patient Care and offer newly diagnosed cancer patients a comprehensive consultation involving all of the specialists contributing to the treatment and diagnosis of their cancer type. By the end of the coordinated one or two-day visit, patients receive a detailed treatment plan recommendation.

"The Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care and the Viragh Scholars program—established through the profound generosity of Skip Viragh—have made the Kimmel Cancer Center a powerhouse in developing new treatments for pancreatic cancer," says **Daniel Laheru**, who cared for Viragh and now serves as co-director of the Skip Viragh Center. "The Viragh family has remained singularly focused on cancer care, helping countless numbers of patients. Skip is the heart of this new building."

L TO R: **DANIEL LAHERU**, CO-DIRECTOR OF THE SKIP VIRAGH CENTER FOR PANCREAS CANCER CLINICAL RESEARCH AND PATIENT CARE; **ELIZABETH JAFFEE**, CO-DIRECTOR OF THE SKIP VIRAGH CENTER FOR PANCREAS CANCER CLINICAL RESEARCH AND PATIENT CARE; **WILLIAM NELSON**, DIRECTOR OF THE KIMMEL CANCER CENTER; **VERED STEARNS**, CO-DIRECTOR OF THE BREAST CANCER PROGRAM

The 10th floor of the Skip Viragh Outpatient Cancer Building will house the Under Armour Breast Health Innovation Center, providing breast health services and information and guidance on nutrition, fitness, and survivorship. "We are incredibly fortunate to have Johns Hopkins in Baltimore, and we are honored to be a partner in making the vision for a breast health center become a reality," says Kevin Plank, CEO and founder of Under Armour, a Baltimore-based sporting apparel company. "We will demonstrate that wellness and illness can co-exist in a continuum."

When completed, the new building will free up space in the Kimmel Cancer Center's Harry and Jeanette Weinberg Building to expand inpatient cancer services, 24-hour urgent care, and blood and bone marrow cancer outpatient services.

"I can't help but think what the future of cancer care will be like," says Kimmel Cancer Center Director **William Nelson**. "In this place, I believe we will see the beginning of the end of cancer."

McConkey Named Director of Greenberg Bladder Cancer Institute

DAVID MCCONKEY was appointed director of the Johns Hopkins Greenberg Bladder Cancer Institute, whose members include experts from the Kimmel Cancer Center, the Brady Urological Institute, and the school of medicine's departments of Radiation Oncology and Molecular Radiation Sciences, Surgery, and Pathology.

The institute was established in 2014 with a \$15 million gift from Baltimore-area commercial real estate developer Erwin L. Greenberg and his wife, Stephanie Cooper Greenberg, and a \$30 million investment from The Johns Hopkins University. Its faculty, which already has drawn \$500,000 in research grants, is dedicated to advancing the scientific understanding of bladder cancer and improving its treatment.

"We are thrilled to bring David on board," says **William G. Nelson**, Kimmel Cancer Center director. "He brings a wealth of knowledge about the biology of bladder and genitourinary cancers, and has proven leadership skills in a top-notch institution. We are especially grateful to **William Isaacs**, for serving as interim director these past 19 months. He led the team through the two rounds of competitive grant awards, the establishment of a national external advisory board and a series of outreach initiatives to physicians nationwide."

"We conducted a very thorough recruiting process where we evaluated the best, most highly qualified candidates in the country, and David stood out to us as someone with both the experience and the collaborative spirit to direct the Greenberg Bladder Cancer Institute to its greatest level of success," says **Theodore DeWeese**, Sidney Kimmel

Professor and director of the Department of Radiation Oncology and Molecular Radiation Sciences.



and served as co-principal investigator of the MD Anderson Specialized Program of Research Excellence (SPORE) in Bladder Cancer, which is now in its third continuous cycle of funding from the National Cancer Institute. He is also chair for translational medicine for the Genitourinary Cancers Committee of the Southwest Oncology Group and has been involved in setting agendas for the Bladder Cancer Advocacy Network's clinical initiatives. McConkey has published more than 200 articles in peer-reviewed journals, served on 90 advisory committees at MD Anderson and won numerous teaching awards for his work.

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"David's recruitment is an outstanding example of high-impact philanthropy. Because of the generous support of Erwin and Stephanie Greenberg, who have been tireless advocates for this and other important causes, we are poised to

set new standards for innovation, treatment and discovery in the field of bladder cancer," says **Alan Partin**, professor and chairman of the Department of Urology and Jakurski Family Director of The James Buchanan Brady Urological Institute at Johns Hopkins.

"I am firmly convinced that team science is the most rapid path to progress," McConkey says. "I look forward to serving as the hub of an institutional and international community of researchers who share a commitment to advancing the scientific understanding of bladder cancer and improving its treatment."

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Margareta Augustine Fellowship Supports Young Investigators

THE RACE TO better understand and treat cancer is often hampered by time and funding constraints, and it is even more difficult for our young investigators. A generous \$1 million gift from Meg Augustine will ease those constraints for some of our dedicated young scientists.

The Margareta Augustine Fellowship will directly benefit the Kimmel Cancer Center's fellowship training program in breast cancer, blood and bone marrow cancers, and brain cancer. "In my association with Johns Hopkins Medicine over the years, I have been enormously impressed with the dedication of everyone whom I have met. It is my hope that this contribution will help bring about one more step of this lifesaving work," says Augustine, who has been a member of the Kimmel Cancer Center Advisory Board since 2001.

"The funding is instrumental in helping all of our three fellows complete their research," says **Ben Ho Park, M.D., Ph.D.** "Typically there is only a limited amount of funds for each fellow, and any additional research support is the responsibility of the mentor and fellow. The Margareta Augustine Fellowship allows us to increase the research training so that fellows can have the time needed to complete their research, publish and then acquire the best academic position possible."

One of the inaugural fellows is **William "Brian" Dalton, M.D., Ph.D.**



"Brian is working on a novel gene that is mutated in a number of human cancers. The goal is to recreate lab models of cancers that carry these mutations, develop targeted therapies and companion diagnostics for these mutations, and then eventually move this into clinical trials," Park says.



ChemoCozy

THROUGH A GRANT from The Johns Hopkins Hospital's Women's Board, a number of Kimmel Cancer Center

patients are receiving *ChemoCozy* jackets this winter. The fleece jackets, stylishly and thoughtfully designed by cancer survivor Greg Hamilton and his wife, provide easy access to peripherally and centrally inserted intravenous lines, implanted devices and pockets for surgical drains. "We are always so excited when we know patients will get a little comfort during their treatments," says Hamilton. Nurses in the infusion center, inpatient floors, and outpatient clinics are distributing the jackets to patients. "We are very grateful to the Women's Board and the Hamilton's for making these jackets available to our patients," says **Sharon Krumm**, Kimmel Cancer Center administrator and Director of Nursing.

Record Funds Swim Across America

WITH SUNNY SKIES and light winds to buoy swimmers, kayakers and volunteers alike, this year's pool and open water events raised more than \$550,000 for the Kimmel Cancer Center. Now in its sixth year, the annual event attracts hundreds of swimmers of all ages and abilities. Some swam in honor or in memory of a loved one. Many were cancer survivors and some donned "rookie" stamps, indicating they were swimming in the event for the first time; while others took on a new challenge this year, swimming a 5 mile course around scenic Gibson Island.

"Because of the efforts of each and every member of the Swim Across America Baltimore family, we have new ways of attacking the deadliest cancers," says **Luis Diaz, M.D.**, director of the Swim Across America Laboratory at the Kimmel Cancer Center.

In May 2015, at the largest world-wide meeting of cancer physicians, Kimmel Cancer Center physician-scientist **Dung Le, M.D.**, and Diaz reported on a study of 48 patients with colon and other cancers who standard therapies failed. The Kimmel Cancer Center team discovered



that mistakes in so-called mismatch repair genes may accurately predict who will respond to certain immunotherapy drugs known as PD-1 inhibitors. Such drugs aim to disarm systems developed by cancer cells to evade detection and destruction by immune system cells. This study builds on genetic discoveries first identified by Johns Hopkins researchers and other scientists two decades ago. But until now, the connection between these genetic mistakes or mismatches and ways to target them was unrealized. "It is only because of the funding from Swim Across America that we were able to pursue this innovative idea," says Diaz.



Cancer Immune Therapies

They are already saving lives.

“With more research, we can harness the full power of the immune system, and when we do, there may not be a single cancer that the patient’s own immune system ultimately cannot defeat.”

—William Nelson, Director
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

14 million cancer patients and survivors need your help. You probably know some of them. **WILL YOU HELP?** For more information or to make a tax deductible donation:

**Johns Hopkins Kimmel Cancer Center
Development Office**
750 E. Pratt Street, Suite 700
Baltimore, MD 21202

To contact our fundraising team by phone or email:
Phone **410-361-6391**
Email: stifler@jhu.edu

Or, make a gift online at hopkinscancer.org and click “Make A Gift.”



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Coming in the next issue:
Kimmel in the Community: Our Commitment to You
Addressing Cancer Disparities
Through Clinical Trials, Laboratory
Research and Patient Care

