# PROMISE & PROGRESS

THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS


## TURNING RESEARCH INTO RESULTS

1973 – 2023

**JOHNS HOPKINS** is one of America's first research universities and home to the Sidney Kimmel Comprehensive Cancer Center. From its inception, our Cancer Center had full support and cooperation of many departments, including Medicine, Surgery, Pediatrics, Radiology, Engineering, Mathematics and more, with the Department of Oncology serving as the academic home for the planning and operation of the Cancer Center at Johns Hopkins. This interdisciplinary focus on cancer continues to expand, and our diverse team of experts now spans five schools and 35 departments and includes oncologists, radiation oncologists, pathologists, radiologists, population scientists, nurses, engineers, physicists, astronomers, bioethicists and more, working together to combat challenging cancer problems.

JON BILOUS

THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS

1973 50 2023

FIFTY YEARS OF TURNING RESEARCH INTO RESULTS

# P&P

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## EDITOR'S MESSAGE

THIS IS PERSONAL for me, and what you will read inside this 50th anniversary issue of *Promise & Progress* truly is from the heart.

I started my career at the Johns Hopkins Kimmel Cancer Center in 1986 as a new college graduate and a newlywed whose husband was battling stage 4 Hodgkin's lymphoma. I was desperately searching for any bit of information about this disease everyone feared, but until this moment had never touched me personally. There was no internet, no email or social media, and the books about cancer in the library were often outdated soon after they were printed.

I yearned for information that would bring us hope and would help us understand the disease we were fighting. Words like oncology, lymphoma, and metastasis were foreign to me. It was then I decided to put my journalism degree to work and write about cancer with the goal of bringing hope and knowledge to others by writing about cancer in a way everyone could understand.

Those books I got from the library when my husband was diagnosed all told me that he was going to die and quickly. They were published before one of the first great success stories in the War on Cancer—a treatment for Hodgkin's lymphoma that made the almost uniformly fatal cancer curable for nearly 90% of patients.

We were about to embark on an era of tremendous progress in understanding how cancer developed, and as a result, how it could be better treated. I had a front row seat with the privilege of being able to tell these stories of promise and progress.

This has always been more of a mission than a job for me.

Dr. David Ettinger, you asked me often, "When are you going to write the history of this Cancer Center?" I hope what you will read in this issue fulfills that request. I hope it honors the journeys of our patients and families, celebrates the amazing work of the many incredible people of a Cancer Center that is second to none, acknowledges the many donors who made the work possible, and brings some comfort and hope to those who are waging their own battles.

With gratitude,

Valerie Mehl

Valerie Matthews Mehl
*Editor and Sr. Writer*
The Johns Hopkins Kimmel Cancer Center
Office of Public Affairs

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# 1980s

Our researchers begin to crack the cancer code, revealing it as a disease caused by an accumulation of genetic mistakes. This becomes the paradigm for much of modern cancer research, ushering in the age of molecular cancer biology with new gene-targeted therapies and paving the way for gene-based screening tests for cancer.

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# 1990s

The field of epigenetics, characterized by chemical alterations to genes that support the growth and spread of cancer without mutating the DNA, becomes part of mainstream cancer medicine. The Cancer Center's discoveries in genetics and epigenetics are regarded as the most relevant in cancer biology, earning the Center the nickname "Cancer Research Powerhouse."

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# 2000s

Translational, bench-to-bedside research continues to be the hallmark of our Cancer Center. Breakthroughs in research and clinical care are facilitated by two new cancer research buildings, and our Center is renamed in honor of philanthropist **Sidney Kimmel**.

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# 2010s

Cancer care moves primarily to the outpatient setting, and the Kimmel Cancer Center expands, occupying the largest footprint at Johns Hopkins. Breakthroughs in immunotherapy, using drugs and vaccines to unleash the natural killing power of the immune system against cancer, are a key clinical advance. Multidisciplinary Clinics, with specialists from all fields related to cancer care working together, become the standard, leading to improved therapies and survival.

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# 2020s

Entering the digital age of cancer medicine, advanced computer technologies, such as machine learning, are making sense of the billions of data points generated in modern cancer research and medicine to predict the best treatment options for each patient, understand disparities and close gaps, improve cancer detection, and reveal novel ways to combat cancer.

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"The charge to take the foundation they put in place and somehow improve upon it has been my mission as the Center's third director."

*—Bill Nelson*

## FROM THE DIRECTOR

AS ONE OF America's first research universities, it was fitting that Johns Hopkins was also one of the first nationally designated comprehensive cancer centers. In 1973, the university and hospital trustees approved construction of our Cancer Center. From the day we opened the doors, a talented and tenacious group of medical pioneers led the way in understanding cancer through research, developing therapies, attending to the complex needs of patients and disseminating findings to communities everywhere.

The pioneers included George Santos, a leader in bone marrow transplant; Paula Pitha, the center's first laboratory researcher; Linda Arenth, who helped develop the standards of cancer nursing; Mike Colvin, who discovered how the chemotherapy medication cyclophosphamide worked and how to best use it to treat patients; Brigid Leventhal, our first pediatric oncologist; Moody Wharam, who revolutionized radiation therapy; and Ray Lenhard, Donna Cox and David Ettinger, who ensured advances were quickly communicated to oncologists and patients around the globe.

Leading this unique new enterprise — a medical center focused solely on the research and treatment of cancer — was Albert Owens Jr. I am humbled to follow in the footsteps of two of the greatest figures in cancer medicine: Al Owens and Martin Abeloff. Dr. Owens helped found the field of oncology and paved the way for our Cancer Center, and our second director, Martin Abeloff, led the center through a period of rapid growth in physical structures and discovery, with particular attention to the care and comfort of patients and their families.

The charge to take the foundation they put in place and somehow improve upon it has been my mission as the Center's third director.

In this issue, you will read about our remarkable, groundbreaking history and the new pioneers who push the limits of human ingenuity to move cancer research and treatment forward.

Today, the Cancer Center occupies the largest footprint at Johns Hopkins, and our collaborations have grown to span five Johns Hopkins schools and 35 departments. Our experts have mapped the genetic blueprints for cancer, deciphered the epigenome, figured out ways to make the immune system fight cancer, brought proton therapy and other advanced technologies to radiation treatment, eliminated the need for perfect matches in bone marrow transplant, expanded community outreach to encompass diversity and inclusion, and entered the realm of digital cancer medicine. This digital technology has led to new frontiers, such as the microbiome and single cell sequencing, that allow us to look at cancer in completely new ways and uncover how individual cells in and around tumors influence cancer growth, spread, and response to treatment.

As we conquer new challenges, we owe a debt of gratitude to our greatest pioneer, Sidney Kimmel. Without his continuing generosity and historic gift in 2001, none of these advances would be possible. To Mr. Kimmel and the many other donors who advance our understanding of cancer and improve our ability to care for patients, and to our patients and their families, we commit to you an even brighter future. As we celebrate our history, we renew our mission to expand the boundaries of our imaginations until cure is possible for every patient.

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

"As we celebrate our history, we renew our mission to expand the boundaries of our imaginations until cure is possible for every patient."

–BILL NELSON


Loading Dye
5x

## 1970s

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# Building a Cancer Center

## *The Early Years*


OWENS JR.

**IN 1968, WITH** a pH meter and a card table as his primary tools, a young doctor named **Albert Owens Jr.** was launching the field of oncology, and at the same time, advocating for a hospital at Johns Hopkins focused solely on the research and treatment of cancer. It was an entirely novel idea.

In most hospitals, including Johns Hopkins, patients were cared for by a wide variety of clinicians — very few with a special interest or competence in oncology. The means of effecting the course of this relentless disease were very limited, and most patients presented with advanced disease," Owens reflected in 1998.

During the 1960s, a handful of pioneering doctors and researchers at Johns Hopkins espoused a different vision and became academic leaders in the field. Our nurses became leaders in the development of oncology nursing as a recognized specialty, and our Patient and Family Services also earned wide recognition. Owens believed that the group he assembled could change the trajectory of cancer.

"Cancer is a challenging scientific and social problem of great magnitude. Science will show us the way to control these diseases. Addressing a major social problem, I would say, is a quite proper pursuit for any university," he told Johns Hopkins University leadership.

In 1973, the trustees of the university and hospital approved the construction of the Johns Hopkins Oncology Center. The Cancer Center at Johns Hopkins was one of the first approved under the National Cancer Act of 1970, and it quickly earned comprehensive cancer center status and recognition as a Center of Excellence.


SANTOS

Owens' vision was to bring together the best and brightest physicians from across the country. His first recruit was Navy officer **George Santos**, who was performing some of the earliest research of bone marrow transplantation for leukemia. Next, he hired pharmacologist **Michael Colvin**, who was already studying cancer-fighting drugs at the National Cancer Institute.

> "WHAT WE WILL ACCOMPLISH TODAY IS CERTAIN TO BE A PALE REPRESENTATION OF WHAT IS TO COME."
>
> –ALBERT OWENS, JR. 1977

Despite the rising incidence of cancer in the U.S. — nearly 1 million people a year diagnosed and the number climbing — and a daunting lack of solutions to address the growing health concern, Owens faced tremendous opposition. A hospital built around this group of diseases called cancer represented a paradigm shift, and one much of the medical community did not embrace.

"Prior to the 1960s, oncology as a field of study or clinical specialty was not represented in the vast majority of academical medical centers.

Others followed, including **Paula Pitha** and **Nancy** and **Joel Shaper**, who were studying the association between viruses and cancer; leukemia experts **Phil Burke** and **Judy Karp; Brigid Leventhal**, a pediatric oncologist, who was heading the fight for cancer's youngest victims; **Moody Wharam** and **Eva Zinreich**, who were building


WHARAM

a radiation oncology program; and **Linda Arenth** and **Connie Ziegfeld**, who developed our nursing program.

Owens required collaboration, and he created an environment where it flourished. He oversaw the construction of the first Cancer Center building, which opened in 1977, and had research laboratories located adjacent to inpatient units to facilitate research focused on the cancer problems clinicians observed at the bedside. Today, we call this visionary approach translational research. This close collaboration of researchers and clinicians became a hallmark of the Cancer Center.


ZIEGFELD

"From that day on, our mission was to promote research and education in cancer and related disorders with a focus on human disease. We are bound by this mission to provide specialized patient treatment reflecting the latest scientific and technological achievements and develop effective methods of disease detection and prevention," said Owens.

This early work has resulted in history-making progress against cancer. Our researchers have made pioneering contributions in cancer genetics, epigenetics, immunology, drug development, community outreach and disparities, and more, applying discoveries across cancer types to facilitate new cancer prevention and detection strategies and therapies.


DESIGNATING MARYLAND'S BMT PROGRAM (1977)


MICHAEL COLVIN

These discoveries informed the genetic and epigenetic landscape of cancer, revealed PD-L1 expression and mismatch repair deficiency/microsatellite instability as biomarkers for response to immunotherapy, and inspired the development of new therapeutics, such as cancer cell metabolism-targeting drugs, POL-1 inhibitors, FLT3 inhibitors and bispecific antibodies. Our experts led studies that resulted in historic FDA approvals of new cancer drugs.

Although the growth of our clinical and laboratory research led to separate research and clinical buildings, the original translational mission of interdisciplinary collaboration continues, as is reflected by the breadth of these initiatives and collaborations throughout The Johns Hopkins University.

The work of our Cancer Center has lived up to Owens' 1977 prediction. He said, "What we will accomplish today is certain to be a pale representation of what is to come."

### TIMED SEQUENTIAL THERAPY

Leukemia experts **Philip Burke** and **Judy Karp** developed Time Sequential Therapy, using short courses of high-dose anticancer drugs specifically timed to be given when cancer cells were reproducing and more sensitive to drug therapy. This treatment resulted in remissions in 70% of patients with leukemia who were treated.

### HIGH-RISK SCREENING

Our Breast and Ovarian Surveillance Service, run by nurse **Patti Wilcox**, for women with a family history of breast cancer or ovarian cancer, and Polyposis Clinic, run by nurse **Susan Booker**, for those at increased risk for colon cancer, were implemented when screening programs were in their infancy. These served as national models, and were instrumental in facilitating prevention, early detection and early treatment.

### THE NUCLEAR MATRIX

Abnormalities in the shape of the cancer cell nucleus are a hallmark of cancer diagnosis. **Donald Coffey** discovered that a superstructure within the cell, which he named the nuclear matrix, was responsible for the misshaped nucleus. The nuclear matrix, he and his research team learned, was the site for DNA replication and shed the first light on the cellular changes that caused normal cells to turn into cancer cells.

### HEMAPHERESIS

The Center's hemapheresis program began as a second-year fellowship project of senior faculty member **Hayden Braine** to provide white cell support to patients suffering infections. Later, it provided platelet support to patients undergoing chemotherapy, bone marrow processing and purification, as well as administration of an unrelated bone marrow donor registry.

### THE CANCER INFORMATION SERVICE

The Johns Hopkins Cancer Information Service (CIS), opened in 1976 and headed by **Donna Cox**, responded to telephone inquiries from patients, families, health professionals and the public. Our CIS was contracted by the National Cancer Institute to provide information on cancer clinical trials, treatment centers, the latest cancer research and more.

### ANTICIPATORY NAUSEA

Nausea and vomiting after chemotherapy were common side effects of cancer treatment, but some patients developed these symptoms before receiving treatment. Termed anticipatory nausea and vomiting, symptoms were triggered by treatment-related stimuli, such as intravenous needles and clinic odors. Anticipatory symptoms most commonly occurred in patients who suffered post-chemotherapy nausea and vomiting. Medical oncologists **John Fetting** and **Stephen Staal** conducted a study to uncover the mechanisms causing the anticipatory symptoms and to study the drug clonidine for its ability to target the mechanism and reduce symptoms.

## *A Tradition of Excellence and Innovation*

# 50 years of cancer nursing

CANCER CENTER nurses had a forward-thinking vision from the time the Center opened its doors. The treatment of patients with cancer required a level of care unique to the emerging field, in which many patients were critically ill, new drugs were being tried and bench-to-bedside research was central. Nurses helped drive improvements in patient care, sharing information about what they were seeing at the bedside. These observations inspired research that advanced patient care and improved quality of life.

Although many things have changed in cancer medicine at Johns Hopkins during the past 50 years, this high level of care and innovation has remained constant. Our nursing program has been a model for the nation, with nurses and nursing students frequently traveling to our center to observe and train with our nurses. Our nurses have played an important leadership role in setting standards of cancer care through the Oncology Nursing Society and National Comprehensive Cancer Network.

These standards of excellence were set with the Cancer Center's first nursing director, **Linda Arenth**.

From the onset, the Center's philosophy was to provide the best bedside nursing care. Special emphasis was placed on the humanistic aspects of patient care.

Cancer Center nurses were key to the development of new treatments, and the drug development program helped establish the role of research nurses in the fight against cancer. Early on, nurses, including **Barbara Vito Clarke** and **Barbara Lubeijko**, became the first to manage clinical trials of new cancer drugs, recalls Ross Donehower, who helped establish the Center's drug discovery program. To this day, when a cancer drug is given for the first time, it is nurses giving the drug and monitoring for side effects and toxicities.


ARENTH

**Sharon Krumm**, who joined the Cancer Center as nursing director in 1988, along with the assistant nursing director, **Connie Ziegfeld**, established the Center's internationally recognized nursing research program in 1985, one of the first in the country.


KRUMM

Nursing excellence was formally recognized in 2003 when the Center first earned Magnet status, a designation Kimmel nurses have continually achieved ever since.

"The level of purposeful care has never changed. It is the ongoing theme of the oncology nurse," says **Donna Berizzi**, current director of oncology nursing. "The desire to innovate is always in the front of our minds. This is what is special about oncology nursing."


BERIZZI

A major advance — which remains one of the most innovative clinical endeavors in cancer medicine — was the nurse-run and developed Inpatient/Outpatient bone marrow transplant clinic (IPOP). Developed by nurse managers **Jane Shivnan** and **Gina Szymanski**, it moved one of the most intensive cancer therapies, which typically required a month or more of inpatient care, to a largely outpatient therapy. IPOP, which allows patients to recover at home or, if they live too far from Johns Hopkins, in apartment-like suites in our Hackerman-Patz Patient and Family Pavilion, improved care while lowering costs, and continues to be a national model.


SHIVNAN

"SUCH INNOVATIONS CAN ONLY TAKE PLACE WHEN A HOSPITAL IS STAFFED BY PROFESSIONAL AND INTELLIGENT NURSES," SAYS KRUMM, WHO WAS NURSING DIRECTOR WHEN IPOP OPENED.

"THE LEVEL OF PURPOSEFUL CARE HAS NEVER CHANGED. IT IS THE ONGOING THEME OF THE ONCOLOGY NURSE."

Known for her forward-thinking vision, Arenth helped establish the standards for oncology nursing care that continue to guide practices today. Patients who came to the Cancer Center were each assigned a primary nurse responsible for overseeing their care. Arenth developed a unique patient acuity system, which provided a formula for determining how much nursing time patients would need based on the severity of their cancer.

Cancer Center nurses also designed the first cancer-specific chemotherapy infusion pump. Our center was the first at Johns Hopkins to recruit a psychiatric liaison nurse and nurse surgery researcher, which was virtually unheard of at the time. The inclusion of social work, counseling and other patient and family services into the treatment plan was also among the cancer care improvements forged by our nursing team.

Cancer Center nurses are successfully treating patients in the outpatient setting whom most National Cancer Institute-designated cancer

centers care for as inpatients, says Berizzi. The skill and training of Center nurses across the inpatient and outpatient spectrum of care allows nurses to be fluid and address the changing needs of patients, she says.

The shift from inpatient to outpatient care was one of the most significant advances made in cancer care, and Kimmel Cancer Center nurses helped lead this progress. Almost 80% of patients were treated as inpatients in 1977 when our Cancer Center opened, says Center Director **William Nelson**. Today, the majority of cancer patients are treated in outpatient clinics.

"Patients do not want to be in the hospital for a minute longer than they have to be. They want to be at home, and we want to help them be at home. We have the capacity to admit them if we need to, but we have built the infrastructure with our Viragh Outpatient Cancer Building and clinics for urgent care and ambulatory care to address every patient need. Our rooms are equipped for just about anything," says Berizzi. "Things we never imagined before, we are imagining and following through on."

This was never more evident than during the COVID-19 pandemic. Within days of the outbreak, **Gina Szymanski**, interim director of nursing and incident commander, and **MiKaela Olsen**, clinical nurse specialist and operations chief of the Kimmel Cancer Center's COVID-19 Command Center, opened the Curbside Shot Clinic — a drive-up treatment delivery system — for outpatients and a special urgent care bio clinic for patients with cancer who were infected with the coronavirus.


OLSEN

History is important, and IPOP taught us that we can treat very sick patients as outpatients," said Szymanski. "We don't wing it, and we don't place artificial limits on ourselves. What we've done to help our patients during COVID-19 is a continuation of what we've always done. We place the right patient in the right care setting with the right care provider and implement safety principles to take what we've traditionally done one way to meet patients where they are now."

In a typical week, about 400 patients visit the Kimmel Cancer Center. One important service our nurses provide is guidance and education for cancer center patients and their caregivers at home, so they know when and how to take their medicines and how to recognize symptoms that require medical attention.

When they need that care, an advanced practice nurse-run urgent care clinic is available. The clinic, which opened in 2013, was developed by the nursing team and run by nurse practitioners.

"Advanced practice nurses make solid, research evidence-based decisions for care, conferring with the patient's oncologist. These nurses are a lifeline for our patients," says Berizzi. This is one of the biggest changes that has occurred over the history of the Cancer Center, she says. "In 1973, there weren't many nurse practitioners. Today, advanced practice nurses are major contributors to patient care," she says. "We have nurse-driven protocols, nurses have a seat at the table when important patient care decisions are made. We are the voice for the needs of patients and families."

MAGNET RECOGNIZED
AMERICAN NURSES CREDENTIALING CENTER

### MILESTONES IN KIMMEL CANCER CENTER NURSING

**1977:** Nursing develops unique patient acuity system

**1978:** Nurse-run screening clinic for women at high risk for breast and ovarian cancers is started

**1983:** **Jennifer L. Brager** Memorial Award for Cancer Research is established to honor research by nurses and other nonphysicians

**1984:** Cancer pain team is organized

**1985:** The nursing research program, one of the first in the country, is started

**1989:** Nurses design the chemotherapy infusion pump

**1992:** Nursing-led research study of pain, fatigue and sleep alterations in patients with cancer is initiated

**1995:** IPOP center opens, moving bone marrow transplant to a largely outpatient procedure

**1998:** Oncology Nursing Society announces new awards given in honor of Kimmel Cancer Center nursing leaders **Linda Arenth, Victoria Mock** and **Connie Ziegfeld**

**2003:** Johns Hopkins nursing earns the highest credentialing honor, Magnet status

**2013:** Nursing-directed urgent care clinic opens

**2020:** Drive up shot clinic and bio-contained COVID-19 unit is established

*Bone Marrow Transplant*

# A Half-Century of Translational Team Science

SOME OF THE earliest research at the Kimmel Cancer Center was in bone marrow transplant. In fact, the first human bone marrow transplant at Johns Hopkins occurred in 1968, five years before the formal approval of a cancer center in 1973.

By the time **George Santos** joined the Cancer Center as the first recruit of its director, **Albert Owens**, he had been studying bone marrow transplantation as a Navy officer at the U.S. Naval Radiological Defense Laboratory.

While studying the effects of nuclear blasts in research models, Santos observed that high doses of radiation destroyed the bone marrow of mice, but if mice received a transplant of bone marrow from a healthy mouse, the donor marrow took over and the mouse could survive.

This led to the idea of bone marrow transplants in humans — killing cancer-filled marrow and replacing it with donor marrow.

Conventional wisdom said it would not work, but true to form, researchers in the Cancer Center, led by Santos, were undeterred.

"I recall his tenacity. He was able to inspire people — his staff and patients — to have faith and belief, inch by inch, that they could make progress," said **Georgia Vogelsang**, professor emeritus of oncology and a former trainee of Santos.

Santos, who was director of the Cancer Center's bone marrow transplant program from 1968 to 1994, was a pioneer in the true sense of the word. His early animal studies became the blueprints for advances in bone marrow transplant and other cancer therapies.

## BONE MARROW

Bone marrow — the spongey substance deep within our bones — is the factory for all blood and immune cells. Without it, we cannot survive. Diseases, such as leukemia and lymphoma, represent a production failure in the bone marrow factory, where an overabundance of abnormal cells overwhelm and crowd out healthy blood and immune cells.

"The only way to kill the patient's cancer is to kill the patient's own bone marrow," Santos explained.

Patients with leukemia were the first to receive bone marrow transplants at Johns Hopkins. It was personal for Santos. Photographs of many of the patients he treated throughout his career adorned the walls of his office. The photographs tell the story of a translational researcher, whose pioneering research was driven by the desire to help patients desperate to survive.

## GVHD ATTACKS

In the early days, it was commonly said that bone marrow transplantation was as bad — maybe even worse — than the disease. The reason for this characterization was Santos' greatest foe, a complication known as graft versus host disease (GVHD).

In GVHD, the immune cells within the donor bone marrow did not recognize its new host and waged a vicious attack against vital tissues and organs that could be as lethal as the cancer.

In fact, it was a rotation on the bone marrow transplant unit, where he witnessed firsthand the power of the immune reaction, that lead **Drew Pardoll,** director of the Kimmel Cancer Center's Bloomberg~Kimmel Institute for Cancer Immunotherapy, to focus on cancer immunology research.

GVHD often had devastating consequences. Patients were hospitalized for months, and many died. The risk of graft rejection — that no bone marrow would grow back in the patient — and GVHD made bone marrow transplant one of the most intensive and riskiest medical therapies of its time. Still, patients who were candidates for bone marrow transplants had blood cancers that were certain to kill them. A bone marrow transplant might not be successful, but at least it offered some chance of survival.

VOGELSANG

## OVERCOMING GVHD

Some of the first major progress made by Cancer Center bone marrow transplantation researchers was in learning how to manage GVHD and even how to manipulate it to help fight the cancer. It also gave rise to a type of drug therapy that could reset the bone marrow factory and take the teeth out of GVHD.

This important advance stemmed from pioneering progress by Santos, combining high doses of the drugs busulfan and cyclophosphamide to replace total body radiation and its dangerous toxicities as the method for killing the patient's diseased bone marrow before transplanting it with healthy donor marrow.

Related studies by Cancer Center investigators **John Hilton** and **Michael Colvin** deciphered how cyclophosphamide worked against cancer and paved the way for the drug regimen to become the worldwide standard.

As is often the case with Cancer Center investigators, they took a gamble in pursuit of better outcomes for patients. Researchers at other cancer centers were following similar paths of discovery, but Johns Hopkins experts, inspired by Santos, often sought less conventional approaches to advancing care.

"A whole generation of Hopkins-trained translational scientists looked to George as their intellectual and spiritual mentor," recalls current bone marrow transplant director, **Rick Jones**, who says Santos embraced the concept of translational research ahead of other scientists. "George was showing the Hopkins community how to do this long before it was in vogue," he says.


JONES

This important research also hinted at the usefulness of using cyclophosphamide after bone marrow transplant to control the severity of GVHD.

Until the early 2000s, researchers believed that donor marrow must come from a "perfect match," a family member who had matching immune system components. This, it seemed at the time, was the only way to make the immune cells contained in the donated marrow see its new host — the patient — as self, and prevent severe cases of GVHD. However, such a match could only be found for about half of patients and was a limiting factor in bone marrow transplant being a treatment option for many who could benefit, particularly underserved minority patients. The National Marrow Donor Program was established in 1986 to match unrelated donors to patients who could not find a donor in their families, but many patients were left without donors.

**Cyclophosphamide worked against cancer and paved the way for the drug regimen to become the worldwide standard.**

## HALF-MATCHED

The portfolio of research expanded, and combined, it led to a paradigm shift — one that overcame the need for a fully matched donor and made bone marrow transplant possible for all patients who needed the treatment.


FUCHS

For decades, GVHD prevented bone marrow transplants from being performed on patients who did not have a fully matching donor.

Pioneering discoveries led by Jones and his Kimmel Cancer Center colleagues **Ephraim Fuchs** and **Leo Luznik** changed everything, and against all prevailing thought in the field, made it possible for almost any patient to receive a transplant.


LUZNIK

Clinical studies showed that when immune cells, called T cells, were removed from the transplant, 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

### MILESTONES IN BONE MARROW TRANSPLANTATION AND HEMATOLOGIC MALIGNANCIES

**1968:** Cancer Center performs first bone marrow transplant

**1977:** Cyclophosphamide and busulfan become alternative to total body radiation as preparative regimen, eventually overtaking it as the most commonly used regimen

**1980:** Post-transplant cyclophosphamide found to prevent GVHD in mice and rats

**1981:** Acyclovir proven effective against common post-transplant viral infection

**1984:** Discovery of CD34 antibody makes it possible to isolate and collect bone marrow stem cells

**1986:** The cancer cell-purging drug 4-HC makes autologous (self-donor) bone marrow transplants possible

**1989:** Combining AZT with bone marrow transplant clears HIV in a patient with AIDS, and the first umbilical cord blood transplant for leukemia is performed

**1990:** Mild GVHD is found to boost disease-free survival

**1993:** Elutriation, which removes T cells while preserving stem cells, reduces bone marrow transplant complications and hospital stays

**1994:** Epstein Barr-Virus is used to mobilize the immune system against cancer cells, and a Center-developed technique shows that almost all AIDS-related brain lymphomas, about half of Hodgkin's lymphomas and all nasopharyngeal cancers contain the virus

**1995:** Nurse-developed and run Inpatient/Outpatient (IPOP) bone marrow transplant center opens, and the pediatric bone marrow transplant center opens

An enzyme called ALDH protects blood stem cells against cyclophosphamide

**2000:** First half-matched bone marrow transplant with post-transplant cyclophosphamide

**2002:** High-dose cyclophosphamide shown to successfully treat severe aplastic anemia and other noncancer diseases

**2014:** Half-identical bone marrow transplant proven as safe and effective as fully matched bone marrow transplants

**2023:** Based on 50 years of research, post-transplant cyclophosphamide becomes the new standard of care for GVHD, and is reported in the *New England Journal of Medicine*.

the most severe cases of GVHD yet a large enough number to allow the immune system to keep the cancer from coming back.

It turns out that cyclophosphamide, the same drug used to treat patients before bone marrow transplant, could be given post-transplant to limit GVHD without hampering the T cell's 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.


BRODSKY

Some of the first clues to how cyclophosphamide works began in the 1980s by Michael Colvin and **Alan Hess**, and were expanded later by Fuchs, Luznik, Jones, **Robert Brodsky** and **Javier Bolaños Meade.** They found that cyclophosphamide kills all of the donor's transplanted bone marrow cells except for stem cells containing high levels of an enzyme called aldehyde dehydrogenase (ALDH). The ALDH-laden stem cells evade the toxic effects of cyclophosphamide and rebuild the patient's immune system.

### ANOTHER BREAKTHROUGH

This breakthrough approach meant almost all parents, siblings and children of patients — and sometimes even aunts and uncles, nieces and nephews, half-siblings, and grandparents or grandchildren — could safely serve as donors.

## Kimmel Cancer Center experts have performed over 2,000 half-matched transplants for adult and pediatric leukemia and lymphoma.

Since developing the treatment more than two decades ago, Kimmel Cancer Center experts have performed over 2,000 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 anemia 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.

"GVHD limited the ability to do mismatched transplants in the past, but today, it is so well-managed — in large part due to cyclophosphamide — that nearly 95% or more of patients survive transplant, providing results in unmatched transplants that are the same or better than matched transplants," says Jones, director of the Kimmel Cancer Center's bone marrow transplant program. "It all started with Al Owens and George Santos 50 years ago."

## IPOP Makes History

The **inpatient/outpatient (IPOP) bone marrow transplantation program** was one of the Center's most innovative clinical endeavors of the time, moving one of oncology's most intensive therapies to a largely outpatient procedure.

Launched in 1995, IPOP was developed by then-bone marrow transplant nurse managers **Jane Shivnan** and **Gina Szymanski,** along with **Georgia Vogelsang** and **Rick Jones**, and was the first of its kind to perform allogeneic (donor) transplants in the country.

Patients participating in many different bone marrow transplant or research protocols come to the IPOP clinic each day for care and spend their nights in their own homes, if they live within an hour of the Cancer Center, or in residential living facilities, such as suites in our Hackerman-Patz Patient and Family Pavilion. A family member or close friend is extensively trained by IPOP nurses to serve as a personal caregiver. If patients have complications like fevers or graft-versus-host disease, they are admitted to the Cancer Center. As they recover, they move back to the outpatient clinic.

Before IPOP, transplant patients spent, on average, 47 days as inpatients. With IPOP, most patients spend less than a week as an inpatient.

"To think we could move these patients to outpatient was mind-blowing," recalls **Beth Onners**, who was a critical care nurse on the bone marrow transplant unit when IPOP opened. "Jane and Gina led the way, and we did it. It worked, and patients loved being able to get out of the hospital and in a personal space with their loved ones."

IPOP was more cost effective than standard inpatient hospital care, and it improved the quality of care.

Among other improvements, it streamlined care by allowing transplant patients to see a single team of specialists throughout their visit. Before IPOP, patients saw one team as inpatients and a different team as outpatients.

"We wanted to add some normalcy to our patients' lives at such a difficult time," says Szymanski, nurse manager for the IPOP clinic. "When we can keep patients out of the hospital with family or people they know in nearby facilities, they do so much better in terms of quality of life and health and wellness measures."

# ADVANCES | BONE MARROW TRANSPLANTS

### ELUTRIATION TO FIGHT GVHD

To stave off graft-versus-host disease (GVHD), a major complication of bone marrow transplant, researchers developed and tried several innovative approaches.

The T cells were seen as the primary culprit in launching the attack against the patient, and one strategy involved syphoning off T cells using a huge centrifuge. The process, called *elutriation*, was developed by **Stephen Noga** and **Albert Donnenberg**. They described it as simple physics. As the donor marrow was spun through a large centrifuge, the cells lined up according to size. Mature T cells were smaller than bone marrow stem cells, and were separated from the rest of the bone marrow. Elutriation made it possible to get the marrow 99.9% clean of T cells or allow for the possibility to leave some behind. Without the T cells, GVHD could be held in check, but researchers soon learned that removing all T cells often allowed the cancer to return, with no immune cells available to mop up rogue cancer cells. Leaving a few T cells behind resulted in a mild and manageable case of GVHD that also had an anticancer effect.

### FIGHTING DEADLY VIRUSES

In 1981, researchers, led by **Rein Saral**, showed the drug acyclovir was effective against herpes simplex virus infections and shingles, common infections in bone marrow transplant patients. The groundbreaking discovery was published in the prestigious *New England Journal of Medicine*.

The bone marrow transplant team also virtually eliminated deadly cytomegalovirus infection by checking for the virus in the blood of the patient and donor. If not found, there is no risk. If they find it, they can treat it early.

### A WORD OF GRATITUDE

Co-leaders **Rick Jones** and **Richard Ambinder** recognize the contributions of the many researchers who advanced the research in bone marrow transplant and hematologic malignancies, including **Bill Burns**, **Mike Graham**, **Kent Holland**, **Carol Ann Huff**, **Herb Kaiser**, **Bill Matsui**, **Scott Rowley**, **Doug Smith**, **Rob Stuart**, J**ohn Wagner**, **John Wingard**, and **Andy Yeager**.

### PEDIATRIC BONE MARROW TRANSPLANT

Pediatric oncologists **Kenneth Cooke**, **Heather Symons** and **Allen Chen** are applying the advances in half-matched bone marrow transplantation to improve the care of pediatric patients.

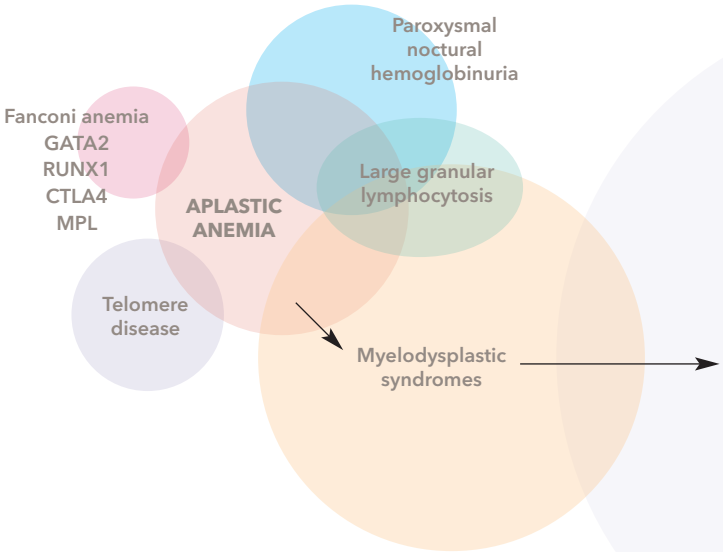
Cooke, Symons and colleagues perform about 50 pediatric bone marrow transplants each year; about 60% of them are with half-matched donors, and about one-third are to treat noncancer diseases.

"At the Kimmel Cancer Center, we are always working to advance and improve care," says Symons.

The improvement in safety that allows them to offer transplants to patients who do not have a fully matching donor has led to tremendous growth in the pediatric oncology bone marrow transplant program. Like findings in adults, their studies have shown that transplant-related toxicities and complications, such as graft versus host disease, are the same for patients with half-matched donors as those with fully matched donors.

### TIME ON FIRE

Actor **Evan Handle**r presented his one-man play *Time on Fire* to the faculty and staff of the Kimmel Cancer Center in 1998. His book by the same name, published in 1996, chronicles his journey through diagnosis and treatment for leukemia, including his bone marrow transplant at Johns Hopkins. He wrote in his book, "From the moment I checked into Johns Hopkins until the moment I left; from the men and women who cleaned my room each day to the man who helped invent bone marrow transplantation, I got the impression that nothing was more important than my getting well."




# Lessons From Cancer History

## *Old research leads to a new treatment*

IN 1996, A Johns Hopkins investigator uncovered and reopened a 30-year-old clinical protocol that offered the promise of a cure for patients with the rare and deadly immune disorder known as severe aplastic anemia (SAA).

The new treatment was based on one developed three decades earlier by one of the first Cancer Center investigators, **Lyle Sensenbrenner.**

In the early 1970s, Sensenbrenner gave 10 SAA patients with no other treatment options very high doses of the immune-suppressing drug cyclophosphamide.

Then, in 1987, Sensenbrenner left Johns Hopkins. Since Sensenbrenner was the sole member of the SAA team, no one kept track of his 10 patients until hematologist **Robert Brodsky** came to town in 1996. On the recommendation of **Richard Jones**, the Center's bone marrow transplant program director and his mentor, Brodsky looked back to see what happened to those 10 patients.

For Brodsky, this meant looking 30 years back in time. Sensenbrenner was among the first to study bone marrow transplantation, a therapy in which the diseased bone marrow is destroyed with high doses of the drug cyclophosphamide and then replaced with marrow from a healthy donor, as treatment for SAA. For patients who could find donors whose immune system matched their own, and were healthy enough to undergo this rigorous therapy, bone marrow transplant offered hope for a cure and became the treatment of choice for SAA.

However, Sensenbrenner found — and documented in his files — that some of the patients seemed to recover some of their own marrow function, not that of their donors. In a last-ditch effort to save the lives of 10 young patients who were not candidates for bone marrow transplant and had exhausted all other treatment options, Sensenbrenner followed his gut instinct and treated them with the same high dose of cyclophosphamide used for transplant but without the transplant.

When following up on these early studies, Brodsky learned that seven of the patients had been cured of their aplastic anemia by the high dose of cyclophosphamide, and six were still alive up to two decades later.

Brodsky wondered how that could be. Immunosuppressant drugs like cyclophosphamide had been used to treat SAA for years, and although they worked for a time, they had never been successful in curing patients. Sooner or later, the disease always came back. Something must have been lost in the translation between 1970 and now, he thought.

"Maybe diagnoses were different then, or there was a subtle drug difference. I had to make sure the treatment really worked," says Brodsky.

Brodsky returned to his laboratory to figure out how the drug worked against the disease. He learned that high doses were strong enough to wipe out diseased blood and immune cells, but did not affect bone marrow stem cells, immature cells that differentiate or change to form all new blood cells — red cells, white cells and platelets. The high doses of cyclophosphamide were enough to kill off abnormal cells, giving the stem cells a second chance to repopulate the bone marrow with healthy, normal blood cells. Now, it was time for Brodsky to test his theory on a new set of patients diagnosed with SAA.

SAA is a characterized by complete failure of the bone marrow factory, which stops producing blood cells. It is a rare disease, striking about 4 in 1 million adults and 2 in 1 million children each year.

Following Sensenbrenner's original protocol to the "T," Brodsky opened a new study of high-dose cyclophosphamide and began seeing similar results. His next step was to figure out why.

The key was the high dose, he found. The doses of cyclophosphamide were high enough to wipe out the abnormal bone marrow cells, but the stem cells — the factory for all types of blood cells — were resistant to the therapy.

"There is no dose high enough to kill a stem cell," says Brodsky. Within their basic biology is an enzyme that makes them untouchable by cyclophosphamide. "The treatment reprogrammed the immune system, wiping out the abnormal cells and allowing the stem cells to rebuild a new, disease-free immune system," he explains.

Sensenbrenner and Brodsky's high-dose cyclophosphamide has turned out to work in other, more common diseases of the immune system, including severe, treatment-resistant myasthenia gravis and scleroderma.

"Efforts to fight SAA in the 1970s with the development of bone marrow transplantation led to major advances in the treatment of cancers like leukemia and lymphoma," says Brodsky. "Now, high-dose cyclophosphamide has a similar legacy."

*Rich's Story*

# Like Father, Like Son

*A three-decade journey that tested and inspired medical research*

RICH JR., WITH HIS FATHER, RICH SR.


Your New Medicines

RICH JR., WITH HIS FATHER, RICH SR.

There are likely few people who understand the value of cancer research as well as Rich. His life was saved three times by discoveries in bone marrow transplantation that spanned three decades.

The pain — and some nudging from his concerned wife, Diane — finally led him to go to a local community hospital. Imaging and diagnostic tests revealed non-Hodgkin's lymphoma, a cancer of the lymphocytes, a type of white blood cell. The lymph system is part of the immune system, and runs throughout the body to help fight infection.

"Cancer was the last thing on my mind. I was shocked," recalls Rich, who was 39 at the time. His thoughts turned to his wife and two sons, one in high school and the other in middle school. He wondered if he would live to see his sons graduate from high school.

When chemotherapy and radiation therapy failed to eliminate the cancer, he somehow remained hopeful.

"I don't scare easy. If the Lord wants me, I'll go," he says. However, he wasn't giving up without a fight.

His doctor recommended he go to the Johns Hopkins Kimmel Cancer Center to explore clinical trials, research treatments aimed at advancing and improving cancer therapies, particularly for patients like Rich, whose cancers do not respond to standard treatments.

At Johns Hopkins, he met with **Richard Ambinder,** co-director of the Cancer Center's hematologic malignancies (blood and bone marrow cancers) and bone marrow transplant program.

Ambinder recommended a new type of treatment called an autologous (self-donor) bone marrow transplant.


AMBINDER

A portion of Rich's bone marrow — the factory that was producing the cancerous lymphocytes — would be harvested and treated with drugs to purge it of cancer cells. After treatment with high doses of a cancer cell-killing drug called cyclophosphamide to destroy his remaining cancer-filled bone marrow, his cleansed marrow would be returned by infusion. Free of cancer cells, the bone marrow cells could go to work repopulating a normal and healthy bone marrow.

It was a long recovery. He remained in the hospital for three months, but in time he was back to playing basketball and the other activities he enjoyed.

Ambinder and team kept a close eye on him, but it seemed as though Rich had overcome the cancer.

As the years went by, Rich and Diane were less focused on cancer and more on their growing sons and their activities. His goal of being there to see them grow up became a reality.

Then, after eight years of remaining cancer-free, Rich learned in 2000 that the cancer was back. He and Diane went back to see Ambinder.

"For me, the glass is always half full. My wife, family, friends and prayer were getting me through. All those things are important," he says. "I asked Dr. Ambinder if there were any treatments he could offer me."

What Rich and Diane didn't know was that during the eight years Rich's cancer was in remission, bone marrow transplant researchers were developing a new kind of bone marrow transplant.

Pioneered at the Kimmel Cancer Center, it was a type of bone marrow transplant called an allogeneic haploidentical bone marrow transplant.

The jargony words describe a new type of transplant developed with patients like Rich in mind, who do not have identically matching bone marrow donors. Many patients who needed bone marrow transplants could not get them, because they did not have bone marrow donors — typically found among siblings or less frequently from an unrelated bone marrow donor registry.

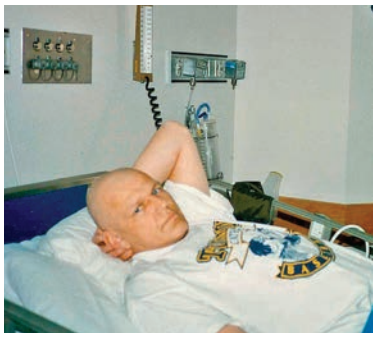
The "matching" part of the bone marrow transplant is important because it helps prevent a complication known as graft versus host disease (GVHD). In GVHD, the donor marrow — and the immune system contained within it — doesn't recognize its new host, the patient. Instead, the donated immune system sees the patient as a foreign invader, much like a virus or bacteria, and unleashes an often-lethal attack against vital tissue and organs.

Since the start of the Cancer Center in 1973, researchers had been studying ways to overcome GVHD, and one of their major goals was to learn how to control it well enough to make bone marrow transplant available to every patient who needed the treatment.

Ongoing research at the Cancer Center found that cyclophosphamide, the same drug given to destroy the cancer-filled bone marrow before transplant, could be given after transplant to stave off serious cases of GVHD. Pioneering studies at the Center showed the drug did not harm blood stem cells, so they could repopulate healthy blood cells and bone marrow while also suppressing the donor immune system from attacking its new host.

**There are likely few people who understand the value of cancer research as well as Rich. His life was saved three times by discoveries in bone marrow transplantation that spanned three decades.**

This monumental breakthrough, the culmination of decades of research, had the potential to revolutionize bone marrow transplant, but Ambinder was honest with Rich and Diane. The new treatment was unique to the Kimmel Cancer Center, and at that time, had only been studied in animal models. It was such a radical approach, many other cancer centers were reluctant to believe it could work. Bone marrow transplants without fully matching donors were simply unheard of at the time.



At a crossroads and battling lymphoma for the second time, the weight of choosing which treatment to pursue was overwhelming. Rich and Diane had done their homework and reached out to several other major cancer centers throughout the country. Experts at these centers had different recommendations.

"We could not decide," remembers Diane.

A few months passed as they contemplated their options. Still unsure which way to go, they woke up one morning to the news that The Johns Hopkins Hospital had been ranked #1 in the U.S. by *U.S. News and World Report*.

The decision was sealed. "It was a no-brainer," says Rich. "You look for that miracle, and we felt like that was it."

They went back to Ambinder and asked if the treatment he told them about was still available.

Ambinder explained to them that the ability to control GVHD meant that less-than-perfect matches could now be safely used. Since children are always half-matches to their parents, Rich's oldest son, Rich Jr., healthy and now 25 years old, could be his bone marrow donor.

If the cancer had come back just a year earlier, this treatment would not have been an option, but now Rich was making history among the first to receive the Kimmel Cancer Center-pioneered half-matched transplant.

Today, hundreds of half-identical bone marrow transplants have been safely performed at the Kimmel Cancer Center, and the approach is now widely accepted, but in 2000, the researchers had just begun to move it from the laboratory to patients.

This time, Rich also benefited from another advance unique to the Kimmel Cancer Center. A nurse-developed and run inpatient/outpatient center opened in 1995, just a few years after his first bone marrow transplant. It moved bone marrow transplantation to a largely outpatient treatment. Rather than spending three months in the hospital as he did in 1991, Rich could live at home in the suburbs of Baltimore with his wife and family and return to the Cancer Center for care as needed.

"I breezed through; no issues." That's how Rich recalls his half-matched bone marrow transplant. Although, wife Diane is quick to point out that he never complains.

A few years went by following the half-matched transplant, with Rich Sr. returning to the Cancer Center for regular checkups to monitor for any sign the cancer had returned.

"You hold your breath," says Diane. Every cough, ache or pain causes concern. Then, they heard the words they prayed for from Ambinder: "We think you're cured."

For several years, things returned to normal.

Then, in 2019, Rich Sr. was faced with another serious medical condition. This time it wasn't cancer. Instead, he learned his kidneys were failing.

Rich Jr., who donated his bone marrow — and as a result, his immune system — to his father was, therefore, a perfect match. With the bone marrow transplant, father and son now had the same bone marrow, so their immune systems were identical.

Ambinder suggested they consider a kidney transplant, and Rich Jr. offered a kidney without hesitation, but Rich Sr. and Diane would not even consider the idea.

They didn't know if Rich Sr. would even be approved for a kidney transplant given his medical history, but, if he was, they agreed their son as the kidney donor was not an option.

It was hard enough to watch her husband, who overcame cancer twice, face another medical challenge. Diane could not bear the thought of her son, a husband and father of three daughters, putting himself at risk.

Rich Sr. agreed. "Our minds were made up," he says.

Instead, Rich Sr. began dialysis, a process that uses a machine to do the job of the kidneys, filtering the blood. He was referred to the solid organ transplant team at Johns Hopkins, and was approved for a kidney transplant, pending a kidney becoming available.

Rich Jr. and his wife, Cynthia, were not taking no for an answer, however. They had done their research, and paid a visit to Rich Sr. and Diane, prepared to persuade.

"They would not let it go," Diane recalls. "We didn't know what to do. I was worried about my husband and my son."

Encouraged by the information Rich Jr. and Cynthia presented, showing risks of kidney donation to be extremely low — a fraction of a percent — combined with the realization that Rich Sr.'s health was declining, they were now open to the kidney transplant with their son as the donor.

With the ups and downs of Rich Sr.'s long journey, he

and Diane knew to expect the unexpected, but even they could not have anticipated the unimaginable COVID-19 pandemic that was now gripping the U.S.

With the kidney transplant set for the Spring of 2020 — the height of the COVID pandemic — Rich Sr. and Jr. sequestered themselves at home. Despite taking every precaution, Rich Sr. became sick with a respiratory illness. It wasn't COVID, but he became so ill, Diane had to call an ambulance.

Rich Sr. was taken to a community hospital near their home. His doctors told Diane that her husband's heart was functioning at only 20%. He went into cardiac arrest three times during his hospitalization, and Diane begged the doctors and nurses to let her stay with him. COVID restrictions prevented it, however, and Diane returned to their home.

Hours later, she received a call from the hospital to tell her that Rich Sr. fell and fractured his leg. It was a spiral fracture, wrapping around his thigh bone like a corkscrew. The injury required surgery, but his heart was too weak to endure the operation. The best doctors could do was to immobilize the leg with a cast that went from his foot to his hip. Worse still, his kidney transplant was postponed until his broken leg healed and his heart became stronger.

Finally, after treatment for a urinary tract infection, which was likely the cause of the fluid buildup that led to his heart issues, and after 10 days in a physical rehabilitation center, Rich began to regain his strength. For the next nine months, however, he remained on dialysis as his leg healed.

In early November 2021, Rich Sr. was cleared for the transplant. Rich Jr. had also completed full medical testing, and was cleared to be his donor.

A date for the kidney transplant was set: Jan. 5, 2022. As the date approached, the family considered everything that could interfere with transplant. Their past experience had shown them how quickly things could change. The possibility of a snowstorm seemed to be the most likely obstacle. Rich Jr. called Johns Hopkins and was reassured that there were steps in place to ensure medical care continued, even amid a snowstorm. "If you can get there, we'll be here," he was told.

Despite the family's preparations and precautions, Rich Jr. tested positive for COVID, leading to another 60-day delay for the transplant surgery. The waiting was grueling for the family, who had already endured so much.

At last, on April 12, 2022, Niraj Desai, director of kidney and pancreas transplant surgery at Johns Hopkins, performed the kidney transplant. With a healthy, new kidney, Rich Sr. began to feel an improvement almost immediately. For Rich Jr., it took a bit longer to recover as his healthy body adjusted to functioning with one kidney.

Rich Sr. refused to leave the hospital before his son, and Diane remained by both of their sides, facing an almost unthinkable burden of seeing her husband and son recover from surgery.

"I was so scared, but the nurses were comforting. They got me through it," she says.

Finally, things were moving in a more positive direction, and now Rich Sr. was not only benefiting from decades of research, but he was the inspiration for a new discovery.

Most patients who receive organ transplants must remain on immune-suppressing drugs for the remainder of their lives to prevent organ rejection. However, since he and Rich Jr. had identical immune systems as a result of the bone marrow transplant, Rich Sr. did not require anti-rejection therapy.

*Bone marrow transplants have become so safe that, today, patients who require a solid organ transplant and do not have cancer may receive a bone marrow transplant solely to prevent the need for organ rejection therapy.*

Research at the Kimmel Cancer Center was exploring the benefit of combining half-matched bone marrow transplant with live-donor kidney transplant to spare patients the immune-suppressing risks and other side effects of lifelong rejection therapy. Rich was also among the first to have a combined bone marrow transplant and kidney transplant.

Bone marrow transplants have become so safe that, today, patients who require a solid organ transplant and do not have cancer may receive a bone marrow transplant solely to prevent the need for organ rejection therapy.

One of the beautiful things about translational — bench to bedside — research is that the patient is both contributor to and beneficiary of the science. Often, the benefits are realized by patients who come later. Rich and his family know things could have gone very differently. It was not lost on them that patients they had come to know did not survive their cancer battles.

Their enduring optimism throughout this circuitous journey is a testament to the strength and power of a loving family, an unshakable faith in miracles and, as they are quick to point out, a complete confidence in their Johns Hopkins medical team.

Rich Sr., now 70, looks back on his three-decade medical journey with nothing but gratitude, a broad ear-to-ear smile giving testimony to his unbroken spirit.

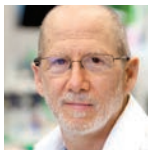
"We are so blessed. It amazes me every day. I have to pinch myself," he says. "Johns Hopkins has a piece of our hearts. We are their biggest cheerleaders."

## 1980s

Our researchers begin to crack the cancer code, revealing it as a disease caused by an accumulation of genetic mistakes. This becomes the paradigm for much of modern cancer research, ushering in the age of molecular cancer biology with new gene-targeted therapies and paving the way for gene-based screening tests for cancer.


# Broken Genes

## *The Mistakes in DNA That Lead to Cancer*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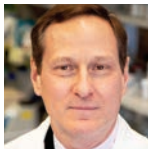

KINZLER

THE DISCOVERIES THAT led the world to understand that cancer is a genetic disease unfolded one by one in the laboratory of **Bert Vogelstein** and **Kenneth Kinzler**.

More than 40 years ago, when they first cracked open the Pandora's box that is cancer, revealing first one and then a series of genetic mistakes responsible for colon cancer, it was a foreign concept. Today, their discoveries have led this lab, and others around the world, to develop genetic tests, screening diagnostics and targeted therapies for colon and other cancers.

"When it comes to cancer genetics, Bert's and Ken's work is on the cutting edge of the cutting edge. They led the world to understand that cancer is a disease of genetic defects, and then led the first laboratory in the world to reveal what those defects are," says Johns Hopkins Kimmel Cancer Center Director **William Nelson**.

The complexity of their genetic discoveries has been likened to finding one two-letter transposition within 20 volumes of *Encyclopedia Britannica* and then figuring out how it got there. Some scientists consider them to be of the magnitude of finding a cause for polio. As transforming as these discoveries have been in the cancer world, they started simply and quietly in 1983 in a converted supermarket on the Johns Hopkins East Baltimore Medical Campus.

### THE EARLY DISCOVERIES


BAKER

At the time, very little was known about colon cancer. "The man who is really responsible for advancing the understanding of colon cancer is **Benjamin Baker**," says Vogelstein.

Baker, a Johns Hopkins internist who followed Vogelstein's work, was intrigued by the concept that cancer was caused by genes gone awry. While others were optimistically in search of the magic bullet that would bring down cancer in one fell swoop, Vogelstein's studies were revealing a much more complicated disease process.

A genetic infrastructure unlike anything that had ever been described in human disease was being described. It centered on a delicate balance between cell growth accelerators, called oncogenes, and cell growth brakes, called tumor suppressor genes.

> "THE REVOLUTION IN CANCER RESEARCH CAN BE SUMMED UP IN A SINGLE SENTENCE: CANCER IS, IN ESSENCE, A GENETIC DISEASE."
>
> –BERT VOGELSTEIN

Ushering in the age of molecular biology, Vogelstein, Kinzler and their co-collaborators were among the first to apply it to the study of a human disease, developing the knowledge and tools to look inside the submicroscopic molecules of the cell to reveal those rare, uncorrected errors in our DNA that put the cancer process in motion.

Alterations to these genes, either inherited or acquired throughout life, disrupted the delicate balance, giving an advantage to cell growth. Fundamentally, cancer is a normal cell that does not die. As the immortal cell divides, it eventually reveals itself in the form of a tumor.

While many researchers focused on the cancer, Vogelstein realized very early on that it was what precipitated the cancer that also mattered. He compared it to an iceberg — the cancer was the tip of the iceberg that could be seen, and the benign tumors were the layers beneath the water. He set out to identify the basis of the invisible layers beneath the surface that began forming decades before.

There was much skepticism about his approach.

"Cancers in animals were considered better to study because they were easier to manipulate," says Vogelstein. "That was true in some ways, but our view was this was a human disease, and we wanted to study the real thing."

The first grants Vogelstein submitted were rejected, but he persevered, and the findings that followed uncovered a genetic infrastructure that is now widely accepted to underlie the basis of all human tumor processes.

Using technologies they invented to see inside the cancer cell, they began to unravel the mystery of cancer.

## SEARCHING FOR THE ERRANT GENES

As Vogelstein began his quest to uncover the hidden layers of the iceberg, Baker, who liked Vogelstein's visionary approach, convinced his wife's family to donate money from their Clayton Fund to the Vogelstein lab. This seed money, which brought together the Bowel Tumor Working Group, was a turning point in Vogelstein's research.

This collaboration of seasoned clinicians and investigators and young up-and-comers began to shed the first light on the origin of colon cancer and, at the same time, triggered other investigators around the country and the world to look for similar patterns in other cancers.

At first, the discoveries came almost more quickly than they could be sorted out. In 1989, Vogelstein's identification of p53 mutations in colon cancer started a media frenzy as investigators around the country, following the Vogelstein lab's lead, found the same mutation in breast, lung and other cancers. "The p53 gene is the most common gene mutation among all cancers," the reports read.

A public eager for a quick fix pinned their hopes on this discovery as the holy grail of cancer. Vogelstein, his own toughest critic, was the first to dash these hopes. While he felt the discovery was important for advancing the science and technology of gene discovery, he was not looking for an answer in one gene. In fact, his lab's work showed that the p53 alteration was a mutation that occurred late in the cancer process, which led them to the next question. What genetic alterations came before p53?

## INHERENT CLUES

Vogelstein hypothesized that colon cancer resulted from a series of genetic alterations that evolved over decades, starting with small clusters of abnormal cells in the lining of the colon, advancing to benign tumors known as polyps, then to a cancerous tumor in the colon, and finally, to where p53 most likely came in, pushing the tumor to its most lethal form, as it spreads outside of the colon to other parts of the body. What Vogelstein wanted to do was identify the whole series of mutations and the order in which they occurred.

He decided to look among the rarest types of colon cancers for the answers — inherited colon cancer syndromes. Although they represented a small percentage of colon cancers, Vogelstein believed the same genetic underpinnings that led certain families to be plagued by an alarmingly high incidence of colon cancer, and typically at a much younger age, would shed light on colon cancers among the general population.

**Using technologies they invented to see inside the cancer cell, they began to unravel the mystery of cancer.**

Each of us inherits two copies of every gene from our parents, one from our father and one from our mother. In inherited colon cancer syndromes, family members are born with only one good copy of a gene. Subsequent random mutations and assaults from diet and other behaviors knock out the one good copy. The cascade of cellular errors that ultimately results in cancer is put in motion.


HAMILTON

Kinzler, Vogelstein's research partner and co-director of their lab, pathologist **Stanley Hamilton** and other members of the Bowel Tumor Working Group looked for inherited genetic alterations in these hereditary cancers.

The Kinzler-Vogelstein team identified a mutation of the APC gene in familial adenomatous polyposis, a rare, inherited syndrome in which affected people get hundreds of benign tumors known as adenomas, or polyps, in the colon. Further studies showed the same mutation to be the one that jump-starts the cancer process in the nearly 140,000 people within the general population who are diagnosed with colon cancer each year.

Other researchers in the Vogelstein/Kinzler lab were uncovering the genetic culprits of two other inherited colon cancers. In particular, they discovered the genetic and biochemical basis of hereditary non-polyposis colon cancer, which accounts for more than 50% of inherited colon cancer syndromes.

In 1998, the team reported a genetic alteration affecting as many as 400,000 people nationwide — 6% of European descendant Jews (Ashkenazi). Gene testing for cancer was catapulted into mainstream medicine because, along with the discovery of the genes that caused these diseases, Vogelstein, Kinzler and colleagues developed tests that detected the mutations. These tests are now part of the routine management for patients with strong family histories of the disease, and dramatically changed how these patients are diagnosed and treated.

For the first time, clinicians could know which family members had inherited colorectal cancer-causing mutations so that those at risk could be monitored closely for cancer. As important, the tests also revealed family members who did not have the gene mutations, so they could be spared unnecessary screening measures. It was the first example of individualized, or precision, medicine for patients with typical forms of cancers.

## A TEST FOR EVERYONE

These finding were key to understanding how cancer originated, and were transforming for families with these hereditary forms, but they represented a small fraction of the cancers. Vogelstein and Kinzler also wanted to develop ways to intercept and prevent the 95% of cancers that occur sporadically among the general population.

They wondered if they could find cancer DNA among colon cells shed and passed in stool. If they could find APC mutations — the mutations that cause normal colon cells to form the benign polyps that occur before cancer — in cells found in stool, they could potentially prevent the cancer from ever occurring.

These studies, first undertaken in 1991 by **David Sidransky**, who later started his own lab using this method to detect cancer-specific DNA in urine, sputum and other body fluids, were moved forward by **Giovanni Traverso** and **Frank Diehl.**

## Anne Jennings Krush

**Anne Jennings Krush** is an unsung hero of cancer research. In 1967, Krush began a research career at Creighton University, working alongside acclaimed cancer genetics expert **Henry Lynch**, a renowned authority in familial predisposition to cancer. During this collaboration, Krush developed an interest in familial colorectal cancer syndromes. In 1973, she came to Johns Hopkins and worked with **Victor McKusick**, continuing her study of hereditary colorectal cancer.

She served as the polyposis registry coordinator, and was a force behind the formation of the Bowel Tumor Working Group, a multidisciplinary team focused on hereditary colon cancer. This interaction initiated her collaboration with leading researchers in the field of cancer genetics, including **Francis Giardiello**, **Bert Vogelstein**, **Stanley Hamilton** and **Gloria Petersen**.

With painstaking attention to detail, she pieced together the medical histories of several hundred families, uncovering what would become the foundation for the Cancer Center's world-renowned discovery of the genetic basis for hereditary colon cancer.

The research led to the first noninvasive genetic screening test for cancer, distributed by Exact Sciences and marketed as Cologuard. The test, which had its origins in the Vogelstein/Kinzler lab, has now been used by millions of people.

Vogelstein and Kinzler developed the test to address the underuse of screening colonoscopy among the general public.

"The stool test is noninvasive and essentially risk-free, and it uncovers the very first genetic event in the colon cancer process," says Kinzler. This mutation could occur years before an actual cancer develops, giving clinicians ample time to cure or even prevent the cancer from occurring, he adds.


SIDRANSKY

## CRACKING THE CANCER CODE

Building upon their colorectal cancer discoveries, researchers in the Vogelstein/Kinzler lab applied their methods to other cancers and cracked the genetic codes of more forms of the disease than any other research team in the world. Their work is considered the classic model, the paradigm for much of modern cancer research.

A foundational gift from the Ludwig Foundation allowed them to bring automated gene sequencing equipment to their laboratory, making it possible to simultaneously sequence millions of gene fragments. Research that once took years could now be done in days for a fraction of the cost of earlier studies. This meant an unprecedented, all-encompassing view of precisely what was happening inside the cancer cell was at last possible.

Despite the complexity, in 2006, they began accomplishing something that would have been impossible just a decade earlier. Using advanced technology, the team analyzed more than 30 million base pairs of DNA in a patient's cancer and provided the first ever comprehensive blueprint of cancer — what goes wrong in the cellular instructional manual to cause cancer.

This task of monumental scope took the cancer world by storm, opened new areas of research and, for the first time, presented a full genetic understanding of one of humankind's greatest threats.

With new, faster computing tools to sequence cancer DNA, the team in the Vogelstein/Kinzler lab completed 88 of the first 100 blueprints of human cancers, and inspired similar research in labs around the world.

> "Knowing the road map of cancer is key to attacking it."

The detailed maps of cancer they created provide guides by which scientists can pinpoint characteristics of each person's cancer and tailor therapies and diagnostics to guide treatment — what we call *precision medicine.*

"Knowing the road map of cancer is key to attacking it. Now that we have identified the key gene mutations, we can focus on determining at what point in the cancer process they occur, whether they guide prognosis, and if they might be good targets for prevention or treatment," said Vogelstein.

## GENETIC TESTS FOR CANCER

These discoveries provided a detailed schematic for how tumors start and how they become progressively more dangerous as a result of heredity, random alterations or outside cell-damaging exposures that change DNA over the course of up to 30 years.

The last stage of metastasis, when the cancer spreads, and the stage that actually kills people occurs only in the last few years of this 30-year process, according to Vogelstein. Unfortunately, this is when many cancers are diagnosed. By this time, they have acquired so many gene alterations they are often resistant to treatment, he says.

He believed that if the cancers were detected before cancer cells spread to other parts of the body, most patients could be cured with surgery and drug treatment or potentially even surgery alone.

This led researchers in the Vogelstein/Kinzler lab to focus on ways to use their genetic discoveries to detect cancers earlier.

As tumor cells divide, they develop their own blood supply to get the nutrients they need to nourish and grow, and as a result, pieces of the cancer's DNA get carried in the bloodstream, leaving telltale evidence of their existence. The DNA contains the alterations specific to the cancer — the accumulation of errors that occur as normal tissue transforms to evasive, deadly cancer. It's been there all along, floating among a sea of normal cells; scientists had to develop the technology to see it and pull it out.

Next-generation sequencing technologies allowed millions of DNA molecules to be simultaneously and individually analyzed, providing the first opportunity to identify mutations in the bloodstream. However, the technology was fraught with inefficiencies and high error rates that limited their clinical application.

To correct for these sequencing errors, researchers in the Vogelstein/Kinzler lab developed a new technology called SafeSeqS (Safe Sequencing System) in 2011, and then built a better version in 2021 called SaferSeqS (Safer Sequencing System). The technology makes it possible to detect rare mutations in blood efficiently and accurately.

Detecting mutations in blood samples, now known as liquid biopsy, rather than via surgical biopsy provided the potential to detect cancer at its earliest stage.

It ushered in a series of screening tests developed in the Vogelstein/Kinzler lab, including PapSEEK, UroSEEK, CompCyst and CancerSEEK.

PapSEEK could be used on cervical fluid obtained during Pap tests (screening tests for cervical cancer) to detect mutations in 18 genes commonly mutated in endometrial and ovarian cancers. UroSEEK scours urine samples for 11 mutations associated with bladder and other urological cancers. CompCyst finds molecular markers in the fluid of pancreatic cysts to distinguish harmless cysts from those likely to develop into pancreatic cancers.

### Sleuthing Out Bladder Cancer

In 1967, when **Hubert Humphrey**, then vice president of the United States under Lyndon B Johnson, sought medical advice for blood in his urine, as many as 12 pathologists examined the cells in the urine. Some thought it was cancer. Others disagreed, and Humphrey was not treated until a few years later, when he developed clear signs of bladder cancer. He died of the disease in 1978.

After learning that Johns Hopkins pathologists had reviewed Humphrey's case in 1967, and that the original slides containing his bladder cells were still in the hospital, pathologist **Ralph Hruban** became intrigued.

He turned to **David Sidransky**, who was working in the cancer genetics lab of Bert Vogelstein and Kenneth Kinzler, researching tests to detect cancer cells in body fluids and secretions. Hruban wanted to put this research to the test and find out if he could prove, once and for all, if Humphrey had bladder cancer in 1967, 10 years before he died from the disease.

In 1994, with Humphrey's widow's permission, the urine specimen was reexamined using Sidranky's test, a genetic probe specific to Humphrey's cancer that would pinpoint the bladder cancer, if it existed, in the 1967 specimen.

Sidransky found mutations of the p53 gene, a common genetic fingerprint of bladder cancer, in 9% of the cells, proving Humphrey had undetected bladder cancer in 1967.

For Sidransky, the most exciting implication of the discovery was looking to the future and how tests like these could be used one day to pick up cancer years before the tumor could be found by normal clinical methods.

It is impossible to know for certain, but if the invasive bladder cancer had been detected earlier, Sidransky speculated, it might have been cured.

"In the not-too-distant future, when people see their doctors, they can provide urine, stool and sputum samples and have them screened for bladder, colon and lung cancers," Sidransky said in 1994.

This science led to the Cologuard stool test for colon cancer, and paved the way for liquid biopsy and the development of gene-based tests, like CancerSEEK, on the horizon.

CancerSEEK is a first-of-its-kind test that screens for eight common cancer types in a single blood test. The cancers the test detects — ovarian, liver, stomach, pancreatic, esophageal, colorectal, lung and breast cancers — account for 60% of cancer deaths, and five of these cancers currently have no screening test. The hope is that the test will detect cancers early when they can be cured.

The test has been licensed by Exact Sciences to continue development as a multicancer screening test for the general population. Quest Diagnostics has licensed the technology to monitor people with cancer for signs of cancer recurrence or progression.

## LOOKING TO THE FUTURE

The complexity of cancer stems from the fact that it originates from our own cells. The genetic mutations that mark the genes of cancer cells are the only thing that distinguishes normal cells from cancer cells. However, it is this subtle difference and research spanning three decades that led to one of the most significant advances in cancer treatment.

It started in 1993, when researchers in the Vogelstein/Kinzler lab identified a genetic cause of Lynch syndrome, a hereditary form of colon cancer.

### MATCHING CANCER GENES TO TREATMENTS

The genetic discoveries made at the Kimmel Cancer Center over the past 50 years revealed a complex landscape. There are at least 1,000 gene defects in every cancer, making the genetic landscape of tumors very complicated. Although these gene findings opened the door to precision medicine, which makes targeted therapy possible, it requires special expertise to match gene targets to the right therapy. The Johns Hopkins Kimmel Cancer Center Molecular Tumor Board has the tools to address these complexities.

Our experts have learned that not every change in a driver gene is driving the cancer.

"It is important to consider the specific mutation and its implications," says **Valsamo "Elsa" Anagnostou**, who directs the center's Molecular Tumor Board, which was previously directed by former faculty member **Ben Park**. "The informatics tools available that pair mutations with targeted therapies generally do so at the gene level, without consideration of the specific mutation. We can help distinguish genetic alterations driving a cancer from those that are incidental. We evaluate the specific alteration and its implication for cancer growth and metastasis."

More recent research also revealed the importance of co-mutations, something Molecular Tumor Board experts uniquely consider in making recommendations for therapies, including combination therapies.

"Commercially available services are generic, with limited information for less common mutations, and they do not capture co-mutations. Oncologists face a vast volume and variety of generic molecular data that our tumor board can help them navigate," says Anagnostou.

Over the past two years, they saw an increasing rate of matches between gene targets and clinical trials or off-label use of FDA-approved therapies.

Mutations to mismatch repair genes, which correct copying errors when DNA replicates and cells divide, cause high rates of additional mutations and an increased risk of developing colon cancer.

PAPADOPOULOS

Vogelstein, Kinzler and lab member **Nickolas Papadopoulos** developed a test to screen for mismatch repair deficiency/microsatellite instability to allow families with a history of Lynch syndrome to be monitored for development of colon cancer.

Fast forward 20 years. Armed with an understanding of the genetic alterations that are responsible for cancer, the Kinzler- Vogelstein group cooperated with cancer immunology researchers to make an unprecedented suggestion. They suspected that cancers from patients with Lynch Syndrome would be extraordinarily sensitive to a new class of drugs, called immune checkpoint inhibitors, being developed by the cancer immunology group.

The discovery was key to a historic 2017 FDA approval of the immunotherapy drug pembrolizumab across all cancer types for any cancer that contains the mismatch repair deficiency/microsatellite instability genetic defect. It marked the first cancer drug approval based on a specific genetic profile and with no regard to where in the body the cancer started. The research community at large had doubts, leading the researchers to perform the clinical study themselves without the benefit of industry sponsorship.

LE

The clinical trial, led by **Dung Le** and **Luis Diaz**, demonstrated astonishing responses in patients with cancers that had mismatch repair deficiency/microsatellite instability. The historic discovery soon led to the FDA approval of the immunotherapy drug prembrolizumab across all cancer types for any cancer that contains the mismatch repair/microsatellite instability defect. It marked the first cancer drug approval based on a specific genetic profile with no regard to where in the body the cancer started.

> "The history of medicine shows that when a disease is understood, it eventually becomes manageable."

"This illustrates the science of discovery, and how long it can take to fit the pieces together," says Vogelstein. "It is a reflection of the strength and support of research at Johns Hopkins. No other institution had ever done something like this before, discovered the basis for a disease and designed a treatment that obtained FDA approval. This is virtually unique in the history of medicine."

Researchers in the Vogelstein/Kinzler lab continue to contribute to immunotherapy discoveries, focusing on new ways to target specific gene mutations with immunotherapy.

"The history of medicine shows that when a disease is understood, it eventually becomes manageable," says Vogelstein. "This understanding truly has been revolutionary in many other diseases. The next revolution is to take this knowledge we and others have gathered and help patients in ways that could only be imagined before this understanding came about."

*Vanessa's Story*

# In Search of a Miracle

**VANESSA** WITH HER GRANDSON, ZION

## When Vanessa was diagnosed with advanced colon cancer in 2014, just before her 60th birthday, the caring mother and grandmother learned the cancer had already spread to her stomach and liver.

Even after a five-hour surgery and nearly a year of grueling chemotherapy, the cancer continued to grow. Her doctor told her there was nothing left to try.

The news was devastating. Vanessa traveled around the country searching for treatment options.

"I was willing to try anything," she says.

She remembers the day her young grandson, Zion, asked her if she believed in miracles.

She did believe, and she began searching for information. Vanessa came upon the Kimmel Cancer Center's Bloomberg~Kimmel Institute for Cancer Immunotherapy website.

"I grew up on Caroline Street in the shadow of Johns Hopkins. As a little girl, my mother brought me to the Harriet Lane Clinic," she says, as she realized that the help she was searching for might be in her own backyard.

A new immunotherapy, based on more than 30 years of research, was being studied in a clinical trial at the Kimmel Cancer Center. Vanessa prayed it was the miracle she needed.

The new drug, called pembrolizumab, allowed immune cells to see and respond to cancer cells. The first studies did not look promising in colon cancer, but one patient whose cancer responded to the treatment left researchers curious.

### MISMATCH REPAIR

The answer, as it turns out, was based in Kimmel Cancer Center genetics research from 1993. Researchers uncovered a gene mutation that allowed DNA copying errors to accumulate, eventually leading to colon cancer in some people.

In 1993, immunotherapy was in its infancy, and researchers had no idea these copying errors could also attract the attention of the immune system.

The large number of mutations caused by this genetic error, known as mismatch repair deficiency/microsatellite instability flagged cancer cells as abnormal. However, when the immune system activated against them, the cancer cells were able to shut down the response through a natural on/off switch of the immune system, called an immune checkpoint.

Pembrolizumab is in a class of drugs known as immune checkpoint inhibitors. It could turn the immune switch back on and unleash the power of the immune system against the cancer.

As Kimmel Cancer Center cancer immunology researchers conferred with cancer genetics researchers, they figured out that the one colon cancer responder had mismatch repair deficiency/microsatellite instability, and in 2013, the clinical trial of the drug was expanded to include any patient with colon cancer whose tumor had mismatch repair deficiency/microsatellite instability.

Vanessa's cancer tested positive for mismatch repair deficiency/microsatellite instability, and she was admitted to the clinical trial of the drug. It was the miracle little Zion had encouraged her to believe in.

### THIS WAS DIFFERENT

Pembrolizumab was different than the treatments Vanessa had tried before that made her feel so ill but did nothing to stop her cancer. With this drug, her tumor was melting away, shrinking by 60%.

"During chemotherapy, I felt like I was dying. With immunotherapy, I felt like my body accepted it," she describes.

"My dream was to see my grandchildren grow up," says Vanessa. "Now I'm a great-grandmother. I truly feel like heaven opened up. Each day is a blessing."

Vanessa, who loves to help others, volunteers with the prison ministry in her church and does some catering, providing sandwiches for local police departments, where her stepdaughter is an officer.

She is certain the treatment saved her life. She shares her story to help others.

"I know other African Americans are afraid of clinical trials," says Vanessa. "If just one hears my story, and it changes that person's life, I've made a difference," she says.

The groundbreaking research built upon a 30-year-old discovery, and Vanessa's inspiring story has been the focus of media attention, including an article in *Smithsonian* magazine and in a local TV news segment showing Vanessa speaking at a *Swim Across America* Baltimore event. The organization was the lead donor for the pembrolizumab trial from which Vanessa benefited.

Zion, who just a few years earlier asked his grandmother to believe in miracles, sees her in these news stories and beams proudly, telling Vanessa, "You're a celebrity!"

Vanessa is grateful to her oncologist, **Dung Le**, and her nurse, **Holly Kemberling**.

They were so wonderful to my family and me," says Vanessa. "They explained everything. It was evident their hearts are in it."

Ultimately, the therapy bought her the one thing she most desired — more time with her family.

"I am so thankful. I've seen my grandchildren graduate and go off to college," says Vanessa, who enjoys gathering her family and cooking for them. "Being diagnosed with stage 4 cancer was the hardest journey. I was sad and hopeless. I thought I was going to die, but that didn't happen. I survived."

## MILESTONES IN CANCER GENETIC DISCOVERIES

**1974:** The nuclear matrix is identified as the site for DNA replication, shedding light on cellular changes that cause cancer

**1983:** Discovery that changes in DNA methylation, now called epigenetic changes, are found in cancers, including early cancers

**1984:** Discovery that chromosome 11p changes are integral to the development of pediatric kidney cancers called Wilms' tumor

**1987:** Discovery of GLI genes and their link to brain tumors

**1988:** A now-classic paper published in the *New England Journal of Medicine* presents the idea that cancers result from the sequential mutations of oncogenes and tumor suppressor genes

**1989:** Discovery of mutations in the p53 gene in human colorectal cancers, that it is a tumor suppressor gene and that p53 genes are common denominators of most common human tumor types. It is now known that TP53 is the most highly mutated tumor suppressor gene in cancer

**1990:** Discovery of the biochemical mechanisms through which p53 suppresses tumor development

**1991:** Discovery of the APC gene, and that inherited mutations in the gene are responsible for the cancer predisposition syndrome called familial adenomatous polyposis (FAP) and that mutations in APC initiate virtually all colorectal tumors, with or without hereditary predisposition

**1992:** Discovery that genetic alterations, such as mutations, can be found in the stool of people with colorectal cancer, leading to the first genetic test approved by the FDA for detecting early cancers and creating the paradigm for liquid biopsies

**1993:** Discovery of gene (MSH2) responsible for a major inherited cancer syndrome, hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome and discovery of the biochemical mechanisms through which APC suppresses tumor development

**1994:** Discovery of mismatch repair genes, such as MLH1, responsible for cases of HNPCC not caused by mutations in MSH2

Discovery of a technique, Serial Analysis of Gene Expression, to evaluate all the genes transcribed in a normal or tumor cell, coining the word "transcriptome"

**1992–1999:** Discovery of now widely used tests to determine whether patients have inherited mutations responsible for FAP or HNCPCC

**1995:** *ScienceWatch* names cancer genetics pioneer **Bert Vogelstein** as the most frequently cited scientist in the world in all fields of science

**1999:** FLT3 gene is cloned and linked to a type of leukemia, with drugs developed to target the mutation along with tests to confirm the drugs hit their genetic target

Discovery of chromosomal instability as a major underlying feature of most cancers

**2002:** First gene mutation in prostate cancer is discovered

**2004:** Discovery of mutations in PIK3CA in colon, breast, stomach, brain and other cancers. Later found to be the most highly mutated oncogene in cancer, paving the way for targeted drugs — now widely used — for the treatment of breast cancers with PIK3CA mutations

**2006:** First analysis of all of the genes in colon and breast cancers, establishing the paradigm for modern cancer genetic research and defining "cancer genome landscapes"

**2008–2010:** First analysis of all of the genes in pancreas, brain, ovarian and other cancer types

Discovery of the IDH1 and IDH2 genes, establishing the importance of mutations in genes that control metabolism, leading to now widely used drugs that target these mutations in brain tumors and leukemias

**2009:** The first use of genome-wide sequencing to identify a gene that causes a hereditary disease — in this case, pancreatic cancer

**2010:** Discovery that the interval from the first, initiating mutation in a tumor cell to the development of a cancer is 20–30 years, providing a broad window for detection and prevention

**2011–2018:** Discovery of the genetic alterations that drive various types of pancreatic cysts

**2012:** The genetic driver of hereditary prostate cancer is identified

Resistance mutations are found in blood of patients shortly after treatment, marking cancers predestined to recur

**2013–2018:** Development of DNA-based tests on urine, saliva and Pap smears that can detect early cancers of the bladder, head and neck, and uterus

**2017:** Discovery that patients with mutations in the mismatch repair genes MSH2 or MLH1 in their cancers are extraordinarily responsive to treatment with immune checkpoint inhibitors, leading to the first FDA approval of a drug to treat a patient on the basis of the genetic alterations within a tumor, regardless of the tumor type

Study reveals genomic roots of many ovarian tumors is in the fallopian tubes

Discovery of a new type of cancer drug, called MANAbodies, that uses the genetic mistakes inside cancer cells to generate an immune response

**2018:** Multicancer blood tests are developed and shown to detect relatively early-stage cancers in a noninvasive fashion, laying the foundation for an immense amount of academic and industry research to develop "liquid biopsies" for cancer screening

**2019:** The largest pancreatic cancer genome-wide association study discovers changes to five new regions in the human genome that may increase the risk of pancreatic cancer

Development of a test that distinguishes precancerous pancreatic cysts that require surgery from harmless benign cysts

**2021:** Discovery of new immunotherapy approaches for treating people with cancer based on the genetic alterations found in their tumors, such as those in p53

**2022:** Successful clinical trial shows that DNA shed from early-stage colon cancer into bloodstream can be used to manage patients after surgery

# Leaders in Cancer Drug Discovery

SOON AFTER THE Johns Hopkins Kimmel Cancer Center opened its doors in 1977, it became one of the first comprehensive cancer centers to receive a grant to begin clinical trials of new drugs. Our experts quickly earned recognition as they aggressively tested the limits and power of existing drugs, and invented new agents when what we had failed to get the job done.

Today, the combination of drug therapy, radiation therapy and surgery is a mainstay of cancer therapy. However, in 1973, there was no such thing as combined therapies.

"There weren't very many drugs, and the ones we had didn't work well and were very toxic. There was no formal drug development program at that time. There wasn't even much of a solid tumor program," says **Ross Donehower**, one of the Cancer Center's first medical oncologists and a drug discovery researcher. "The Center had three medical oncologists working on solid tumors. The solid tumor program began to grow in the 1980s, and drug development fostered the expansion."


DONEHOWER


COLVIN


ETTINGER


GAILLARD

## LAUNCHING DRUG DISCOVERY

Things started to change with **Michael Colvin** and his foundational work in deciphering the activity of the cancer drug cyclophosphamide and how to use it in bone marrow transplant.

Colvin recruited Donehower, who worked with another Center medical oncologist, **David Ettinger**, to win a grant from the National Cancer Institute to conduct clinical trials of new cancer drugs.

Many in the fledgling field of oncology scoffed at the idea of a drug discovery program, and took little notice when the Kimmel Cancer Center earned a grant from the National Cancer Institute for phase I trials of new drugs, Ettinger remembered. The prevailing thought at the time was that viruses were the likely cause of cancer, and antiviral drugs were the only thing worth studying. Although we had wonderful expertise in **Paula Pitha Rowe**, **Nancy** and **Joel Shaper**, and others, who were conducting pioneering research in the study of viruses and cancer, Kimmel Cancer Center researchers did not place artificial boundaries on improving the understanding and treatment of cancer.

"That was what was so special about our center. There was always support and encouragement to be innovative. We take it for granted, but this truly is an amazing place of healing and discovery," said Ettinger.

The drug discovery grant Donehower and Ettinger submitted led to one of the most promising new anticancer drugs of the time, Taxol. It was the first drug Donehower studied.

## MOLD, DIRT AND BARK

In the early days of cancer drug discovery, scientists looked everywhere for compounds and chemicals that contained the power to destroy the immortal cancer cell. They collected mold, dirt and plants, and even scraped organisms from the bottom of boats in search of new chemicals and compounds that could attack and kill cancer cells.

Taxol was no exception. It was made from the bark of the Pacific yew tree, and shown by researchers at other medical institutions to be effective against cancer cells.

In 1984, it was heralded as the most promising new drug in the battle against cancer in more than 15 years. However, it might not have made its way to patients if not for Donehower's ingenuity and determination. The problem was that, although the drug was effective against cancer, it was too toxic to give to patients. It caused severe side effects in about one-third of patients, says Donehower.

## FIXING TAXOL

The promising drug was headed for abandonment when Donehower worked with Johns Hopkins allergists to develop premedications that allowed Taxol to be safely given to patients.

Donehower, who says he always enjoyed taking on tough problems, was driven by a desire to take care of people who really needed help and could benefit from research rooted in clear-headed thinking and compassion. **Al Owens**, the Center's first director, called it science in human service, he says.

**Eric Rowinsky**, another recruit of Colvin's, and ovarian cancer expert **Bill McGuire** drew national attention when they began to show in clinical studies that Taxol was effective against ovarian cancer, a cancer type that was in great need of new therapies.

Reporters descended upon the Kimmel Cancer Center when one clinical study showed that 30% of women taking the drug experienced a 50% decrease in tumor size.

McGuire became the national study chair of ongoing trials of Taxol, and Rowinsky worked to improve its effectiveness even further, launching a new clinical trial of the drug in combination with the anticancer drug cisplatin and a white blood cell stimulating growth factor called GCSF. Other clinical studies followed.

## EXPANDING THE BENEFIT

Taxol remains a mainstay of cancer therapy, and is now used as a treatment for additional cancers, including breast and lung cancers.

Today, gynecologic cancer expert **Stéphanie Gaillard**, in collaboration with ovarian cancer and drug discovery experts **Deborah Armstrong**, **Ie-Ming Shih** and **Tian-Li Wang**, leads new studies of the drug.

"Taxol is critical in the treatment of gynecologic cancers, including ovarian, uterine and cervical cancers," says Gaillard, director of gynecologic cancer trials and co-director of the developmental therapeutics/phase I clinical trials program.

The drug is typically given in combination with the anticancer drugs carboplatin or cisplatin, and she is working to figure out why some patients' cancers grow resistant to the drug combination.

Gaillard, who studied mechanisms of treatment resistance in ovarian cancer during her fellowship training from 2009 to 2012, is focused on helping patients whose cancers come back after initial therapy.

Although Taxol continues to provide a good response in about 20% of patients, Gaillard wants to see if she and her colleagues can figure out how to expand the benefit to more patients.

## Ross Donehower Honored for Training Leadership

In addition to his pioneering work in drug discovery, for the last three decades, **Ross Donehower** served as director of the Medical Oncology and Hematology Fellowship Training Program.

"Every year, I'm amazed by the incredibly talented group of people we have an opportunity to interview for positions in our hematology and oncology fellowship program. They come from a wide variety of backgrounds with varied interests. We provide a robust clinical training that prepares them to treat patients, but we also give them a strong research base. When they leave our program, they are prepared for anything," says Donehower, reflecting on his tenure as fellowship program director.

A reception was held in his honor at the 2023 annual meeting of the American Society of Clinical Oncology.

**Kristen Marrone**, who was co-director of the fellowship training program, was appointed director.

She identified a protein called SYK that was present at high levels in tumors that have recurred after prior exposure to Taxol. In laboratory studies, cells from recurrent tumors continued to grow, even in the presence of Taxol. However, when Taxol was combined with an SYK inhibitor — a drug that blocks the protein's function — ovarian cancer tumor cell growth was blocked.

Although a SYK inhibitor has been FDA approved for the treatment of an auto-immune condition, it has never been used in combination with Taxol. In 2018, Gaillard launched a Phase 1 study to determine the appropriate dose of the SYK inhibitor, frostation, to use in combination with Taxol for the treatment of platinum-resistant ovarian cancer.

The study team found that the combination of drugs was tolerable to patients and identified a dose to move forward in future studies. While this small study of 27 patients was not large enough to rigorously evaluate the efficacy of the combination, treatment results were promising with partial response (measured as at least 30% tumor reduction) seen in 39% of patients and stable disease in an additional 28% of patients.

"We are encouraged by these results and hope future studies will confirm that this combination is an improvement over what we've seen historically," she says.

Gaillard says new research is aimed at understanding how levels of SYK correlate with response to treatment and how low levels may interfere with response. She is also looking at other cellular factors that might predict response to Taxol.

"It is a long process, but shows how continued work can make an already useful drug more successful," she says.

### THE BEST IN THE WORLD

It is studies like these that have earned the Kimmel Cancer Center its reputation as a leader in drug development.

"Our clinical infrastructure grew around drug development," says Donehower. "In the beginning, there was no recognition for drug development, and now we are known for it."

Like Gaillard, a new generation of drug discovery researchers has taken on the charge, including **Michael Carducci** and **Nilofer Azad**, among many others.


CARDUCCI


AZAD

Our experts continue to be among the best in the world at discovering cancer-promoting changes that can be targeted with therapy, finding or developing drugs that promise to go after the cancer target, and developing tests — known as assays — that show whether the drug is having its intended effect on the target.

"We are seeing things happening now we would have never expected in 1973," says Donehower. "Melanoma patients, lung cancer patients, virtually no one back then lived five years. Now, because of targeted drug therapies, immunotherapy and other drug discoveries, these patients are living many years with advanced cancers."

Still, he is not content to rest on prior successes. The bold and adventurous spirit of inquiry remains strong. "We have to continue to look for better drugs and better targets," says Donehower. We must look beyond to the next great discovery."

*Janice's Story*

# The Greatest Gift

IN 1999, WHEN Janice was diagnosed and treated for stage 3 ovarian cancer at a community hospital, her doctor didn't give her much hope. Janice, 38, had three young children: a 12-year-old daughter and 10-year-old twins. She worried that she would not see them grow up, and that led her to seek a second opinion at the Johns Hopkins Kimmel Cancer Center.

## "Don't tell me how bad it is. I've heard all of that. Just tell me what you are going to do to fix it."

"Don't tell me how bad it is. I've heard all of that," Janice told Kimmel Cancer ovarian cancer expert and surgeon **Robert Bristow**. "Just tell me what you are going to do to fix it."

Bristow and colleague **Deborah Armstrong**, a medical oncologist and ovarian cancer expert, had no intentions of giving up.

He removed a new ovarian tumor detected on imaging, and referred Janice to Armstrong for treatment with a promising new cancer drug called Taxol.

Taxol was one of the great research discoveries in ovarian cancer in the mid 1980s. It was Kimmel Cancer Center researchers who developed delivery methods that allowed the drug to be tolerated by patients. After a series of clinical trials, it was hailed as the most promising new cancer agent in more than a decade. It is now part of standard therapy for ovarian cancer and other gynecological cancers.

Janice received the drug in 1999 and again in 2001 when her cancer came back. In addition to Taxol, she benefited from a half-century-old method for delivering chemotherapy directly into the abdomen. A seven-year study of more than 400 women, led by Armstrong and reported on in the *New England Journal of Medicine,* found increased survival rates in women with advanced ovarian cancer, which resulted in renewed interest in the abandoned method.

"This method appears to be better at destroying lingering cancer cells," said Armstrong. The findings led to a new recommendation in 2006 by the gynecology oncology group, making the treatment, known as intraperitoneal therapy, standard of care for many women with ovarian cancer.

After three ovarian cancer recurrences, four surgeries and nine years of treatment with Taxol, cisplatin and other drug therapies, Janice has been cancer-free since 2008. Now 62, she is grateful for the science and doctors who saved her life, and she does her part to pay it forward.

She volunteers for Survivors Teaching Students at Johns Hopkins, a program in which cancer survivors speak to third-year medical students to help them better understand the experience of patients with cancer and to prepare them to be better-informed and compassionate doctors. She also participates in the Woman to Woman mentoring program, sharing her experience in navigating ovarian cancer with newly diagnosed women.

She recently was invited to attend the annual conference of the National Ovarian Cancer Coalition, which supports survivors and caregivers and funds ovarian cancer research. Janice had the distinction of being the longest survivor of ovarian cancer there.

She attributes her survival to her Kimmel Cancer Center doctors and the research that led to new treatments.

Janice, who worried in 1999 that she might not live to see her children grow up, has celebrated many milestones with them — high school and college graduations, weddings and the births of five grandchildren.

## "They never gave up on me, and I'm alive because of that. It's the greatest gift."

"Knowing there are doctors always looking for new and better cancer drugs gives patients like me such hope," says Janice. "They never gave up on me, and I'm alive because of that. It's the greatest gift."

## MILESTONES IN DRUG DISCOVERY

**1979:** National Cancer Institute grant for new drug development is awarded

**1980:** Clinical trials of cyclosporin prevent graft versus host disease following bone marrow transplant

**1981:** Acyclovir proven effective against herpes simplex virus in bone marrow transplant patients

**1982:** Johns Hopkins is selected by NCI as site for Phase I clinical trials of anticancer drugs

**1984:** Taxol is refined; it is hailed as most promising new anticancer drug in a decade

**1986:** Cyclosporin is found to inactivate immune response

**1987:** Biodegradable, drug-containing wafers implanted at tumor site are approved for clinical trials in brain cancer to get anticancer drugs through the blood-brain barrier

Intravenous BCNU and cisplatin therapy reduces size of glioblastoma and astrocytoma brain cancers

**1989:** New drug regimen for pediatric acute lymphocytic leukemia moves survival rate from 50% to 90%

Topoisomerase inhibitors induce death of leukemia cells

**1992**: Sulforaphane, a compound found in cruciferous vegetables, is identified and studied for its ability to block cancer growth

**1993:** Topoisomerase inhibitors initiate antitumor responses in treatment-resistant cancers

**1994:** Endothelin 1, a potent blood vessel constrictor linked to heart disease, is associated with advanced prostate cancer

**1997:** Therapeutic pancreatic cancer vaccine goes to clinical trials

**1999:** Drugs are developed to target FLT-3, a common mutation in acute myeloid leukemia

**2003:** High doses of anticancer drug cyclophosphamide are successful against moderate and severe forms of lupus

**2004:** Phase I trials of therapeutic cervical cancer vaccine begin

**2005:** Cholesterol-lowering drugs called statins are linked to lower risk of advanced prostate cancer

The drug atrasentan stabilizes the spread of prostate cancer in men who stopped responding to hormone therapy

**2006:** Half-century-old method of abdominal delivery of chemotherapy is reestablished and improves ovarian cancer survival

**2009:** Hedgehog inhibitors are studied in basal cell skin cancer and medulloblastoma brain cancer

**2010:** First therapies targeting epigenetic alterations are tested in clinical trials

**2011:** Our researchers lead clinical trial of pomegranate extract, given in capsule form, to slow the rise of PSA in patients with prostate cancer

**2012:** Anti-PD1/PD-L1 immunotherapy drugs restore the immune system's response to cancer cells

**2014:** BMH-21 is developed to prevent cancer cells from accessing POL-1, a cellular machinery they need to survive

A clinical trial studies anti-parasitic drug mebendazole in glioblastoma brain cancer

**2015:** Analytical Pharmacology Core tests drugs used in the NCI Experimental Therapeutics Clinical Trials Network

**2016:** Cancer Chemical and Structural Biology Program is established to accelerate cancer drug discovery

Honokiol, derived from the magnolia, is studied for its ability to slow breast cancer growth

Immunotherapy given before surgery is found to reduce cancer recurrence and extend survival in lung cancer, and leads to similar studies across cancer types

**2017:** A discovery leads to first FDA approval of a cancer drug across all cancer types when pembrolizumab is approved for all cancers with a genetic alteration called mismatch deficiency/microsatellite instability

**2018:** Short, intensive bursts of pharmacologic testosterone is used to treat prostate cancer

Novel, low-dose combination of five drugs works against pancreatic cancer

**2020:** Immunotherapy/chemotherapy combination improves survival for patients with mesothelioma; shows promise as first-line treatment

Phase I trials show epigenetic-targeted/immunotherapy drug combination benefits patients with advanced cancers that have not responded to other therapies

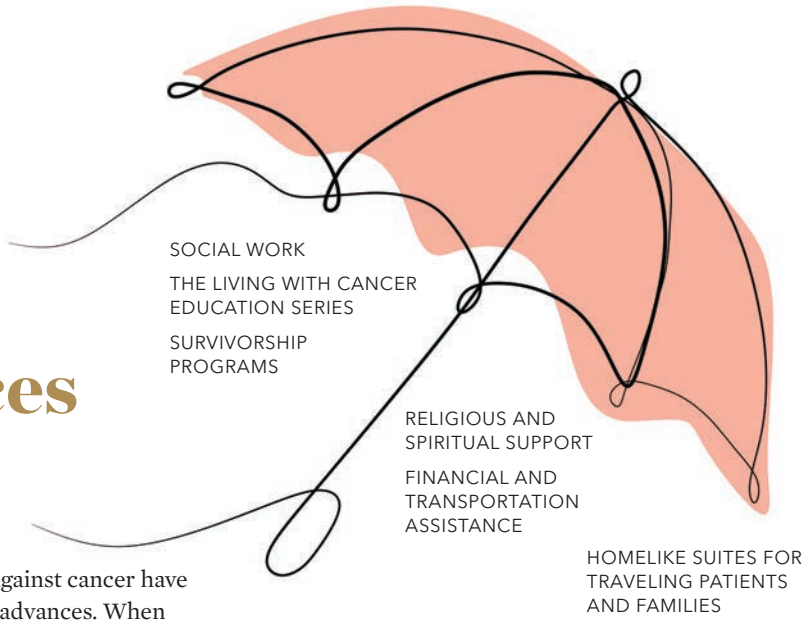
Cabozantinib and immunotherapy drug nivolumab makes curative liver cancer surgery possible for some patients

**2021:** A vaccine given in combination with two immunotherapy drugs is used to treat rare liver cancer with no standard treatment

**2022:** Prodrug DRP-104 is developed to release its payload only in tumors, and advances to clinical trials in solid tumors. It is based on an earlier discovery of a drug called DON that cuts cancer cells off from nutrients

Anticancer drug RK-33 is shown to fight SARS-CoV-2, the virus that causes COVID-19

**2023:** A clinical trial of enoblituzumab is the first that promises antibody-based immunotherapy against prostate cancer




# Patient and Family Services

## *An Umbrella for Supportive Services*


KNIGHT


LOSCALZO

As monumental as the therapeutic successes against cancer have been over the past 50 years, so have the social advances. When our Cancer Center first opened its doors in 1977, cancer was taboo and shrouded in fear.

"In those days, if a family member had cancer, families didn't talk about it to many people. The myth was that it was contagious," recalls **Louise Knight**, director of the Duffey Family Patient and Family Services Program. Knight's predecessor, **Matthew Loscalzo**, was director from 1997-2002.

We worked hard to dispel those myths, to be an advocate for patients and families, and to help them through this journey, she says. Today, our patients and their families are very knowledgeable about their disease. They are active participants in their care.

> **"Our Cancer Center is a family place. If someone is struggling, we help them. It is a place of hope."**

Recognizing that patients are more than the disease they are battling, the Cancer Center's Duffey Family Patient and Family Services Program addresses all patient and family needs, and these improvements are as significant as the advances in therapies.

"Our Cancer Center is a family place. If someone is struggling, we help them. It is a place of hope," says Knight.

Patient and Family Services is an umbrella for a breadth of services aimed at supporting patients and families from diagnosis through survivorship: social work; the living with cancer education series; survivorship programs, including an annual day of celebration; financial and transportation assistance; religious and spiritual support; and the Hackerman-Patz Patient and Family Pavilion, which provides homelike suites for patients and families traveling to the Cancer Center for treatment. Two earlier residences, the Joanne Rockwell Memorial House and the Hackerman-Patz House, provided this home away from home until the Pavilion opened in 2008.

Patient and Family Services also hosts the annual Service of Remembrance to offer support and reflection to the families of those who died during the year.

As they work to help others, she can't help but think of the people who make their work possible. "Mrs. Harry J. Duffey was the engine who started this program and her family continues to move us forward. Mrs. Duffey's gifts allowed us to launch the Duffey Pain and Palliative Care Program in 2007," says Knight.

In addition, Paul Reed Smith, whose *One Night, One Show, One Cause* music event, also helps sustain the important work of the Patient and Family Services Program.

"The kindness of so many others, that's what helps support us in our missions. It's really quite beautiful," she says. "We continue to hold true to our mission of caring for patients and families and the full scope of their psychosocial needs. Sometimes that means helping patients with mortgage payments and utilities, providing no-cost counseling to the spouse, providing education about Advance Directives, or helping a family plan for care at home after treatment. I think Mrs. Duffey would be smiling knowing all we have accomplished."

There is a painting that hangs by Knight's desk. It captured her attention several years ago when she visited a consignment shop that supports hospice care. In many ways, it illustrates the mission of Patient and Family Services, she says.

"Everyone who looks at it sees something different," she says of the painting, which shows a path lined by flowers and shrubbery on each side. Where the path leads, she says, is up to the interpretation, imagination and hope of each patient's and family member's journey through cancer diagnosis and treatment. It's different for each one, Knight says, but she and her team are there to help guide patients and families along the path they choose.

# PATIENTS AND FAMILIES | ADVANCES

### PLANS FOR EXPANSION OF CANCER CENTER ANNOUNCED

Citing overcrowding and increased demand for cancer care and research, the Johns Hopkins Health System announced plans for the construction of a new, $100 million, 88 bed Cancer Center in March 1987. Center Director **Albert Owens** and other Johns Hopkins officials said the existing Center, which opened in 1977, was unable to meet the growing surge of cancer patients. The number of cancer patients coming to Johns Hopkins tripled, and the number of patients under active treatment rose from 6,200 in the 1970s to more than 17,000 in 1986, Owens reported. He added that since its 1977 opening, the Cancer Center operated at capacity. There was also a critical need for additional research space. Owens said that 49 of the 64 full-time faculty had grants totaling more than $11 million, which could support a double amount of research immediately, if space was available.

### EARLY TELEMEDICINE AND COMMUNITY OUTREACH

The Cancer Center established collaborative radiation oncology services at Saint Agnes Hospital in Baltimore and Chambersburg Hospital in Pennsylvania in 1989. Patient information from Chambersburg, such as X-rays and charts, was relayed to the Center via computer, fax and video hookup. A telephone and video conference system brought physicians from the facilities together for case review.

### DESIGNING NEW THERAPIES FOR BREAST CANCER

Led by **Martin Abeloff**, and later **Nancy Davidson,** Cancer Center clinicians were continually developing innovative therapies to treat all stages of breast cancer. For newly diagnosed patients, our physicians examined the interaction of chemotherapy and several new hormonal therapies to prevent recurrence. They also found a way to effectively administer very high doses of several certain drugs in a timed sequence.

### DISCOVERIES IN CANCER DEVELOPMENT

**Stephen Baylin, Mack Mabry, Barry Nelkin, Rob Casero** and **Andree de Bustros** found that two cancer-promoting oncogenes – c-myc and a mutated form of the ras gene – induced changes in small cell lung cancer and provided a model for studying mechanisms of change in human cancers. In laboratory models of medullary thyroid cancer, they found that the most aggressive tumors lack the protein hormone calcitonin. Inserting genes, such as ras, restored normal calcitonin production. The research provided a model to study the events that disrupt normal cell behavior to promote cancer development.

### BEFORE THE HACKERMAN-PATZ PATIENT AND FAMILY PAVILION

Two residential facilities, the Joanne Rockwell Memorial House and the Hackerman-Patz House, opened in the mid 1980s and offered patients and their families a home away from home during treatment. The 20 efficiency apartments just a block from the hospital provided communal dining, garden and living areas, classrooms, counseling programs and physical therapy rooms to create a natural circle of camaraderie and support.

### ANTI-NAUSEA TREATMENT FOR PATIENTS WITH CANCER

Noting that control of nausea and vomiting was essential in patients undergoing chemotherapy, **David Ettinger** noted in this 1984 news interview: "Antiemetic (anti-nausea and vomiting) therapy should be instituted before the start of chemotherapy in cancer patients, it should be continuous, and it should be tailored to each patient's special needs."

### MILESTONES IN PATIENT AND FAMILY SERVICES

**1985:** The Cancer Center launches Oncology Social Work Program

**1986:** The Joanne Rockwell Memorial House opens, providing homelike suites for patients and families traveling to the Cancer Center for treatment

**1988:** The Hackerman-Patz House opens, increasing the number of homelike suites available to out-of-town patients and families

**1990:** The Cancer Counseling Center is established with a gift from Mrs. Harry J. Duffey

**1992:** The first Cancer Survivors Day celebration is held, a collaboration among Baltimore hospitals

**1997:** The Art of Healing Program starts, infusing art and music into the Center

**2003:** Oncology social work with Patient and Family Services merge to form the Harry J. Duffey Family Patient and Family Services Department

**2007:** The Harry J. Duffey Family Pain and Palliative Care Program is established

Johns Hopkins marks social work centennial

**2008:** The Hackerman-Patz Patient and Family Pavilion opens

**2010:** The first Service of Remembrance is held

## 1990s

The field of epigenetics, characterized by chemical alterations to genes that support the growth and spread of cancer without mutating the DNA, becomes part of the mainstream cancer medicine. The Cancer Center's discoveries in genetics and epigenetics are regarded as the most relevant in cancer biology earning the center the nickname "Cancer Research Powerhouse."

# The Abeloff Era

## *Building on Excellence*

ABELOFF

IN 1992, AFTER a lengthy national search, **Martin Abeloff**, was selected as the second director of the Kimmel Cancer Center. During his 15-year tenure as Cancer Center director, Abeloff doubled the size of the Center's faculty and increased research funding sixfold. He expanded the footprint of the Center to include nearly 1 million square feet of treatment and research space.

However, in 1961, when he entered the Johns Hopkins University School of Medicine, Abeloff said he had no intention of staying beyond medical school. An introduction by school of medicine Dean **Julius Krevans** to then-Cancer Center Director **Albert Owens** and the announcement of plans for a Cancer Center, led him to return in 1972 as an oncology fellow.

Abeloff also recalls it as an uncertain time. Mystery surrounded the disease. No one knew what caused it, and often patients seemed to go from healthy to sick to dead in short order.

"There was an urgency about the disease that demanded a merging of laboratory and clinic," said Abeloff.

Recognition of the new specialty of oncology was just beginning. There were a few surgeons treating patients with chemotherapy, but the medical oncology clinic was brand new.

As they awaited construction of the Cancer Center, Abeloff and other doctors who had agreed to specialize in cancer treatment saw patients in a clinic in the Carnegie Building. Abeloff nicknamed it the "Under the Door Clinic" because as he sat reviewing notes related to a new patient he was about to see, a note would often be passed under the door. The contents of the notes were always similar. They told of a loved one — father, mother, sister or brother — who was unaware of his or her cancer and warning Abeloff not to reveal the diagnosis to the patient.

Of course, Abeloff could not treat patients without being honest with them, and more often than not, he found they already knew, and saying it out loud freed them to talk openly.

"Many patients felt guilty, as if it was their fault they had cancer," Abeloff said. "This blaming-the-patient mentality was common at the time and added to the stigma of the disease."

He saw getting beyond this stigmatization of the disease as one of the most important early advances. Abeloff believed it led to the forceful and thoughtful patient activism that raised public awareness.

Abeloff's interest in oncology was inspired, in part, by his mother's battle with breast cancer in the 1950s, when standard treatment was an operation known as a radical mastectomy. This entailed removing the entire breast, the underlying muscle, and substantial tissue from the armpit. He recalled observing her struggle in pain to regain mobility of her arm.

"THERE WAS AN URGENCY ABOUT THE DISEASE THAT DEMANDED A MERGING OF LABORATORY AND CLINIC."

–MARTIN ABELOFF

It was an exciting time in the fledgling field, with Johns Hopkins on the forefront. Abeloff believed it was a place that could make a difference in the management of cancer.

As he became one of the world's leading breast cancer experts, Abeloff's care of the patient rather than the disease inspired the direction of clinical care.

His list of accomplishments is impressive. He was chief of medical oncology and developed the Cancer Center's breast cancer program. He headed the American Society of Clinical Oncology, the world's leading organization of clinical oncologists, chaired the U.S. Food and Drug Administration's cancer drug advisory board, and was a member of the National Cancer Institute advisory board. He pushed for clinical trials legislation that led to insurance coverage of experimental cancer therapies.

Like his predecessor, Albert Owens, he recruited many talented cancer clinicians and scientists to the Cancer Center and oversaw the construction of an expanded Cancer Center, including the Harry and Jeanette Weinberg building, the clinical hub of the Cancer Center, and two cancer research buildings — the Bunting Blaustein Cancer Research Building and the David H. Koch Cancer Research Building. In 2002, he also secured the historic $150 million gift from Sidney Kimmel, leading to the renaming of the Center to the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.

Under his leadership, the Center's Art of Healing Program was established, boasting a collection of museum-quality artwork on display in the Weinberg Building and a concert-hall quality music program.

"You simply can't treat cancer without paying attention to the psychological and social aspects of the disease," he said.

Abeloff was key to expanding the Cancer Center's research focus to include solid tumors, including breast, lung and colon cancers. In those days, there were no cancer-specific specialists. The Cancer Center's doctors saw all patients.

Abeloff's first clinical research was in small cell lung cancer. He began a collaboration with young investigators David Ettinger and Stephen Baylin.

When he became chief of medical oncology and later when he became center director, Abeloff began to form multispecialty teams to address cancer. He continued the tradition of bench-to-bedside research that Owens initiated.

"The real gains are made when we take laboratory findings and use them to improve the treatment and life of patients with cancer. This is an area where our scientists have excelled. I don't think any institution in the world has an edge on us," said Abeloff.

Abeloff, who died in 2007 from leukemia, is remembered by his colleagues and employees for his kindness and humility. Late in his tenure as Cancer Center director, he credited the Cancer Center's growth and advances against cancer to the faculty and staff, calling himself lucky to work among individuals whose intellect and values made coming to work an absolute joy.

## Martin Abeloff

**SERVED AS KIMMEL CANCER CENTER DIRECTOR, 1992-2007**

Remembering Dr. Martin Abeloff: The Martin D. Abeloff Scholars Program in Cancer Prevention and Control was established in Abeloff's memory in 2007. During the Kimmel Cancer Center's 50th anniversary celebration, the auditorium in the Harry and Jeanette Weinberg Building was rededicated in his memory as the Martin D. Abeloff Auditorium.

Abeloff worked to make sure research against cancer was shared with clinicians and scientists around the world. He was co-editor-in-chief of the journal *Oncology* and founding editor-in-chief of *Oncology News International*. In 2007, the other co-editor, James Armitage, described Abeloff as the "physician everyone wanted to be."

Abeloff considered patient care to be the most satisfying aspect of his long and impressive career. He said when he heard a patient with brain cancer tell him that the Kimmel Cancer Center was the only place that gave him any hope, or another patient say that our doctors fixed the unfixable, he knew he knew he had set the right course as director.

# PROGRAMS AND SERVICES | ADVANCES

## BRAIN TUMOR REGISTRY

The **National Familial Brain Tumor Registry,** the first of its kind, was established in 1990 by **Stuart Grossman**, leader of the brain cancer program at the time, to explore the possibility that brain tumors may have a hereditary component. A nationwide, computerized record of families in which two or more first-degree relatives, such as parents or siblings, were affected contains the largest series of families of this kind in the world. The registry collected medical records, including brain scans and pathology reports, and some personal history that could contribute to a better understanding of the cancer.

Some early findings observed by researchers were that about half the registrants included patients and siblings who developed their cancers at approximately the same age, with the other half composed of parents and children who developed their cancers at the same time. The registry also documented several cases in which husbands and wives developed brain cancers. The registry findings led researchers to explore infectious, environmental and genetic contributors to brain cancer development.

## PANCREAS TUMOR REGISTRY

The **National Familial Pancreas Tumor Registry** was launched in 1994 to help identify the causes of pancreatic cancer. A main goal was to identify genes associated with clusters of the cancer among families. Currently, **Allison Klein** directs the registry, and several gene candidates have been identified and used to predict pancreatic cancers and guide treatment.

## WEINBERG BUILDING OPENS

**The Harry and Jeanette Weinberg Building**, home to the Kimmel Cancer Center's comprehensive clinical services, opened in 1999, with a formal dedication held in 2000. It included complete outpatient services with 24 private exam rooms, 11 consultation rooms, pathology, radiology and pharmacy services, 16 surgery suites, a 20-bed intensive care unit, a same-day surgical center and two floors of inpatient beds.

## SPORES LAUNCHED

In 1993, the National Cancer Institute launched **Specialized Programs of Research Excellence** (SPORE) to focus on specific organ site cancers and groups of related cancers, such as gastrointestinal cancers. The new funding was aimed at speeding the translation of laboratory research to patient care. The Kimmel Cancer Center was awarded SPOREs in prostate cancer, lung cancer and gastrointestinal cancers – the only cancer center at the time to earn multiple SPOREs.

In 2002, the Kimmel Cancer Center added to this unprecedented number of SPOREs, earning one for lymphoma. In 2004, the Kimmel Cancer Center's epigenetics research in lung and esophageal cancer was recognized by the National Cancer Institute as the most outstanding SPORE project.

Our research continues to earn multiple SPOREs, with current SPOREs in gastrointestinal cancers, ovarian cancer, cervical cancer and epigenetic therapies.

## THE ART OF HEALING

The Kimmel Cancer Center, long recognized as a leader in cancer research and patient care, gained new recognition in 1997 as a free-standing art gallery and music performance venue.

With the opening of the **Harry and Jeanette Weinberg Building**, the new clinical hub of the Kimmel Cancer Center, Center Director **Martin Abeloff** had a vision to create a new type of environment. It included all of the medical equipment and technology needed to heal the human body, of course, but it also had a softer side aimed at healing the human spirit.

***The Art of Healing*** – a unique art and music program – was established. With the help of curators Ted Cohen and Peggy Heller, and donor Lorraine Levin, the Center became an art gallery, home to a collection of 122 pieces of museum quality art, including watercolors, prints, silk screens, photography, quilts and sculpture showcasing Maryland artists. The bone marrow transplant unit was decorated with original Ansel Adams prints.

A Young Chang piano was donated by Steve Cohen and placed in the ceremonial lobby. The beautiful sounds of patients and family members playing are often heard. Music performances were soon added and continue today.

## CANCER BIOLOGY PIONEER

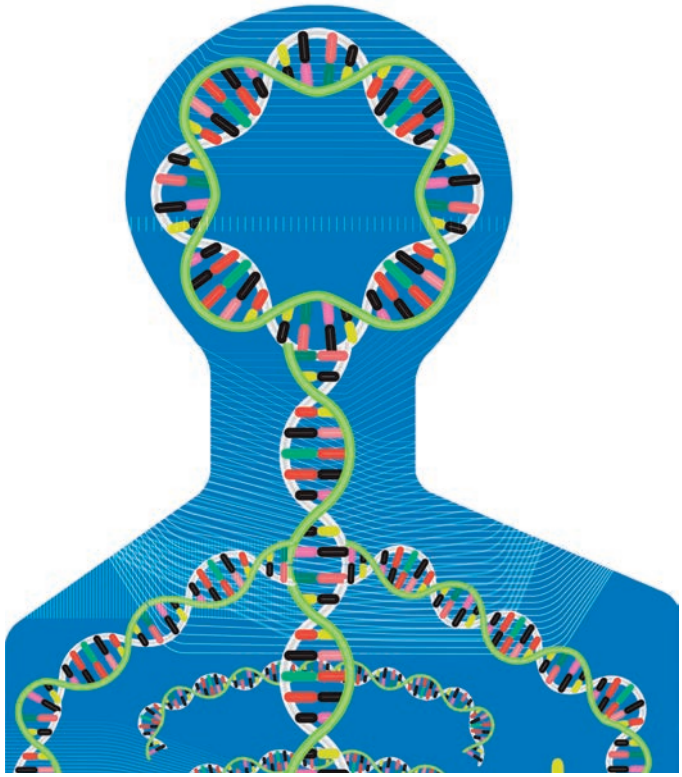
**Victor Velculescu**, co-director of the Cancer Genetics and Epigenetics program and a leading cancer biology researcher, developed methods for global gene expression analyses and coined the word "transcriptome" to describe the patterns in cancer and other cells. More recently, his group has developed non-invasive liquid biopsies approaches for early detection of cancer and for monitoring of cancer patients. These discoveries provide new paradigms for our understanding of human cancer and have created opportunities for precision diagnostics and personalized medicine for cancer and other diseases.

VELCULESCU

# The Story of Epigenetics

## *The Software in Cancer Cells*

Literally translated, epigenetics means around or above genetics. It refers to natural control mechanisms that influence gene expression. Their role is often compared to computer software. Think of DNA and the genes we are born with as the human hard drive. Everything a cell does is controlled by this hard drive, but a hard drive cannot work without software.





Epigenetics is the software package. Researchers believe that every cancer may have 50 to several hundred genes that have working "hard drives," but their epigenetic "software" is causing them to act in a way that can lead to cancer development.

Renowned veteran cancer scientists such as **Donald Coffey**, **Stephen Baylin**, **Peter Jones**, **Andrew Feinberg** and current Kimmel Cancer Center Director **William Nelson** have been studying this biological process for decades.

BAYLIN

FEINBERG

As a field of study, epigenetics did not gain widespread acceptance until the early 2000s. Technologies that allowed science to analyze DNA at the molecular level and the tenacity of a relatively small group of scientists proved its validity. The long-concealed mysteries of what some have referred to as the "ghost in our genes," referring to epigenetic mechanisms' ability to alter gene expression without leaving a permanent mark on DNA, were uncovered.

With a group of epigenetic scientists, whom Nelson characterized as "second to none," the Kimmel Cancer Center became a hub for epigenetic discovery and clinical translation.

Findings by Feinberg, director of the Johns Hopkins Center for Epigenetics in the Institute for Basic Biomedical Sciences, and Baylin, the Virginia and D.K. Ludwig Professor of Oncology, blazed trails in this field.

Feinberg described a global demethylation of the cancer genome. In normal human development, when the sperm and egg come together and form that first cell, how that one cell divides and determines what its fate will be to eventually form a complete human body was controlled through epigenetic mechanisms, he showed. Gene expression is what makes a cell behave the way it behaves, but how a cell figures out what proteins to express is controlled through epigenetics.

Feinberg suspected that this process was somehow getting hijacked in cancer. Corruption of the mechanisms that makes an undifferentiated cell know to become a liver cell could be at the root of the transformation of that same liver cell into a cancer cell.

Baylin's focus was on chemical changes to protein-expressing regions of cancer genes, mainly tumor suppressor genes. The chemicals act like punctuation marks, turning off or accelerating gene expression, and provided a therapeutic target. Drugs that blocked methylation of the gene could, in principle, turn a tumor suppressor gene back on or a tumor accelerating oncogene off.

These promising advances inspired the research of young investigators entering the cancer field.

Kimmel Cancer Center Director William Nelson, was one of them. He did not set out to become an epigenetics researcher. In the early 1990s, he was beginning his career as a prostate cancer clinician and scientist when his research on cancer drug resistance led him to what remains today as one of the most classic examples of gene silencing through hypermethylation driving the development of cancer.

Baylin and former Kimmel Cancer Center faculty member **James Herman** had already introduced a scenario in which tumor suppressor genes could be rendered inactive through the epigenetic process of a chemical change to DNA, called hypermethylation, but they had not uncovered a real-life example.

Nelson's research led him to a gene called GSTP1, which he found was hypermethylated in prostate cancer. His discovery was used to create the first noninvasive, epigenetic-based test for the disease.

Baylin and Herman built a tool that allowed scientists to look laterally at many genes across many cancers and establish a pattern of silencing through gene methylation. These hypermethylated genes were the subjects of promising innovation in the form of biomarker tests that could tease out aggressive cancers from more indolent forms and provided new targets for novel treatment strategies.

Laboratory findings in leukemia and lung cancer paved the way for clinical trials of a drug that appeared to have the ability to fix some of the epigenetic-initiated changes to genetic code that helped cancers grow and thrive.

The world was beginning to take notice, and Baylin's laboratory model was becoming a clinical model. Crucial to these advances was a new type of drug recognized by Jones in the 1970s as a demethylating agent. Too much methylation in the active regions of tumor suppressor genes was found to shut the genes down, giving advantage to one of the cancer cell's iconic behaviors — uncontrolled growth. Blocking the methylation of the gene turned the suppressor gene back on.

Research published in the 1980s led Baylin and team to take a closer look at a demethylating drug called 5-azacytidine, which had largely been abandoned because of its toxicity. Laboratory studies in lung cancer and leukemia led to a clinical trial for patients with a pre-leukemia condition called myelodysplastic syndrome (MDS). The drug worked well, with some patients disease-free for 10 years and counting. Based on this work and the research of others, including former Kimmel Cancer Center faculty member **Jean-Pierre Issa,** 5-azacytidine received FDA approval for treatment of MDS. Baylin wondered if the drug might also work against other cancers.

In 1992, the Kimmel Cancer Center earned a new type of funding offered by the National Cancer Institute to speed the translation of laboratory research to new diagnostics and therapeutics for cancer. The program was called SPORE, for Specialized Projects of Research Excellence. The Kimmel Cancer Center was the only NCI-designated cancer center to earn multiple SPOREs.

**In 1992, the Kimmel Cancer Center earned a new type of funding offered by the National Cancer Institute to speed the translation of laboratory research to new diagnostics and therapeutics for cancer.**

One SPORE helped Baylin and team advance epigenetic discoveries. They began using methylation levels as an early indicator of a developing cancer and to predict whether a cancer would respond to specific cancer drugs, and if it was likely to come back after treatment. Kimmel Cancer Center epigenetics researcher and surgeon **Malcolm Brock** used epigenetic markers as a guide during lung and esophageal cancer surgeries to help him determine if all of the cancer was removed. He dubbed it molecular staging. Although there was no visible evidence of cancer, Brock and others were using methylation as an epigenetic trail of evidence to reveal cancer cells hiding in tissue, such as lymph nodes.

Working with Herman, Brock revealed that the evidence of small cell lung cancer's inevitable return was in the methylation patterns of four genes. Depending upon the combination of genes abnormally methylated, the risk of a cancer returning was 2% to 25%. The overmethylation of two genes — p16 and H-cadherin — proved to offer the worst scenario, foreshadowing a swift return of the cancer.

In 2004, their body of epigenetic research was recognized by the NCI as the most outstanding in the SPORE program.

Similar work soon expanded to prostate, head and neck, breast and other cancers.

## BREAST CANCER TEST

Breast cancer researcher **Saraswati Sukumar** modified a test called MSP to detect breast cancer. The test was originally developed by Baylin and Herman in 1996 and used in the Cologuard test to detect abnormally methylated genes in stool samples. The Liquid Biopsy for Breast Cancer Methylation test measures DNA methylation in 10 tumor-specific genes from fluid aspirates of the breast lesion and sometimes an enlarged lymph node. The test has three cartridges that hold chemicals to detect methylated DNA from fluid obtained from the patient's breast growth or lymph nodes, and includes a computer pre-loaded with software to analyze the data and return results within five hours. The test can detect new breast cancers and help detect breast cancer recurrence.

"Our goal was to develop an assay that would be sophisticated yet simple to perform worldwide and could be used at the point of care to provide same-day feedback to clinicians and patients," Sukumar says.

## CLINICAL STUDIES

**Nilofer Azad**, director of the Center's Colorectal Cancer Research Center of Excellence and the Developmental Therapeutics Program, led clinical studies of epigenetic-targeted therapies in colon cancer. She worked to develop epigenetic biomarkers that predicted sensitivity to specific chemotherapy drugs.

She used the MSP test developed by Baylin and Herman to identify a specific epigenetic biomarker that indicates cancers that should be susceptible to a class of anticancer drugs called taxanes, which were once thought ineffective in colon cancer. With drug treatments for colon cancer limited, Azad believes an individualized epigenetic approach could significantly expand the options for patients.

"Many drugs have been tested and looked inactive when they are given broadly to large groups of patients, but we are finding that there are subsets of patients who may benefit, and we can use epigenetic biomarkers to identify these patients," says Azad. "Drug treatments are limited for colorectal cancer patients, and this is one approach that could help us significantly expand options for patients."


BROCK


SUKUMAR


HERMAN

## DREAM TEAMS

In 2008, the Entertainment Industry Foundation and Major League Baseball formed Stand Up To Cancer (SU2C) to mobilize the public to donate money for cancer research and to motivate the scientific community to collaborate on promising areas of research that could quickly be moved to clinical trials. "Dream teams" made up of clinicians and scientists from across the country — the best in their fields — were selected after rigorous review by another panel of esteemed cancer experts and directed to take on specific cancer research projects. When the epigenetics dream team was announced, Baylin was selected as co-leader.

## DNA PACKAGING

His research of the role of DNA methylation in cancer had led him to a molecular co-conspirator. He observed that it wasn't just DNA methylation that affected gene expression but also the way DNA was packaged in a cell. It reflected Nobel Prize-winning work on how DNA is wrapped in a structure, called the nucleosome, an area of research also extensively studied by Jones.

The nucleus is a structure so tiny that more than 50,000 of them can fit on the head of a pin. If the DNA contained within one cell was extracted and stretched out end to end, it would extend 6 feet, yet all of that molecular material is compacted and packed inside the nucleus of a human cell. Chromatin, a complex combination of proteins, mainly histones, which defines the nuclesosome, is responsible for compressing the DNA to fit inside a cell.

**The nucleus is a structure so tiny that more than 50,000 of them can fit on the head of a pin.**

This packaging also plays a role in gene expression and the copying of DNA as cells divide. A loose chromatin results in normal gene expression, but add methylation to the mix, and this compacts the position of nucleosomes on DNA and silences gene expression. Baylin and team found this tightened chromatin could keep genes, including tumor suppressor genes, in a constant state of non-expression. It also caused cancer cells to behave in a primitive, embryonic-like manner. Unlike normal embryonic cells, which receive and respond to signals that tell them to stop making new cells, epigenetically altered cancer cells maintain their ability to replicate, renew and divide.


ZAHNOW


AHUJA

Scientists do not know what prompts the cancer-promoting changes in chromatin structure. They suspect it may be a repair mechanism engaged in response to cell injury, such as chronic inflammation. Baylin and colleagues reported that these dynamics can initiate and maintain the abnormal DNA methylation, associated tumor suppressor gene silencing, and the malignant properties of established cancer cells. In the laboratory, when he and his team combined a demethylating drug with a histone-blocking drug (HDAC inhibitor) in human cancer cell lines, the chromatin structure loosened, and some gene expression was restored. Blocking inflammation-induced dynamics can have the same result, says Baylin. These discovery findings were the focus of the first SU2C Epigenetic Dream Team patient studies.

## COMBINATIONS

The first clinical study of the combined demethylating agent and histone-blocking HDAC inhibitors was in patients with advanced lung, breast and colon cancers. The drugs were not given at the highest dose that patients could tolerate, as is usually the case in early studies of anticancer drugs. Rather, low doses were given. The goal was to kill the cancer cells by reprogramming their DNA, instead of obliterating them with chemotherapy agents. In essence, the researchers were using the drugs to convert cancer cells back to normal cells.

At high doses, the drug killed cancer cells, but at lower doses over time, it reprogramed cancer cells to behave like normal cells, a much less toxic and more permanent cancer fix. It was a radical departure from the standard approach of blasting cancer cells with as much poison as possible, but there was significant laboratory evidence to show that it could work.

The responses, although small in number, were unprecedented. Patients with resistant, lethal lung cancer that had spread to other organs and was resistant to other treatments were seeing their tumors melt away. In a few other patients, tumors stopped growing. The cancers didn't go away, but they seemed to be dormant.

Still, most patients treated did not respond, and responses in patients with breast cancer and patients with colon cancer were not nearly as dramatic as those seen in the small group of patients with lung cancer. This did not surprise or deter Baylin and team. Earlier work by him, Herman and Brock showed that specific epigenetic biomarkers provided a signature that could differentiate patients who were likely to respond from those who would not.

This trial was open to all patients with resistant cancers, and with no analysis for the epigenetic signature of their tumors, the expectation was that a small subset of patients would see results. The analysis would come later with Baylin, basic scientist **Cynthia Zahnow** and cancer surgeon and former faculty member **Nita Ahuja** taking cells back to the laboratory for gene expression analyses.

## REIGNITING RESPONSES

With funding from SU2C, Baylin and team had the opportunity to follow up on patients who were taken off the trial because their cancers continued to grow despite treatment with the experimental epigenetic therapy. These patients had end-stage cancers that had spread and were unresponsive to three different attempts at chemotherapy, so they expected most had passed away. However, when the team went back and reviewed the records of these patients, they learned that many of the patients with lung cancer were still alive because their cancers had suddenly begun to respond to a wide variety of anticancer drugs.

Patients whose tumors seemed to progress while they were on the experimental therapy — some who had only received two or three treatments — were alive and doing well. Cancers that had continued to grow and spread despite every effort were suddenly transformed. They pored over every scan, piece of clinical paperwork and biopsy report available.

"There could only be two explanations," says Baylin. "Either the epigenetic therapy sensitized the cancers to subsequent treatment with standard drugs, or their improvement was a direct response to the epigenetic therapy."

## PRIMING EFFECT

The team needed to complete further studies in the laboratory to solve the mystery.

These new epigenetic-targeted therapies do not work like the old cell-killing cytotoxic chemotherapies that do not discriminate between normal cells and cancer cells. Instead, Baylin says they worked slowly over time as they made repairs and returned genes to normal function. Baylin, Herman, Brock, Ahuja and Zahnow also found that the epigenetic drugs had a priming effect on the tumor and made formerly resistant cancer cells begin responding again to treatment with anti-cancer drugs.

## IMMUNE EVASION

As they began to study the cell lines in the laboratory, they found that the epigenetic drugs had the capability to impact almost every type of cell mechanism, including cell division, cell repair, and cell cycle and death. Of particular interest to the researchers was the treatment's effect on genes related to immune response.

Immune cells are on patrol at all times in the human body, differentiating between foreign invaders and normal cells. Cancer cells are derived from normal cells, so they can fly beneath the radar of the immune system. However, as the science of cancer immunology has advanced, researchers are finding that there is more to the cancer cell's ability to evade the immune system than its similarities to normal cells. Cancer cells use epigenetic controls to corrupt immune responses to cancer cells. By hijacking the mechanisms that allow the immune system to differentiate an invading virus cell from a body's own cells, it causes the immune system to tolerate cancer.

In their laboratory analyses of gene expression in cell lines derived from patients in the epigenetic treatment studies, one immune target jumped out at them. This target was a gene called PD-L1.

Epigenetic treatment turns on a number of silenced genes. Some of them encode molecules in the immune system that turn on immune responses and some that turn them off and lead to immune evasion. Immune-inhibiting genes turned on by epigenetic therapy include PD-1, part of the intricate checkpoint system hardwired into the immune system, and its partner PD-L1.

Normal human cells need the ability to communicate with immune cells that they are the good guys and should be left alone. Unfortunately, cancer cells exploit the same process to avoid an immune attack.

Baylin and Zahnow sought out the help of Cancer Center immunology expert **Drew Pardoll**. In some patients in the study, the PD-L1 gene was already active, and laboratory studies indicated that its expression by lung cancer cells might be enhanced by epigenetic therapy. Pardoll believed that using a drug to block PD-L1 or PD-1 in conjunction with epigenetic therapy could alter the balance of immune effects of the treatment toward an activated immune response right within the tumor.

Pardoll recruited the help of other Kimmel Cancer Center colleagues, including cancer immunology expert **Suzanne Topalian** and lung cancer expert **Julie Brahmer**.

It has been well established that cancer has an immune evasion signal. To survive, cancer cells need to at least partially adapt to their environment. They send out a "don't look at me" signal to immune cells. Treated with epigenetic drugs, however, the ability to evade the immune system is broken and cancer cells send new signals — on one hand, they beckon the immune cells to come and get them, and on the other, they shield against immune attack by expressing PD-L1.

## BACK TO THE LAB

Baylin, Zahnow, Ahuja and colleague **John Wrangle** 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 that get turned on in cancer cells with demethylating drugs. Lots of genes, they found, get reactivated, but about 20% of them are related to immune regulation. Their findings revealed that a significant part of what the epigenome does is regulate the immune system.

Their research revealed a set of genes that are epigenetically programmed to evade detection by the immune system. Using a drug to reverse this programming may force the cancer cells out of hiding and make them more vulnerable to treatment, or even better, allow the immune system to see the cancer and kill it.

SU2C support included a study of a combined therapy of a demethylating agent, a histone-blocking HDAC inhibitor and anti-PD-1 treatment.

There were two components to the trial, one aimed at verifying the immune responses and the other at further testing the epigenetic priming effect — the ability of epigenetic therapy to sensitize cancers to subsequent chemotherapy. At the same time, a number of trials were launched at the Kimmel Cancer Center and elsewhere studying a wide variety of epigenetic drug combinations and single agents.

Kimmel Cancer Center experts accumulated 70 cell lines from breast, colon, ovary and lung cancers and patient biopsies that they were comparing to the cell lines. Gene expression data, methylation data, proteomics data — anything that could be measured in a cancer cell was being analyzed.

There is some evidence that demethylating agents have a stronger effect on the epithelial cells where cancers most often originate. The histone-blocking HDAC inhibitors appear to influence the immune cells and microenvironment.

Other Kimmel Cancer Center experts also believed that epigenetic therapy might be more powerful in combination with immunotherapy.

Epigenetic alterations are common in breast cancer, so breast cancer experts **Vered Stearns**, **Roisin Connolly and Evanthia Roussos Torres** collaborated with leading cancer immunology


PARDOLL


TOPALIAN


BRAHMER

expert **Elizabeth Jaffee**, deputy director of the Kimmel Cancer Center, to develop a study of combined epigenetic/immune therapy for breast cancer. In their study, they gave an epigenetic drug called an HDAC inhibitor two weeks before treatment with an immunotherapy that released restraints on immune cells in an effort to prime the immune response to the cancer. They continue to study tumor samples and blood samples from patients to identify biomarkers that help identify those most likely to benefit from the combination therapy.


STEARNS

"There was still so much we needed to learn," says Zahnow. "What is the best way to give the drugs? Should they be given simultaneously or consecutively? What are all of the targets the drugs hit?"

## EPIGENETICS AND GENETICS


CONNOLLY

Cancer genetic and epigenetic research has advanced dramatically at the Kimmel Cancer Center, with the leading experts in both disciplines working together. The interplay between genetics and epigenetics was revealed because of Kimmel Cancer Center excellence in both fields.


TORRES

"It's interrelated," says **Vasan Yegnasubramanian**, who runs the Kimmel Cancer Center Next Generation Gene Sequencing laboratory. "Many epigenetic problems may have their basis in genetic abnormalities. The genes that get mutated in cancer are often genes that control DNA packaging."


YEGNASUBRAMANIAN

A prime example of a genetic mutation having epigenetic consequences is the brain cancer gene called IDH1, identified by Ludwig Center cancer genetics researcher **Nickolas Papadopoulos** and team in 2008. IDH1 produces an enzyme that regulates cell metabolism, but a mutation in the gene results in increased production of a metabolite that can affect DNA methylation. IDH1 mutations are very simple genetic changes, but they cause a cascading effect of alterations to the epigenetic landscape that ultimately become a major driving force behind the cancer.

Investigators believe there are many more examples of the genetic/epigenetic collaboration in cancer. Although it is impossible to fix a mutated gene, the epigenetic changes can be targeted and disrupted with drugs.

In a study of prostate cancers from men who died of the disease, Yegnasubramanian found increased methylation in genes not methylated in normal tissue. In each patient studied, this pattern of hypermethylation was consistently maintained across all of the metastatic prostate tumors and occurred near genes in cancer-related pathways that control development and differentiation.

"We need to do more research, but it looks like the areas that have increased methylation are being selected by the cancer cell to keep its advantage," says Yegnasubramanian. "We know these were resistant cancers because we obtained the tumor samples from men who died of prostate cancer. Perhaps if these methylation alterations could have been reversed, the cancer cells might become sensitized to treatments."

The opportunity to offset the collateral damage to epigenetic functions caused by broken genes is one of the newest and most promising iterations of epigenetic research, and one that is rapidly revealing new targets for treatment. Driving this progress is new technology that allows investigators to catalog epigenetic changes and align them back to the genome.

"There are striking differences in how DNA is organized in the cancer cell and how it is organized in the normal cell," says Yegnasubramanian. "Now we have the technology to go in and look at this at the molecular level."

This ability has become critically important with growing evidence that some mutated tumor suppressor genes establish cancers through many subsequent epigenetic alterations.

"Although the mutation is the initiating event, it is the epigenetic alterations that are involved in driving the cancer, and unlike mutations, the epigenetic changes can be targeted and halted with drugs," says Yegnasubramanian.

## A CANCER RESET

In this era of personalized cancer medicine, many experts believe that epigenetics could be a master control of sorts, so intrinsic to the initiation and spread of cancer that it could potentially provide opportunities to globally reset cancer cells. The panel of epigenetic alterations that drive a particular cancer may vary, but if they can be identified in individual patients, then maybe we have found the Achilles' heel of cancer.

Still, most experts agree that science has only scraped the surface when it comes to epigenetics. The understanding of the full power of epigenetic mechanisms to read, write, erase and move genetic code is just beginning to be understood, but already we have promising treatments.

> "If we looked at all of the genes silenced epigenetically in cancer and could turn them all back on, no cancer cell could withstand it."

"If we looked at all of the genes silenced epigenetically in cancer and could turn them all back on, no cancer cell could withstand it," says Nelson. "We can do that in the laboratory, and now we are learning how to do it safely and effectively in humans. We have tremendous opportunity and unparalleled ingenuity. All we need to do is connect the dots."

## MILESTONES OF EPIGENETIC DISCOVERIES

**1982:** Chemical changes in the tumor predict the behavior of medullary thyroid cancer

Inhibiting polyamines, which facilitate cell growth, kill small cell lung cancer cells in laboratory experiments

**1987:** Epigenetic events leading to progression of medullary thyroid cancer are deciphered

Epigenetic regulation of the calcitonin gene in human tumors is discovered

**1988:** First laboratory model of small cell lung cancer reveals epigenetic changes leading to treatment resistance

Hot spots of increased DNA methylation, a chemical change to the signaling region of genes, is found to play a key role in genetic instability of cancer

**1994:** Epigenetic silencing of the GSTP1 gene is linked to prostate cancer initiation

**1995:** Hypermethylation of a series of important genes, including the von Hippel-Landau gene in the most common type of kidney cancer; the p16 gene, a common tumor suppressor gene; and the p15 gene in leukemias are linked to cancer initiation and progression

**1996:** Hypermethylation of a series of genes is associated with the development of all types of cancer, including lung, breast, colon, prostate, kidney and leukemias

Investigators show in laboratory experiments that epigenetically silenced genes can be turned back on using drugs that inhibit methylation

**2004:** A test that measures methylation of specific genes is used to detect breast cancer from a tiny drop of breast fluid

Kimmel Cancer Center epigenetics research earns National Cancer Institute recognition as the most outstanding in its SPORE program

**2006:** The genetic and epigenetic discoveries made at the Kimmel Cancer Center lead it to be dubbed by *ScienceWatch* a "cancer research powerhouse"

**2010:** Clinical trials of the first therapies that target epigenetic alterations begin

**2017:** A combination of two epigenetic drugs – a demethylating drug and an HDAC inhibitor – prime non-small cell lung cancers to respond better to immunotherapy

Epigenetics expert **Stephen Baylin** is selected to lead one of 10 *Stand Up To Cancer* Catalyst clinical trial projects

**2018:** Tumor-associated epigenetic states are found to evolve erratically during early stages of tumor development, eventually selecting for a subset of genes that undergo the most changes during normal aging and in early tumor development

**2019:** Epigenetic changes common to aging are found to play a role in colon cancer initiation

Researchers successfully block the activity of portions of a protein known as UHRF1, restoring the function of hundreds of cancer-fighting genes

**2020:** Turning on the inflammasome – a protein-signaling network that is activated to rid the body of virus or bacteria-infected cells – with epigenetic therapy makes cancer cells targets of the immune system and responsive to drugs known as PARP inhibitors

The epigenetic drugs 5-azacitidine and entinostat target certain tumor-promoting immune cells and reduce cancer spread and recurrence in lung, esophageal and breast cancers

Researchers associate higher levels of methylation with a greater risk of five-year recurrence of triple negative breast cancer

**2021:** Breast cancer detection assay examines cells from enlarged lymph nodes in the armpit adjacent to a breast and measures methylation to differentiate metastatic breast cancer from a benign condition, such as an infection

**2022:** The diagnostic accuracy of random fine needle biopsy, a breast cancer detection test, is found to be insufficient alone to detect methylation in small, premalignant breast lesions

**2023:** An assay called the Liquid Biopsy for Breast Cancer Methylation detects methylation in several breast cancer genes, predicting disease progression and response to therapy

# Pediatric Oncology

## *Helping Our Youngest Cancer Patients*

THERE WAS A TV commercial in the 1970s that showed an empty football stadium. The empty seats symbolized the astonishing number of children killed by leukemia each year in the U.S.

Very few children survived cancer during this time. There were no drug therapies. Surgeons could cut out tumors that occurred in and around organs, but if the tumor came back after surgery, there was little to offer. It was worse still for young patients suffering from cancers that formed in the blood, including leukemia, the most common childhood cancer. The disease was almost always fatal.

### BRIGID LEVENTHAL


LEVENTHAL

This was the scenario in which **Brigid Leventhal**, a Harvard Medical School graduate and National Institutes of Health-trained researcher, was recruited to Johns Hopkins in 1976 as the Cancer Center's first pediatric oncologist and director of pediatric oncology.

Under Leventhal's leadership, the Kimmel Cancer Center started to change the landscape of pediatric cancer research and treatment.

"Brigid Leventhal was a master clinical researcher," says **Donald Small**, the Kyle Haydock Professor and current director of pediatric oncology. Her laboratory research focused on drug therapies to treat leukemia and lymphoma and paved the way for the first clinical studies of drug therapies in pediatric cancers.

She established a fellowship program to develop the specialty knowledge that was needed to advance the field. She was also a founding member of the Pediatric Oncology Group, one of two U.S. cooperative groups leading research against pediatric cancers.

"Fortunately, pediatric cancers are rare," explains Small, "and early on, pediatric oncologists realized they had to band together in groups to treat patients with the same cancers in the same way to find the treatments that would improve cure rates."

Leventhal and colleagues began treating pediatric cancers with drug therapies, first single agents and later with combinations of drugs. They began to see the first cures.

"Before chemotherapy, there were few survivors," says Small. "Survival was measured in weeks to months."

With chemotherapy came toxicities, and Leventhal also led the way in recognizing and managing the impact of early drug therapies on young patients with cancer.

"Beyond the aura of risk always hanging over them, they face huge difficulties getting good jobs, breaking into careers and getting insured. The drugs produced wide swings of mood and unlovely behavior for which they blamed themselves. Family and friends and teachers don't always understand. Even physicians expected patients to be grateful they were alive. Many viewed demands for more of the good life, friends, college education, insurance, careers, marriage and kids as greedy, and if appropriate at all, it must at least be way down on the list of priorities," said Leventhal in 1986.

Patients disagreed, and so did Leventhal, becoming one of the first to lead the charge for scaled back therapies when possible and management of treatment side effects.

Most pediatric oncologists shied away from taking on this challenge. Leventhal was undeterred. She began a pioneering study of Hodgkin lymphoma, which led to refinements in therapy that allowed certain patients, based on specific characteristics, to receive less radiation or forgo it all together without increased risk of recurrence.


WHARAM

She worked closely with radiation oncologist **Moody Wharam**. He developed the standard of care for a pediatric cancer of the connective tissue that attaches muscles to bone, called rhabdomyosarcoma. Working with the Pediatric Oncology Group, he developed a chemotherapy/radiation therapy combination that led to improved survival and that remains the foundation for how children with this cancer are managed today. It also earned the Center's radiation oncology program distinction as one of just a select few in the nation with expertise in treating pediatric patients with cancer.

## CURT CIVIN


CIVIN

These refinements in cancer therapy continued. In 1984, when Leventhal stepped down and **Curt Civin** took over as director of pediatric oncology, he began taking a closer look at the treatment for acute lymphocytic leukemia, the most common cancer in children.

Chemotherapy had made dramatic improvements, but still only half of patients diagnosed survived. By reclassifying the subtypes and changing the way chemotherapy was administered, Civin dramatically improved survival rates to nearly 90%.

Civin also expanded the pediatric oncology program to six faculty members. In addition to providing clinical care to patients, he required all faculty members to conduct laboratory research, earning the pediatric oncology program a reputation as a translational research powerhouse. He earned a training grant from the National Institutes of Health to support this in-depth training in laboratory research.

This bench-to-bedside approach was aimed at improving survival among patients with pediatric cancers.

"We're specialists. We take the toughest cases — the patients that others cannot help — and give them a chance," said Civin in 1995. "When I became a pediatric oncologist, just 30% of patients were cured, and a few decades later that improved to 70%. I am proud to say that Johns Hopkins has played an instrumental role in changing these statistics."

Civin's laboratory research focused on leukemia and was aimed at understanding what went wrong in the development of blood cells that leads to cancer. Research into blood-forming cancers at the time was limited because of the inability to isolate and study blood stem cells. These cells reside in the bone marrow and make up just 1% of bone marrow cells, but they are critically important because they give rise to every other type of blood cell.

It is in these cells, Civin theorized, that something went awry, causing unchecked growth of one type of cell at the expense of all other blood cells.

After two decades of tracking the elusive blood stem cells, Civin developed the CD34 antibody, which worked as a literal stem cell magnet, picking out these rare cells. The breakthrough made it possible to transplant healthy stem cells into people with cancer to help repopulate a patient's blood and immune system after treatment to destroy cancer cells. It also provided a better understanding of how leukemia and lymphoma originated.

The use of the CD34 antibody was approved by the U.S. Food and Drug Administration in 1996, and since that time, thousands of patients have been treated worldwide using Civin's technology.

## MICHAEL KASTAN


KASTAN

Another pediatric oncologist, **Michael Kastan**, was also leading pioneering research as he determined the function of the p53 gene, the most commonly altered gene in cancer.

Kastan identified the biochemical pathway of the P53 gene, and found that this gene causes damaged cells to stop reproducing. When this gene is missing or mutated, damaged cells grow unchecked, potentially resulting in cancer.

Although chemotherapy and radiation resulted in significantly improved survival rates, researchers noted that some cancers grew resistant to the treatments. Kastan began studying the cellular and genetic responses to chemotherapy and radiation, which work by damaging tumor cell DNA. This damage results in a sequence of intracellular events that lead to cell death, but in some cases, rather than dying, the tumor cells keep growing or temporarily stop growing for a time and then start growing again.

The signal for cells to die after DNA damage caused by radiation or chemotherapy works through the P53 tumor suppressor gene, he found. Researchers in the Kastan lab discovered that certain growth factors can also play a role in the cell's decision to live or die. If the growth factor is present or if the tumor cell contains cellular molecules that are usually stimulated by the growth factors, the tumor cell is better able to survive cancer therapy.

This research led to some of the first studies in targeted therapies — drugs that block these signals that drive cancers to grow and spread.

## ROBERT ARCECI


ARECCI

**Robert Arceci** followed Civin as director of pediatric oncology and continued to build the strength of the Center's research and patient care. He increased the number of faculty members to 10 and led research of acute myeloid leukemia in the Children's Oncology Group, helping identify molecular targets that led to improvements in therapy in pediatric and adult patients.

Arceci also worked with the Histiocytosis Society, and helped uncover mutations linked to histiocytosis, a cancer-like disease characterized by abnormally increased numbers of a type of white blood cell called histiocytes. The disease had been largely considered a mystery until Arceci helped identify the mutations.

Describing what drove him to focus his career on pediatric cancers, Arceci said, "Children are going to be the people who help the adults. They are going to save us. I think it is truly phenomenal."

## DONALD SMALL


SMALL

Small says he was impacted by all of his predecessors. He was an M.D./ Ph.D. student under cancer genetics pioneer **Bert Vogelstein**, a pediatric hematology/ oncology fellow trainee under Leventhal, and a young, new faculty member hired by Civin, when he established his own laboratory after his postdoctoral training with **Tom Kelly**, who headed the Molecular Biology and Genetics program.

Small's work ultimately led to a pioneering discovery in a type of leukemia called acute myeloid leukemia (AML). He cloned a gene called FLT-3, the most frequently mutated gene in AML and one associated with poor survival.

"Having an FLT-3 mutation reduces the chances of curing an AML from about 50% to less than 20%," says Small, who identified a drug to target FLT-3 and worked with Kimmel Cancer Center colleague **Mark Levis** to develop a test to tell if the drug was hitting its FLT-3 target.

With Arceci's encouragement, Small served as vice-chair of the AML committee of the Children's Oncology Group for five years, helping him bring FLT-3 inhibitors to clinical trials in pediatric patients.

Better iterations of FLT-3 inhibitors are now being studied alone and combined with other drugs for the treatment of AML in adults and children.

Small also grew the pediatric oncology program to 22 faculty members and built subspecialty programs in sarcoma, neuro-oncology, leukemia/lymphoma, and bone marrow transplant.

He also a launched an annual lecture honoring pediatric oncology founder **Brigid Leventhal**, and notes that today, half of pediatric oncology faculty members are female.

Leventhal was a strong advocate for pediatric oncology patients, believing they did not get enough support after treatment. Small continues to strengthen programs that aid pediatric patients with cancer, including its long-term survivors program — one of the first childhood cancer survivors programs in the country to study, monitor, treat and develop methods to prevent and address long-term complications of cancer therapy.

With only 4% of the National Cancer Institute budget going toward pediatric cancer Small also realized the importance of fundraising. Working first with **Stephanie Davis** and later **Kelli Schneider** from Development, he increased annual fundraising from about $200,000 to more than $3,000,000 a year.

"When you think that just a couple decades ago, few children survived a diagnosis of cancer, and that today, the reverse is true, you realize the power of research and the kind of change it can bring," says Small. "This kind of translational research is the hallmark of our Cancer Center."

## A STATE-OF-THE-ART HOSPITAL

The Charlotte R. Bloomberg Children's Center, a technologically advanced but patient- and family-friendly building, is home to our pediatric oncology inpatient unit and outpatient clinic. The inpatient unit and outpatient clinic are located on the 11th floor. The state-of-the-art Children's Center inpatient unit has 20 private rooms with the ability to expand to 22. It includes a playroom for children and a separate room for teenagers, and a host of amenities for the comfort of families, including sleeper sofas in every room, lounges, showers, laundry facilities and 24-hour food service. The outpatient unit has eight exam rooms for private infusion areas and a beautiful, two-story open infusion area with five additional chairs and beds. It has two waiting areas separately and distinctively designed for the different interests and needs of children and teenagers, and also has an on-floor pharmacy.

## THE FORGOTTEN DEMOGRAPHIC

A study published in 2008 found that 16- to 20-year-olds with acute lymphocytic leukemia, a cancer that occurs in children and adults, who receive pediatric care had nearly 20% higher survival rates than those who received adult care.

"Overall cure rates among pediatric cancer patients are 50% higher than the rates among adult cancers," says **Donald Small**, Kyle Haydock Professor and Director of Pediatric Oncology. "It makes a lot of sense. An adolescent's or young adult's organ systems are more like a 10-year-old than a 65-year-old. The therapy that we give is more intense, but it turns out that young adults can tolerate that, and as a result, cure rates are higher."

This realization inspired Johns Hopkins Hospital leadership, in 2019, to raise the cutoff age of patients who could be treated in pediatric oncology from 21 to 25.

"The new age can be modified, leaving plenty of room for pediatricians and adult doctors to work together and recommend patients to each other," says **Kenneth Cooke**, the Herman and Walter Samuelson Professor of Oncology and head of the pediatric oncology blood and bone marrow transplantation program. "We are all under one roof at The Johns Hopkins Hospital, which gives our patients an important advantage, but there's still work to be done to ensure that each patient gets the correct treatment regardless of age."

He points out that there are some cancers that occur in pediatric and adult patients but are more common among children, teens and young adults. In these cases, age cutoffs for treatment can be arbitrary and even detrimental. Doctors may refer a 17-year-old

# PEDIATRIC ONCOLOGY | ADVANCES

diagnosed with cancer to a pediatric oncologist, but another patient with a few months' difference in age and with the same diagnosis might be sent to an adult oncologist, says Cooke, who treats children, teens and young adults up to their late 20s.

Kimmel Cancer Center pediatric oncologists and nurses find most teens and young adult patients prefer the pediatric setting, which offers more one-on-one care and generally provides more logistical and emotional support than adult units.

## THE STORY OF CAMP SUNRISE

What began in 1987 with seven campers has grown into the Kimmel Cancer Center-maintained and operated Camp Sunrise, with more than 100 campers and 70 trained volunteers and medical staff members. For one week each summer, campers and volunteers come together at Elks Camp Barrett in Crownsville, Maryland, for hiking, swimming, dancing, crafts, games, sports, campfires and reunions with friends.

Camp Sunrise may be the only place where cancer takes a backseat to childhood and teenage fun. The goal of the camp is to give campers the best week of their lives. Beyond the fun, campers treasure the direct connection to other kids who understand and share their unique experience.

Camp Sunrise is for former and current cancer patients who are 4 to 18 years old. The 4- and 5-year-olds participate in a day camp, and campers 6 to 16 years old come for a traditional residential sleepover camp, complete with rustic cabins and plenty of outdoor adventures. The older, 17- and 18-year-old campers take part in a leadership training program so, if they choose, they may join the ranks of the Camp Sunrise volunteers as camp counselors.

About one-quarter of the campers are actively being treated for cancer when they come to camp. They rely on the Kimmel Cancer Center physicians, nurses and physician assistants who care for them in the medical room campers have dubbed the "Funny Farm." A member of the medical team is on hand 24 hours a day to administer chemotherapy, draw blood for lab work and provide any other care needed. Campers also come to the Funny Farm for care of camp-related bumps, scrapes and bruises.

For most kids, a cancer diagnosis makes summer camp an impossibility. It becomes one more thing that makes them different from others their age. At Camp Sunrise, cancer doesn't call the shots. Prostheses are hung behind doors on coat hooks, wigs and scarves are often put aside in favor of bald heads, and no explanations are necessary. Everyone fits in, and everyone there — campers, counselors and volunteers — understands.

## CHILDREN WITH CANCER

Thousands of schools transitioned to online learning in 2020 due to the COVID-19 pandemic, during which time many children with cancer and other chronic health needs, as well as those with special education needs, faced significant challenges to learning online.

Children undergoing cancer treatment may have symptoms such as fatigue, pain, motor impairments or vision/hearing loss that make learning more challenging, says **Kathy Ruble**, director of the pediatric oncology survivorship clinic at the Johns Hopkins Kimmel Cancer Center. Additionally, therapy frequently induces deficits in attention, executive function, processing speed, behavior regulation and overall IQ.

She and her team developed a continuing medical education course on the Coursera platform. Kids with Cancer Still Need School: The Providers Role helps oncology health care providers navigate the challenges associated with the neurocognitive impacts of therapy.

Ruble is also co-founder of the SUCCESS (Supporting and Understanding Childhood Cancer: Education, Strategies, and Services) lab at Johns Hopkins, which works with families of children with cancer and pediatric oncology teams to find better ways to help survivors thrive in school.

## HELP ALONG THE WAY

Pediatric oncology patient care and research has been advanced by a number of generous donors:

Ginny and Fred Mitchell established the **Joel B. Mitchell Memorial Fund and Pediatric Oncology Friends** in 1994 after losing their son to cancer, raising more than $1 million for pediatric oncology research at the Kimmel Cancer Center.

**Children's Cancer Foundation** funded a variety of programs and discoveries, donating more than $17 million for pediatric cancer research and facilities at Johns Hopkins since 1979. Donations supported renovations to the pediatric oncology outpatient and inpatient units, the pediatric bone marrow transplant center, and clinical investigators, including **Kenneth Cohen**, **Charles Eberhart**, **Alan Friedman**, **Yiouli Ktena**, **Nicolas Llosa**, **Patience Odeniyide**, and **Donald Small**.

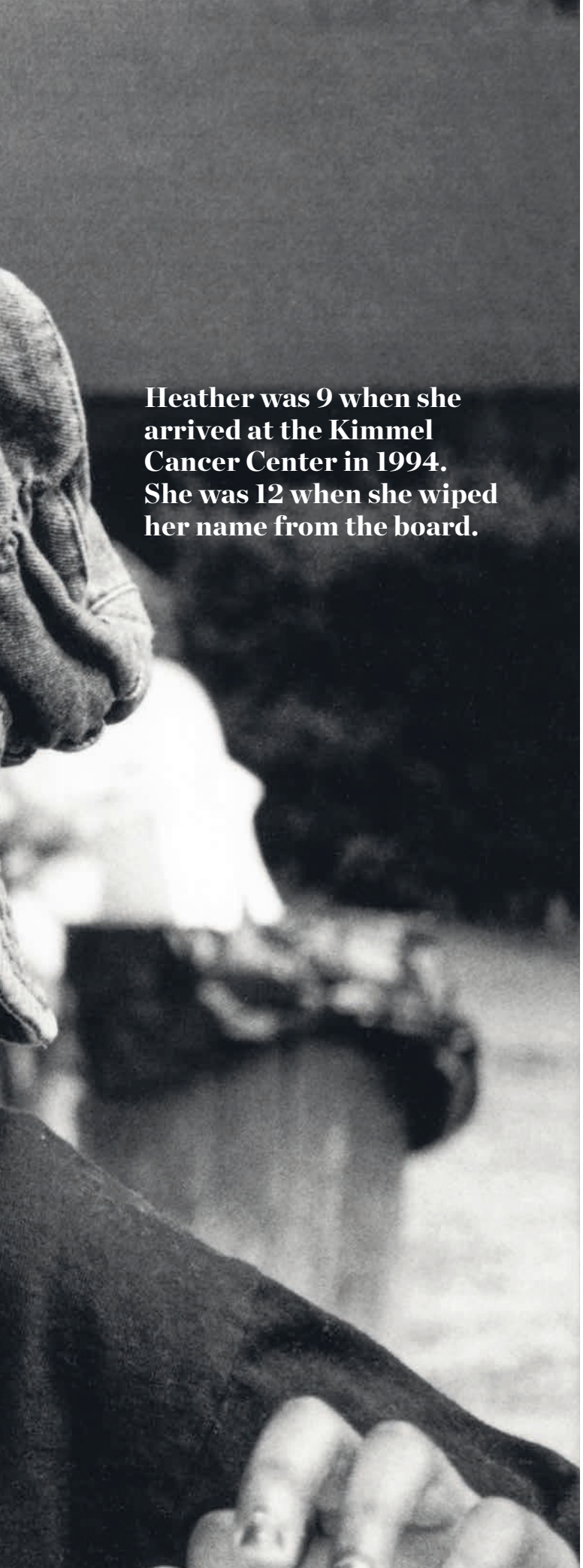
**Giant Food**'s annual campaign has provided up to $1.6 million each year over the last 19 years to pediatric oncology. **Challice Bonifant** is a current recipient with funding to support her research of stem cell transplantation for high-risk leukemia and the development of immune therapies.

**Hyundai Hope on Wheels** has donated more than $4 million to the Johns Hopkins Kimmel Cancer Center for pediatric oncology research. The latest recipients are **Michael Koldobskiy** and **Patience Odeniyide**.

**Optimist International** established an endowed research fellowship grant and innovation fund, providing the largest support ever by a youth-focused community service organization. Optimist fellows have included **Emi Caywood** for retinoblastoma research, **Kenneth Cooke** for bone marrow transplant research, **Eric Schaffer** for leukemia research, **Brian Ladle** for immunotherapy research, **Sama Ahsan** for glioma brain cancer research, and **Cara Rabi** for leukemia research.

*Heather's Story*

# A Fighting Spirit



**Heather was 9 when she arrived at the Kimmel Cancer Center in 1994. She was 12 when she wiped her name from the board.**

IT HAPPENED 29 years ago, but Heather remembers it like it was yesterday.

"Some things a person just never forgets," she says.

Heather was 9 years old and excited about a family outing to the circus. The next day, however, she felt so ill and tired, she could not go to school. As the day went on, her mom, Phyllis, became increasingly concerned and took Heather to the emergency department of a hospital near their home.

There was blood work, imaging and other tests. Heather heard the young doctor taking care of her mention cancer and leukemia to her mom, but Heather didn't know what that meant.

Her mom remembers the doctor telling her that they planned to transfer Heather to Johns Hopkins. Phyllis recalls the doctor saying, "The great thing is that you live in a city where Johns Hopkins is." He assured her it was the best hospital for childhood cancer.

Still reeling from the news, Phyllis and Heather's five siblings — Team Heather, as they would come to be known — raced to Johns Hopkins to be by Heather's side.

It was a lot for the young fourth grader. As she began to learn about the lengthy treatment ahead of her, all she could think about was her friends and school.

"I was 9, and I just wanted to be a kid. I wanted to be outside with my friends, and I was stuck in a hospital. I didn't understand what was going on," remembers Heather.

She was angry, but that was OK, that fighting spirit, her doctors said, would benefit her as she began a grueling three years of treatment to destroy the cancer growing in her bone marrow — the body's factory for blood cells — that was crowding out her healthy blood cells.

Family, friends and classmates sent cards to her hospital room. A volunteer brought her a basket filled with 30 days' worth of gifts. Heather began to understand she wasn't going home any time soon. Her first hospital stay was 21 days. She had another that lasted 47 days. When she wasn't in the hospital, she was going back and forth to the outpatient clinic. Cancer consumed her life.

Waking up every day to a new gift to open provided some consolation, she recalled. Over the years, she's learned to compartmentalize, keeping the good memories, if one can even call them good, and somehow tucking away in a secret place in her mind, the ones she chooses not to recall.

"Looking back, I don't want to say that cancer took my childhood, but that's the kind of relationship I had with it, so I choose not to remember the negative," says Heather. For her, carrying the bad memories with her would make the experience even worse.

As she recalls her journey, however, a few of the unpleasant memories resurface. The therapy, Heather says, made her feel ill and tired most of the time, but what made her most unhappy was losing her hair. It was the most visible reminder of her battle with cancer. It was the thing that made her look different from her friends and classmates, and she had to go through it three times, with different rounds of treatment that spanned three years. The treatments also left her with some late effects. Heather has diabetes and suffers from some gastrointestinal issues.

**HEATHER** WITH HER MOM, PHYLLIS

Still, now at 38, she says she chooses to focus on the positive.

"The good things are being here today, of course, meeting the people who I met throughout the time, and the support system that I had and still have," she says.

She also fondly remembers her "I Did It" party. That is the day when everyone on the pediatric oncology inpatient unit celebrates patients who finished treatment. One way patients mark their day is by erasing their names from a board that contains the names of patients being cared for on the pediatric oncology inpatient unit.

It's their way of saying, "Take that, cancer. I'm out of here."

Heather was 9 when she arrived at the Kimmel Cancer Center in 1994. She was 12 when she wiped her name from the board.

Her battle against cancer consumed the latter part of her elementary school years and most of middle school, so she was ready for high school. She called it "Heather's New Journey."

"I had been Heather the sick kid all through middle school. I didn't want to be that anymore. I just thought, I want to be Heather, not Heather that had cancer or Heather with leukemia," she says, and high school felt like a fresh start.

"She shined," recalled Phyllis.

Heather developed a love of finance and accounting during high school. That interest stayed with her, and she continues to work in the field today.

She recognizes that as much as she hates cancer, it helped her become the person she is today. That special spark her oncologist noticed remains.

"I do think that experience is what made me who I am — strong, a fighter," says Heather. "At 9 and 10, I didn't realize what it meant then, or what I was fighting for, but now, at this age, I really understand, and it means something different to me today. I had to fight to be here today."

It has taken her some years to come to terms with her own story, to be able to hate cancer but recognize the good that has come from her experience.

"I don't want to say I embrace it, but I'm starting to unbury it," says Heather. "It is a part of me."

She is planning to start a nonprofit to help other young women though their own struggles.

"I want to create a sisterhood/women empowerment for young ladies and women. We want to be that listening ear for them," says Heather. "I feel like a lot of African American females don't have that support system, and we want to be that for them."

As Heather looks back on her journey, she says the best outcome of being a survivor was becoming a mom. Her son KJ turned 12 this year. She admits that her battle with cancer makes her worry a bit more. When KJ turned 9, she remembered how her life changed in a moment. She couldn't imagine that happening to her child. It almost made her not want children of her own. It also gave her a new perspective on the courage and devotion of her own mother.

## "Take that, cancer. I'm out of here."

"I don't think I will ever stop worrying about my son, and that makes me realize how much my mom went through and how strong she had to be for me. We talk about the kids who go through cancer, but I think the parents experience it the same. Maybe not the same physical aspects, but I feel like my mom has been through it all with me," says Heather.

Phyllis, on the other hand, sees Heather as the hero in this story, but she is quick to mention a few other heroes.

"I am so grateful to the doctors and nurses," says Phyllis. She thinks back to the day in the emergency department with Heather when the doctor told her how lucky she was to have Johns Hopkins in her hometown. "They took care of my baby. They fought for her."

*Keith's Story*

# Making Peace

**Keith was 16 when he was diagnosed with non-Hodgkin lymphoma in 1998. He and his parents traveled 85 miles from the family's farm on Maryland's Eastern Shore to the Johns Hopkins Kimmel Cancer Center.**

Keith was 16 when he was diagnosed with non-Hodgkin lymphoma in 1998. He and his parents traveled 85 miles from the family's farm on Maryland's Eastern Shore to the Johns Hopkins Kimmel Cancer Center.

Without warning, cancer intruded on his goals and dreams. It remains difficult for Keith to look back on his battle with cancer. The life a survivor has after cancer is not necessarily the one imagined before diagnosis, he points out.

His memories, he says, are blurry, making it feel almost like an out-of-body experience.

Beyond survivorship, for which he is grateful, Keith prefers not to look back.

"One day you are on the Eastern Shore going to school, and then you're at Hopkins," says Keith.

The journey for teens is perhaps one of the most difficult among pediatric cancer patients. There are missed experiences, strained and lost friendships, and other changes that impact the day-to-day life of a teen.

Of the nearly 2 million cancer cases diagnosed each year, only about 5,000 are teens between 15 and 19 years old. Although their cancer treatment may be similar to what older or younger patients receive, the social and emotional experiences are different.

In 1998, Keith described that experience to author Harry Connelly: "When you get cancer, some of your friends become acquaintances. People act differently. My best friend wants to take the pain from me; so does my dad. Some people are scared of me, can't look at me or talk to me," said Keith.

Keith's therapy was very aggressive, including two years of powerful anticancer drugs, ones known as cytotoxic because they kill cancer cells but are also very toxic to normal cells. These are the drugs that cause patients' hair to fall out and nausea and vomiting in the short term and lasting changes, such as learning impairments and damage to healthy tissues and organs, in the long run. For Keith, the long-term toxicities have included chronic joint damage and pain, depression and memory issues.

"There are brilliant minds at Hopkins. They are incredible, the best in the world, and I would trust them again to treat me, but it was not a fun experience," he says.

He is aware of the advances that have been made since his diagnosis. He mentions immunotherapy and targeted therapies that are aimed at sparing patients from the toxic side effects like those that plagued him.

It took longer for Keith to heal the mental and emotional scars left by his battle with cancer than to physically overcome the disease. He credits his parents with getting him through the darkest times.

"The reality for me is that the treatments were not as hard as picking up the pieces," says Keith.

Ultimately, picking up those pieces required building a life away from Maryland. Keith wanted to put some distance between himself and the memories of his cancer diagnosis

**KEITH** ON HIS FARM

and treatment, so in 2016, he moved to a farm in Virginia.

His 8 acres of rolling hills in southern Virginia has been the best medicine. Within six months of moving, he said he could feel the pressure lift, and he slept better. He met his wife Meggin there in 2016, his son Noah was born there last April, and he found faith again.

He says it was divine intervention.

"Prayer works. Have faith. That's the one thing I missed when I was going through this," says Keith. He understands that the toxic effects of the treatments that saved his life were what they were going to be, but he is confident the mental anguish that gripped him for many years could have been alleviated if he had faith then.

When he first moved to Virginia and was renovating his home, he found a New Testament pocket Bible in a pile of trash. He was rewiring the home, so there was no electricity. He couldn't watch television, and to occupy his time when he needed a break from working on his house, he read the Bible.

"I realized I had been disconnected from God, and that I was bitter. I remember fighting with God when I was at Hopkins," says Keith. "I guess I was mad at God. You think, why did I deserve this? You feel slighted. Then I realized, it was not God that abandoned me, it was I that abandoned God."

Now, through his suffering, he has gained hope, and faith remains an important part of his life. He wishes it for everyone.

"At 16 we listen to the world, which says we do not need God. Through life experience, we learn we do need God regardless of what the television, media or educational institutions imply," says Keith.

It is the experiences of patients like Keith that drive the Kimmel Cancer Center to become better. In the early years of the Cancer Center, the primary focus was on saving lives, with cancer taking the lives of nearly 70% of pediatric patients diagnosed. As research led to improved therapies and longer survival, another focus was added. Clinicians and scientists worked together to decrease toxicities of cancer therapies and added a long-term survivorship clinic to monitor patients for late effects and develop ways to prevent and treat them.

Today, Keith says his cancer experience has made him a more understanding and empathetic person. It most certainly has made him insightful.

"Life moves on, but you are too busy looking over your shoulder to notice," he says.

Part of the challenge is letting go of what the cancer takes — the stolen or altered experiences of his teenage years, not to mention the lasting reminders of the cancer that come in the form of treatment toxicities. Added to that is the looming threat of cancer returning.

Keith can't go back to the way it was before cancer. No cancer survivor can, but now having a family of his own and immersing himself in his farm, for the first time in many years, he feels like he can finally look ahead.


Curious George


*Eli's Story*

# Giving Back

**Eli's cancer story began in December 1993 at age 2, when he was diagnosed with acute lymphocytic leukemia.**

Eli's memories of December 1993 and his diagnosis with cancer at age 2 are faint. It's difficult for him to distinguish his own memories from the stories others have told him.

"I know I had acute lymphocytic leukemia, and I went through a few rounds of chemotherapy, but the extent of my medical knowledge stops right about there," says Eli.

The few things he remembers are all good experiences — Orioles players visiting the pediatric oncology unit, playing in the game room and picking out toys from the treasure chest.

He considers himself fortunate in that regard and also because he has no lasting side effects from his cancer treatments.

Still, surviving cancer changed Eli's life in a unique way. It inspired him to want to give back to the people who saved his life, he says.

**ELI,** WITH HIS WIFE JAYNE AND DAUGHTER NORA

## "Whether I realized it at the time, I think growing up in Baltimore you understand just how much respect there is for the doctors and nurses and work done at Hopkins."

"I don't think I could have been in better hands than the doctors at Hopkins. Whether I realized it at the time, I think growing up in Baltimore you understand just how much respect there is for the doctors and nurses and work done at Hopkins," says Eli. "Looking back, it definitely had a profound impact on putting me on this philanthropic path and finding my way to continue to support Hopkins."

When he was 12, Eli started Cartridges for a Cure, a program that collected and recycled used printer cartridges to raise money for pediatric cancer research at the Johns Hopkins Kimmel Cancer Center. He raised nearly $100,000 through the program, and earned an additional $50,000 donation as a winner of the Volvo Hero Award.

Charitable giving remained a focus for Eli, and when he graduated from college, he worked for a nonprofit foundation, helping to develop grant-making strategies.

He went on to earn an MBA from Duke University, and his career path shifted. Currently, he is director of corporate strategy for a national home improvement chain.

His cancer experience intersected with his studies while he was at Duke. Eli visited one of his doctors, **Michael Kastan**, now executive director of the Duke Cancer Institute, who treated him nearly three decades earlier at Johns Hopkins.

"I walked into his office, and front and center behind his desk was a picture of him treating me at age 3 or 4. He has a stethoscope, and I'm sitting on my mom's knee," says Eli. "It was great connecting with him after 25, almost 30 years."

Eli's career path is not the only thing that has changed for him since fighting cancer as a toddler. Today, the 32-year-old is married to Jayme, and they are parents to Nora, born earlier this year.

"With my little one, I think I've definitely gained a newfound appreciation of how difficult it must have been for my parents," says Eli.

He admires them for providing him with stability and optimism throughout his treatment and survivorship.

"I think it had a profound impact on me, and now, looking at Nora, I can't imagine how difficult it must be for parents and siblings in this incredibly difficult situation, to be able to communicate to young patients that everything's going to be OK," he says.

As a young father, Eli hopes he will never need it, but he is comforted knowing a place like Johns Hopkins exists. He says, "There is no other place in the world I'd want my kid to be treated."

## MILESTONES IN PEDIATRIC ONCOLOGY

**1976:** Division of Pediatric Oncology is established

**1982:** Pediatric neuro-oncology program begins

**1984:** CD34 antibody is discovered, making it possible to isolate and collect bone marrow stem cells

Dual chromosome losses are linked to pediatric kidney cancer known as Wilms tumor

**1989:** New drug regimen for pediatric acute lymphocytic leukemia improves survival from 50% to 90%

**1992:** The p53 gene – the most commonly mutated gene in cancer – is deciphered and shown to stop damaged cells from reproducing, but when mutated, growth of damaged cells is unchecked and can result in cancer and resistance to treatment.

FLT3 gene cloned and target of therapy for a lethal subtype of acute myeloid leukemia

**1993:** Pediatric oncology long-term survivors program is launched, becoming one of only a few in the country to treat and make recommendations to prevent long-term effects associated with therapy

**1995:** Pediatric bone marrow transplant center opens

**1996:** First drug against FLT3 discovered and shown to preferentially kill FLT3 mutant AML cells

**1997:** Kimmel Cancer Center and the National Institutes of Health establish joint fellowship training program in pediatric oncology

**1998:** Pediatric Oncology Inpatient/Outpatient, called POP IN opens, allowing many pediatric patients to receive their care as outpatients

**2001:** FLT-3 gene is cloned and becomes target of therapy for a lethal subtype of acute myeloid leukemia

**2019:** CAR T-cell therapy extends survival in pediatric leukemia patients whose cancer did not respond to standard therapies

**2020:** The Johns Hopkins Proton Therapy Center is one of two in the U.S. with a dedicated pediatric facility and proton research program; the first pediatric patient with cancer is treated

**2022:** Pediatric oncology survivorship program study during COVID-19 pandemic finds that children with cancer face significant challenges to online learning

**2023:** New biomarker distinguishes subtypes of the pediatric brain cancer medulloblastoma

## 2000s

Translational bench-to-bedside research continues to be the hallmark of our Cancer Center. Breakthroughs in research and clinical care is facilitated by two new Cancer Research buildings, and our Center is renamed in honor of philanthropist **Sidney Kimmel**.

# Leading in the New Millenium

## *The Right Treatment to the Right Patient at the Right Time*

In 2008, **William G. Nelson**, became the third and current director of the Kimmel Cancer Center.

He has overseen significant expansions in the physical footprint of the Kimmel Cancer Center, moving most cancer care to the outpatient setting and opening satellite locations throughout the National Capital Region. The expansions included the addition of the Skip Viragh Outpatient Cancer Building, the Kimmel Cancer Center at Sibley Memorial Hospital in Washington, D.C., the Johns Hopkins Proton Therapy Center, and the Kimmel Cancer Center at Johns Hopkins Bayview Medical Center. He also added cancer services at Johns Hopkins Health Care & Surgery Center — Green Spring Station in Baltimore County and at Suburban Hospital in Montgomery County.

The treatment of cancer as an outpatient would have been unthinkable when our Center opened its doors in 1977. It is a testament to the progress that has been made over the last 50 years.

"In the future, as cancer evolves further into a disease managed through drug and outpatient treatments, I expect the Center's expanded locations to provide convenient, local treatment instead of requiring people to visit central locations," says Nelson.

The number of people who work for the growing Kimmel Cancer Center and who come to us for treatment has also greatly increased. Today, the Center has 285 full-time faculty, 349 nurses and more than 500 support staff members. There are more than 90,000 patient visits and 9,000 new patients seen across all Kimmel Cancer Center locations in a year.

Nelson also broadened and restructured clinical services and research programs. The Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care, the Ludwig Center, the Lung Cancer Center of Excellence, the Colorectal Cancer Patient Care and Research Center of Excellence, two Precision Medicine Centers of Excellence, one for prostate cancer and another for pancreatic cancer, the Greenberg Bladder Cancer Institute, the Bloomberg~Kimmel Institute for Cancer Immunotherapy, and the Convergence Institute opened. To address higher death rates among minorities and other underserved populations in Maryland, he established the Community Outreach and Engagement and Diversity and Inclusion in Clinical Research programs.

With emerging discoveries in genetics, epigenetics and immunotherapy showing that cancer cell growth and behavior was less about where it occurred in the body and more about the instruction manual that is contained within cancer and surrounding cells, Nelson reorganized Kimmel Cancer Center research programs to enhance the understanding of how cancer develops, grows and spreads.


NELSON

He integrated studies of specific cancer types into existing programs in cancer genetics and epigenetics, cancer immunology, new drug and drug target development, cancer prevention and control, cancer imaging at the molecular and functional level of cancer cells, and blood cancers and bone marrow transplant. He also added a new program to research cancer invasion and metastasis, aimed at better understanding the leading cause of cancer deaths — the lethal spread of cancer from the place in the body it originated to other tissues and organs.

The restructuring deepened the understanding of the basic biology of cancer within the context of translational — bench-to-bedside — research to develop better prevention, detection and treatment strategies.

"The hope, the ultimate goal, is that we're going to eradicate the ability of cancer to threaten your life and its quality, and ensure that treatment isn't a drag on your life and happiness," says Nelson.

He incorporated the multidisciplinary model — commonly referred to at the Kimmel Cancer Center as the multi-D clinics — into the treatment of all cancer types. The multi-D clinics, pioneered first in prostate cancer and pancreatic cancer, bring together all of the experts involved in treating a patient with cancer to develop the best treatment plan.

"What people need when they hear the words 'I think you have cancer,' is an answer and a plan," says Nelson. "The multidisciplinary clinics bring

THE KIMMEL CANCER CENTER
AT SIBLEY MEMORIAL HOSPITAL

"Whether it's in the basic sciences, or in the clinical research arena where we determine which new therapies and which new drugs we can develop to treat cancer, this is how we make progress and provide the best outcomes for patients."

ASHWANI RAJPUT, DIRECTOR OF THE KIMMEL CANCER CENTER, NATIONAL CAPITAL REGION

together surgeons, medical oncologists, pathologists, radiation oncologists, nurses — any specialist involved in the treatment of a specific cancer — all working together to the benefit of the patient."

With the shift of most cancer care to the outpatient setting and more cancer therapies coming in pill form, Nelson also proposed a new paradigm for drug discovery to address the high rate of cancer drug failure. To illustrate the problem, he explained that in 2008 alone, the year he became director, there were 750 cancer drugs in clinical trials, with less than 5% of them ever ultimately performing well enough to get approved for cancer treatment.

"Pharmaceutical companies estimate it costs them about $1 billion to discover, develop and get a cancer drug FDA approved. These costs are passed on to people with the disease in the form of high costs for treatments. I believed our Cancer Center could be a part of the solution. We have the drug discovery engine that could help pick the winners from the losers before large sums of money are spent, and we did it," says Nelson. "Kimmel Cancer Center research led to the first FDA approval of a drug across all cancer types based on a specific biomarker that our researchers discovered and then later determined could pinpoint pretty successfully who would respond to a type of immunotherapy drug. We will continue to look for these kinds of opportunities."

Inspired by his own experience at Johns Hopkins, Nelson also gathered together the entire brain trust of Johns Hopkins in the fight against cancer. He refers to himself as "homegrown," as he went to medical school and graduate school at Johns Hopkins and completed his residency and fellowship here.

"I have never delivered any health care of any kind as anything other than a Johns Hopkins physician," he said. "By being around the institution for so long, I've ended up a professor in six departments, and this helps me bring people together across Johns Hopkins. It gave me a good sense of how great we can be when we work together across departments."

Today, under his leadership, the Kimmel Cancer Center spans 35 Johns Hopkins departments and five schools.

The Kimmel Cancer Center represents a broad number of disciplines, with cellular biology, structural biology and DNA research playing roles alongside engineering and computer sciences. Researchers are working to understand how proteins that disrupt cancers can be tucked into drugs and to apply artificial intelligence (AI) tools toward managing cancer gene data — which can number in the billions — speeding research and discoveries, he says.

Nelson also ushered in the era of precision medicine, tailoring research, screening, detection and new therapies to what has been revealed about the unique molecular and cellular characteristics of cancers.

"Our research showed that people carry genetic vulnerabilities that they inherit from their parents, and about 15% of all cancers occur in people who seem to have these genetic predispositions. It doesn't mean they're fated to get cancer, just that they are more susceptible to getting a cancer. What is newer are tests for some of these genes that predict increased risk for cancer among the general populations so that we can use early detection and screening strategies to intervene and diagnose people at the very earliest stage," says Nelson.

This means, he says, that our experts can determine who is not as likely to develop cancer and economize our use of screening tests. In terms of therapy, gene alterations and cancers may predict which treatments will be successful and which will not.

With precision medicine, Nelson set a new direction for the Kimmel Cancer Center, moving it away from a model in which patients are seen for the first time when they experience symptoms and toward one that detects, manages and many times eradicates cancers before patients even know they have them. This new model, he says, preserves health by preventing cancers very accurately, predicting who will get them, and personalizing screening and therapy to each individual.


## TWO CANCER RESEARCH BUILDINGS OPEN

**The Bunting-Blaustein Cancer Research Buildin**g opened in 2000, the first of two new cancer research buildings. Its unique interstitial design allowed building services to be installed and modified without interruption to of research activities on floors above or below. The ten-story, 122 square foot building cost $59 million to build. The Bunting family and Jacob and Hilda Blaustein donated $10 million each toward the construction. It housed programs in cancer biology, hematologic malignancies, urologic oncology, gastrointestinal cancer, pediatric oncology, solid tumor research, including in breast cancer, pharmacology and experimental therapeutics; immunology, and cancer prevention and control.

**The David H. Koch Cancer Research Building** opened in 2007. The $80 million, 267,000 square foot building, expanded the complex for cancer investigators. New York businessman David Koch donated $20 million toward its construction. With five floors of laboratories and 10 stories of office space, the building is home to researchers of prostate, brain, skin, lung, and head and neck cancers A-250 seat high tech auditorium, named in honor of **Albert H. Owens, Jr.**, the Center's first director, connects research tower to its twin, the Bunting-Blaustein Cancer Research building.

"We are beginning to use our scientific discoveries to determine which treatments and screening interventions will work best for each patient, and just as important, we are using this knowledge to spare patients the risk and adverse effects of treatment and procedures that will not work," says Nelson.

In many ways, the accomplishments and direction of his leadership to date have been guided by his overarching goal to use science to improve the benefits of cancer therapy and reduce its ill effects by "getting the right treatments to the right patients at the right time." This iconic phrase for which Nelson has become known is at the heart of precision (individualized) medicine.

"Over the next decades, the discoveries and developments in treatments will be enhanced by the vast influx of AI-influenced data that will help Kimmel Cancer Center physicians and researchers further tailor treatments on the individual level," he says.

"THE STATE OF THE ART IS JUST THE STARTING POINT OF WHAT WE CAN OFFER. THAT KIND OF TREATMENT OPPORTUNITY – THE LATEST, PLUS SOME – IS WHAT WE HAVE AND ALWAYS WILL DELIVER."

With this long list of accomplishments, it's hard to imagine that Nelson had not set out to become a doctor. He was a soccer standout and chemistry major at Yale University, and planned to study law. A summer job in the laboratory of a cell biologist looking for molecular biomarkers of a rare skin disorder called ichthyosis changed his mind.

"There were clinical trials of some new drugs, and I was in contact with many of the participants. I was struck by how well they understood their disease and their reason for joining the trial. They knew it was an experimental therapy that may not help them, but could help others. That's when I decided I wanted to be a physician," says Nelson.

For most of his career, his research and clinical interests have been focused on prostate cancer.

"When I started in oncology, men were commonly diagnosed at an advanced stage. We had some limited success with treatments, but death rates were far too high," says Nelson. "Since that time, we've gotten PSA (prostate specific antigen), a blood test that made it possible to diagnose men far earlier, so they could benefit from surgery and radiation. We've also developed new treatments. That allowed us to cut prostate cancer death rates almost in half over the last 30 years."

He'd like to see similar progress made against all cancers, and he believes the Kimmel Cancer Center has the talent to make that goal a reality.

"This place is special," says Nelson. "I've been a researcher trying to invent new treatments and take them into the clinic. I've been a clinician working directly with people with cancer. I understand the promise and limitations before us, and I think the time is right to really take some major shots that can transform the cancer problem."

Once of those "shots," he says, has to be in cancer prevention.

"There are about 1.4 million new cases of cancer each year, and this number is expected to increase as our population ages. Cancer is a major health concern, not just in the United States but worldwide. I believe we can prevent people from having some of these devastating diseases," says Nelson. "When we look at screening and early detection that we already do — Pap smear, mammography, colonoscopy, PSA — their use leads to improvements in survival and treatments that are far less deforming and have fewer side effects."

Nelson is also optimistic about laboratory discoveries in prevention that he believes may be able to both stop a cancer from developing and treat cancer. He has stewarded efforts to address behaviors and other underlying causes of cancer, such as chronic inflammation and infection, and directed research and resources to help minorities and other underserved populations that suffer disproportionately higher rates of cancer deaths. Part of this effort includes increasing minority participation in clinical trials.

Building upon the accomplishments of his predecessors, Nelson says the Kimmel Cancer Center remains true to its founding as a place that uses science to improve the care of patients. The labs are no longer physically adjacent to patient rooms, but they remain adjacent in spirit and practice, and this translational research remains at the core of the Kimmel Cancer Center.

"I believe nearly every challenge facing the field of cancer medicine can be solved through translational research," says Nelson.

This expertise in translational research is what makes the Kimmel Cancer Center so special, he says, adding that he wouldn't want to be a director at any other cancer center.

"The major difference at a place like the Kimmel Cancer Center is that the state of the art is just the starting point of what we can offer. That kind of treatment opportunity — the latest, plus some — is what we have and always will deliver," says Nelson. "There is so much we have accomplished here already, but I believe there is much more we can do. This is a great place to be, and the right time to be here. We have tremendous opportunities."

# Sidney Kimmel:
## Helping Others
### *Historical and transformational giving*

"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." These are the words of philanthropist and Kimmel Cancer Center benefactor **Sidney Kimmel**. In 2001, he made Johns Hopkins history with his $150 million donation — the largest single gift to the university at that time — to support cancer research and patient care.

The Cancer Center was renamed the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in his honor.

This historic gift is one of many he has made in support of the Johns Hopkins Kimmel Cancer Center. Since 2001, he has contributed nearly $210 million in total, including $2.4 million to support 12 of our cancer scientists as part of the national Kimmel Scholars Program. Kimmel provided the lead funding for the Hackerman-Patz Patient and Family Pavilion, and subsequently he and Michael Bloomberg provided the lead gifts — contributing $50 million each — to establish the Bloomberg-Kimmel Institute for Cancer Immunotherapy in 2016.

"I am blessed. To be able to support one of the leading institutions in the world and build on its momentum gives so much meaning to what we have all done thus far to defeat cancer and provides even more hope for what can now be accomplished. My goal with this gift is to make meaningful advances in our knowledge of cancer," said Kimmel in 2001.

His efforts in the world of cancer research have changed the face of the disease. He led the charge at the *March: Coming Together to Conquer Cancer* in Washington, D.C., in 1998, which resulted in a doubling of the National Cancer Institute's budget. In addition, he has funded and named cancer centers at Thomas Jefferson University and Memorial Sloan Kettering Cancer Center. Among his most significant achievements in cancer research, Kimmel established the Kimmel Scholars Program, which funded the startup labs of nearly 300 of the nation's most highly regarded researchers, giving birth to the next generation of cancer leadership. He is the recipient of numerous awards, and is the lead individual donor to Stand Up to Cancer, which raises millions annually to fund cancer research.

As 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," he said.

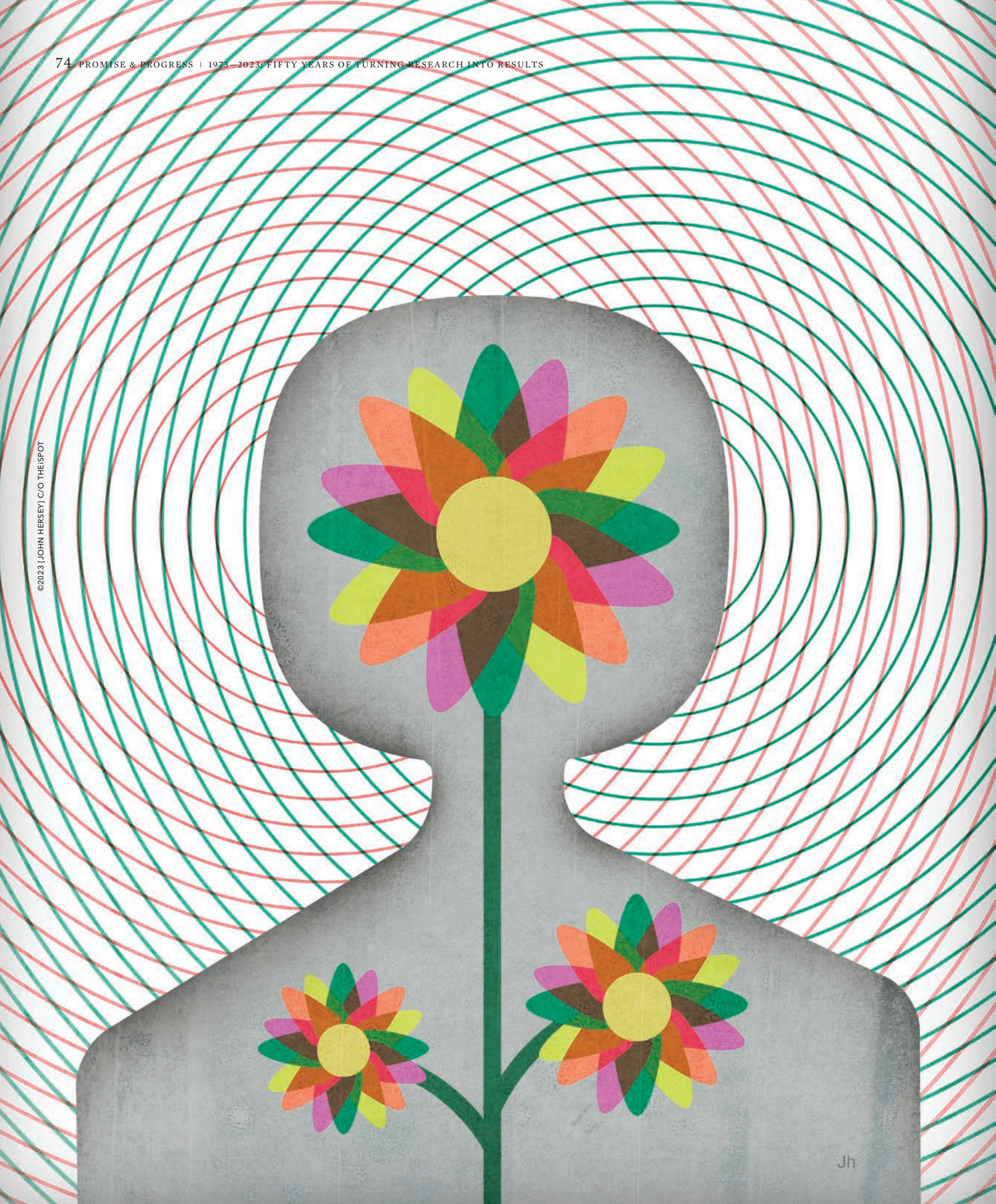
Kimmel, 95, earned his fortune as chairman and CEO of Jones Apparel Group Inc., which he founded in the mid-1970s. The women's clothing manufacturer included such iconic labels as Jones New York, Nine West, Stuart Weitzman and Lauren. His "second career" was in the motion picture industry, where he pursued his love of film. Establishing Sidney Kimmel Entertainment, now SK Global Entertainment, he led the production of more than 75 pictures, which included the highly acclaimed *United 93*, *Hell or High Water* and *Crazy Rich Asians*.

> **"Sidney Kimmel is one of the great philanthropists of our age. His impact on the field of cancer research is without equal."**

He is part of "The Giving Pledge," a commitment by the world's wealthiest individuals to dedicate the majority of their wealth to philanthropy, a commitment that Sidney Kimmel has more than fulfilled already.

Kimmel's philanthropy has reached deep into communities to support the arts, education and medicine, but, above all, his support of cancer research has helped advance the understanding of cancer and bring new and better treatments to patients.

"Sidney Kimmel is one of the great philanthropists of our age," says William Nelson, Kimmel Cancer Center director. "His impact on the field of cancer research is without equal."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Jh

# Healing Beams

**Radiation Oncology has come a long way since its origins as an offshoot of the Department of Radiology and later as a program of the Department of Oncology. Although it didn't receive departmental designation until 2003, the history of excellence in cancer research and patient care and the integral role it has played in the management of cancer have deep roots.**

What started 120 years ago with the first radioactive isotopes brought to Johns Hopkins to build a gynecologic brachytherapy program to treat cervical cancer in Baltimore, evolved in the second half of the 20th century to a broad system built around the cancer fighting power of targeted X-ray beams and other radiation therapies. These healing beams are still essential to the care we provide, but since becoming a department 20 years ago, it has grown into much more. Molecular radiation sciences, knifeless radiosurgery, proton therapy, radiopharmaceuticals, radiosensitizers, nanoparticles, targeted and immune stimulating therapies, large database-driven clinical informatics, informatic systems, efficiency models, and inventions that propel research and make the clinical care safer are now part of our 21st century cancer science and medicine.

Building upon the strength and the work of early pioneers, Radiation Oncology and Molecular Radiation Sciences experts have earned recognition as world leaders in developing transformational concepts and translating basic developments into novel therapies that have changed the standard of care and improved the lives of patients with cancer.


VISWANATHAN

"Caring about our patients is our top priority," says **Akila Viswanathan**, Director of the Department of Radiation Oncology and Molecular Radiation Sciences. "Combining advanced technology with compassionate care is the hallmark of Johns Hopkins Medicine. Innovations beyond standard technology set us apart from a routine experience."

## BOLD GROWTH

Radiation Oncology started with a small team working in the basement of the Halstead Building as they awaited the opening of the Cancer Center in 1977. Computer technology was limited as were the machines that delivered radiation to patients.

**Stanley Order**, who was director of the Division of Radiation Oncology from 1975-1990, and **Moody Wharam**, director from 1990-2000, were the first two faculty members in Radiation Oncology. The existing radiation-delivering machinery had not caught up with the forward thinking ideas of the Cancer Center's early radiation oncology pioneers, and Order and Wharam worked together to get the equipment up to date. They converted two antiquated cobalts, treatment machines no longer in use today that produced a beam of gamma rays from a cobalt isotope, to five linear accelerators, which use targeted, high energy X-rays. They also added a cobalt unit and two simulators.

The Radiation Oncology Department at Johns Hopkins was among the first in the nation to break off from the Department of Radiology and Radiological Sciences to join forces with the Department of Oncology to tackle the cancer epidemic that had warranted a national war against cancer. Johns Hopkins was home to one of just a handful of strong academic programs in radiation oncology.

When the Center opened in 1977, it had all the latest technology and equipment available at the time. It also had more cancer patients than the physical space could accommodate. The radiation oncology clinic had to expand to twice its original size to accommodate the growing patient load.

"COMBINING ADVANCED TECHNOLOGY WITH COMPASSIONATE CARE IS THE HALLMARK OF JOHNS HOPKINS MEDICINE. INNOVATIONS BEYOND STANDARD TECHNOLOGY SET US APART FROM A ROUTINE EXPERIENCE."

Years later, there were two additional expansions, one with the opening of the Kimmel cancer Center's Harry and Jeanette Weinberg building and another with the satellite facility at Greenspring Station. Additional facilities were again added at Suburban hospital in Montgomery County and Johns Hopkins Sibley Memorial Hospital in Washington, D.C., which would later become home to the proton therapy center.

## PIONEERING DISCOVERIES

Strong leadership has helped pave the way for pioneering discoveries. Order developed radiolabeled antibodies to treat liver cancer. He was also ahead of his time, developing a version of telemedicine. In 1989, the Cancer Center developed collaborative radiation oncology services with St. Agnes Hospital in Baltimore and Chambersburg Hospital in Chambersburg, PA.

Patient information from Chambersburg, such as X-rays and charts, was relayed to the Cancer Center via computer, fax, and video telephone hook-up. A telephone conference brought physicians from all of the hospitals together for case review.

Wharam, who specialized in pediatric oncology, was also a pioneer. When our Center opened, just 50% of children diagnosed with cancer survived. The National Cancer Institute appointed four study groups to investigate common childhood cancers, and Wharam received the unusual distinction of being named to two of these groups. From 1980 to 1990, he served as director of the radiation oncology committee of the pediatric oncology group, a U.S. and Canadian collaborative group that studied childhood cancers. His roles in these premier groups made him an active participant in all of the pivotal pediatric cancer research at the time. it was research which led to dramatic increases in pediatric cancer survival rates. The four separate groups have since merged into one known as the Children's Oncology Group.

Wharam, who passed away in 2018, was part of another first, when he collaborated with pediatric oncologist Bridget Leventhal in a groundbreaking 1980s study of treatment reduction in Hodgkin's lymphoma to prevent harmful toxicities. Their research led to refinements in therapy that allowed certain patients to receive less radiation or forgo it altogether without an increased risk of recurrence.

He also developed the standard of care for rhabdomyosarcoma, a childhood cancer of the connective tissue that attaches muscles to bones, combining chemotherapy and radiation therapy, a treatment so effective it remains the standard today.

In the early 1990s, years before advanced radiosurgery equipment had been developed, he innovated a way to deliver radiation very precisely to preserve vision for a toddler diagnosed with cancer in both eyes.

Wharam's pioneering influence earned the department the distinction as one of just a select few in the nation with expertise in treating pediatric patients, and this was instrumental in helping the department gain approval for a proton therapy center, which includes a specialized pediatric team.

"Our program grew into the best one in the country. We have first class scientists and clinicians and the finest physicists, residents, nurses, radiation therapists, and dosimetrist in the business," said Wharam.

**Theodore DeWeese**, now Interim Dean of the Johns Hopkins School of Medicine, was named the first Director of the Department of Radiation Oncology and Molecular Radiation Sciences.

DeWeese, a prostate cancer expert, collaborated with researcher Shawn Lupold, to develop aptamers, small molecules that work like antibodies to target unwanted things in our bodies, like cancer. The aptamers deliver silencing RNAs specifically into cancer cells to render cancer cells vulnerable to the DNA damage caused by radiation therapy while protecting normal cells.

DeWeese was instrumental to bringing proton therapy to the Kimmel Cancer Center and advancing radiation oncology research, recruiting **Marikki Laiho** to head Molecular Radiation Sciences and inventor **John Wong** as Chief Physicist.

## AN INVENTOR

"Radiation oncology requires the right balance of technology development, laboratory research and dissemination of knowledge for clinical decisions," said Wong, now retired.

He was the inventor of many key instruments used in radiation oncology treatment and the research of cancer.

Among his inventions are the ABC interactive device that coordinates breathing with radiation treatment. As patients breathe, tumors move, and ABC locks the breath in place for short, comfortable periods to make sure the radiation hits its cancer target.

ABC has been enhanced with 4D CT and MRI imaging. Radiation oncologist and lung and esophageal cancer expert **Russell Hales** explains that the fourth dimension is the capture of movement. The 4D imaging captures a few seconds of patient's breathing, and these data are used to predict how and where the tumor will move throughout treatment.

Hales is conducting the critical research to validate the ability of image-based technologies to predict tumor movement during radiation treatment.

"We are one of the few places that are doing this kind of research," says Hales. When completed he says the research should produce the most accurate measurement of tumor movement."

Wong was also the inventor of cone-beam computed tomography, which has become an integral part of radiation oncology treatment and research. CT imaging delivers clear images of bone, soft tissue, and tumor, making it a desirable guidance system for radiation treatment.

The Raven quality assurance device, which connects to machines and quickly performs a series of measurements to ensure they are functioning correctly, and the CT couch, which integrates image guidance with treatment delivery, are also among Wong's inventions.

Another one, called the Small Animal Radiation Research Platform (SARRP), gave researchers the ability to study human therapies in animal models before they are taken to the clinic and was essential to developing more effective and safer therapies. SARRP is a downsized version of a human machine, allowing researchers to perform human-quality radiation delivery in animal models.

"In radiation oncology, we don't have the means to study mechanisms in a living animal subject, and this machine helps us do that," said Wong.


DEWEESE


WONG

## MOLECULAR RADIATION SCIENCES

"When we think about radiation therapy, it is high technology, but the complexity of cancer requires that we have a better understanding of the biology," says Marikki Laiho, Director of Molecular Radiation Sciences and Willard and Lillian Hackerman Professor of Radiation Oncology.


LAIHO

The work of Laiho and molecular radiation sciences researchers is aimed at better understanding the mechanisms cancer cells use to survive radiation therapies. They are looking for kinks in cancer cells' armor that can be exploited to prevent them from sensing and repairing the DNA damage caused by radiation therapy.

"DNA damage is not unique, but our research focus is," says Laiho. "There is not a radiation and molecular radiation sciences research program anywhere with the depth and focus we have here."

Among the research projects are studies of cell repair molecules known as PARPs. Drugs called PARP inhibitors can sensitize cancers to radiation therapy and stop cancer cells from making repairs after therapy.


HALES

Understanding the signaling pathways involved in DNA damage, and in particular the role they play in deadly glioblastoma brain cancer is another area

of study. Researchers are investigating the relationship between DNA and its marking by epigenetic tags and how they contribute to cancer cell development and survival. Although each has been studied individually, Molecular Radiation Sciences researchers were among the first to explore how they work together in cancer.

Researchers also want to figure out why some tumors respond to radiation therapies and chemotherapies while others do not. Using genetic tools created to selectively introduce cancer mutations into tumor cells, researchers can explore and observe how the cells respond to cancer therapies and devise strategies to combat treatment resistance.

Heat increases the sensitivity of cancers cells to radiation therapy, and another approach uses magnetic nanoparticles that generate heat when exposed to magnetic fields. Sensitizing cancer cells with heat, could make it possible to lower radiation doses or treat cancers that would be otherwise unresponsive.

Testosterone, a hormone that prostate cancer cells need to survive can also play a role in its demise. Researchers believe testosterone causes breaks in the DNA that could make cancer cells more vulnerable to treatment with radiation therapy. Short pulses of testosterone—enough to stimulate the brakes but not too much to stimulate the cancer—followed by radiation therapy to cause even more DNA breaks, can overwhelm and kill prostate cancers.

A biodegradable hydrogel with the consistency of toothpaste could help protect vital organs from damage during radiation therapy. The hydrogel separates the tumor from organs by about a finger's width, and this extra space allows the radiation to fall off and protect surrounding tissue and organs. Hydrogel spacers are most commonly used in the treatment of prostate cancer, but they are being studied in pancreatic cancer, liver cancer, gynecologic cancers, and head and neck cancers.

Laiho's own research project is focused on a cellular machinery, called POL1, that cancer needs to survive. POL1, she says, is necessary for cancer cells to maintain their rapid growth. In her laboratory studies using human cells, new small molecule inhibitors break down this critical activity. The next step is clinical trials.


McNUTT

## ONCOSPACE

Radiation Oncology researchers led the way in applying technology to precision medicine—treatments tailored to the unique aspects of each patient's cancer.

Physicist **Todd McNutt** developed a computerized data mining system called Oncospace that analyzes data from prior patients who received radiation therapy to improve the treatment of new patients. It sorts through all of the data on cancer patients treated at the Kimmel Cancer Center, taking into account and connecting all of the variables: age, underlying health conditions and other treatments patients are receiving and figures out how all of these variables relate and influence toxicity and response to treatment. It evaluates the therapies that worked best for a particular cancer—as well as those that resulted in less than favorable outcomes—and generates an optimal treatment plan.

"The practice of cancer medicine naturally creates data," says McNutt, "but for the first time in history we have the technology to sift and sort through this data in completely new ways."

The success of precision, individualized medicine, including the ability to determine which patients will benefit from a particular drug or treatment and which ones will not, rested on the ability to conquer big data. Oncospace was one of the first practical demonstrations of this promise.

"Todd has proven that large data warehouses of patient information collected from previously treated patients can be used to individualize treatment decisions for new patients," said Ted DeWeese, Interim Dean of the Johns Hopkins University School of Medicine and former Director of the Department of Radiation Oncology and Molecular Radiation Sciences.

Oncospace does more than collect and store data. It takes informatics to the critical next level with the capability to perform interactive analysis that informs clinical decision making. Radiation oncologist and head neck cancer expert **Harry Quon** provided the crucial link to put the system to test in the clinical practice.

"I could tell you very accurately where the radiation dose goes," says McNutt, "The important question in treating patients is where should it go and where shouldn't it go."

Head and neck cancer patients were the ideal choice for testing Oncospace in the clinical setting because they are among the most difficult cancers for radiation physicists and oncologists to plan. They often require 20 treatment revisions as they work to design a treatment plan that hits the cancer without causing damage to vital organs and glands, such as the voice box and salivary glands.

"We can build predictive models of toxicities and other side effects based on data we have collected from prior patients. including indicators that a patient may be at higher risk for certain treatment toxicities and use this information to adjust the treatment plan," says McNutt.

More recently, they have begun incorporating data on disease response: Is the cancer stable? Has it progressed? Did it recur? Imaging used for treatment simulation are also being incorporated into the collected data to track the history of a tumor throughout treatment. It could help tell early on in the treatment of a cancer if a tumor is responding or if a change to the treatment plan may be necessary.

McNutt says this latest variation is the radiation oncology version of the work being done in cancer genetics and molecular biology using genetic biomarkers to track and monitor the response of cancers to drug therapies.

"It's real time, in-treatment monitoring" says McNutt. "The same way we use the system to relate the dose of radiation to the salivary gland to the loss of gland function we can use it to relate treatment plans to treatment responses."

The success in head and neck cancer has led to Oncospace now being applied to a variety of cancers, including lung, pancreatic, and prostate cancers.

## RADIOSURGERY

Stereotactic body radiosurgery (SBRT) is an option for some cancer patients who have tumors that cannot be removed through traditional surgery. This treatment, sometimes referred to as knifeless surgery, uses high but super-focused doses of radiation to destroy tumors while also limiting side effects to nearby normal organs and tissue.

When pancreatic cancer SBRT is performed, tiny gold seeds, about the size of a grain of rice, are inserted by needle into the pancreatic tumor. They serve as reference points to help guide the radiation oncologist as they treat the cancer. Using the same needle that places the seeds, radiation oncologists removed tiny pieces of the tumor for genetic sequencing.

This unique research study proved that tumors could be sequenced through this small sampling of cells, and the genetic information could be used to individualize treatment in patients with inoperable pancreatic cancer.

"We were the first ones to try this, and we proved it could be done," said **Joseph Herman**, former radiation oncology faculty member who led the initial study.

Stereotactic radiosurgery is also being used by **Amol Narang** to get more pancreatic cancer patients to surgery. Building upon earlier research, he is using SBRT in pancreatic tumors that have attached to nearby blood vessels, making surgical removal of the entire tumor difficult or impossible.

Combining chemotherapy with radiosurgery in these cases helps shrink tumors away from the blood vessels, making surgical removal of the tumor possible for more patients. The immune priming ability of radiosurgery is also being studied in clinical trials of pancreatic cancer patients.

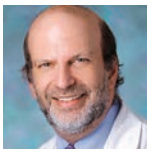
The prevailing opinion in cancer research was that chemotherapy and radiation therapy suppressed the immune system, but Kimmel Cancer Center radiation oncologists proved that may not be the case.

Focused radiation, like what is used in stereotactic radiosurgery, they found may actually stimulate an immune response. Collaborating with Kimmel Cancer Center cancer immunology experts, radiation oncology experts used the small animal radiation research platform to study a combination of radiosurgery and an immune therapy drug in animal models.

Radiation therapy is considered a localized treatment but when combined with immune therapy, it gains an added systemic activity. Immune therapy prevents cancer cells from deploying immune dampening regulatory cells, and with the regulatory cells taken care of, they could use radiosurgery to enlist the entire complement of immune cells to fight the cancer. Killer T cells that, as the name implies, kill cancer cells, memory T cells that remember the tumor cells and have the power to keep the cancer in check indefinitely, and B cells which generate antitumor antibodies that interfere with the cancer cells DNA and stop them from replicating new copies.

This initial study was led by former radiation oncology resident **Andrew Sharabi** and former Bloomberg~Kimmel Institute for Cancer Immunotherapy researcher **Charles Drake**. Sharabi's research was selected from thousands of submissions as a featured presentation at the 2014 annual meeting of the American Society of Radiation Oncology. It was the first basic science research to be highlighted at the meeting in over a decade.

For brain tumor expert **Lawrence Kleinberg**, SBRT means he can safely treat the spread of cancer in the brain.


KLEINBERG

"Before we had radiosurgery, we had to treat the entire brain with radiation and that, of course, caused many side effects, said Kleinberg. "Now, in most situations, we can treat very small areas of the brain with almost no side effects."

As a result, the Kimmel Cancer Center radiosurgery team offer one of the few treatment options for patients with spread of cancer to the brain.

## BRACHYTHERAPY

Brachytherapy is a widely used and promising tool of radiation therapy and commonly used in the treatment of prostate cancer and gynecologic cancers as an alternative to surgery.

In prostate cancer, radiation is delivered to the prostate via tiny seeds about the size of a grain of rice. Accurate placement of these seeds has been the biggest challenge, but brachytherapy expert **Danny Song** has been a leader in pioneering guidance systems that ensure the seeds are deployed correctly.


NARANG


SONG

To destroy prostate cancer, about 50 to 100 seeds are placed by needle in the prostate while the patient is under general anesthesia. The greatest limitation to brachytherapy, Song says, was that there was no good real time way to see if the seeds were getting to the correct place. X-ray showed the seeds but did not provide a clear image of the prostate, and ultrasound shows the prostate well but not the seeds.

He decided to combine the two technologies into one. In a collaboration with Johns Hopkins University engineers, Song developed RadVision. As seeds are placed, multiple X-rays are taken and fed into a computer to generate a three-dimensional arrangement of seeds. The seed positions are then superimposed over ultrasound images to ensure the right number of seeds has been placed and to guide the placement of additional seeds, if needed.

RadVision received FDA approval after a clinical study that proved it provided the most accurate seed placement. Patients who have received brachytherapy often also require external beam radiation to compensate for an inadequate seed placement, but Song says seed placement with RadVision is so accurate it may eliminate the need for additional radiation treatments.


KUMAR

In addition, a high dose rate prostate brachytherapy program was launched at the Kimmel Cancer Center at Sibley Memorial Hospital in 2023 under the direction of **Rachit Kumar**.

In gynecologic cancers, Akila Viswanathan, Director of the Department of Radiation Oncology

and Molecular Radiation Sciences, was the first in the U.S. to use real time magnetic resonance (MR)-guided interstitial brachytherapy for the treatment of gynecologic cancers.

Using active magnetic resonance imaging guidance, physicians insert several hollow catheters into the tumor. Tiny, radioactive seeds, tethered together by a long thread are inserted into catheters and remain there for about 10 minutes, providing a rapid but high dose of radiation to control cancer cells. A computer controls the insertion and removal of the seeds, ensuring a precise dose throughout the tumor.

"Gynecologic cancers can grow very fast and require very focused high dose to attack the tumor," Viswanathan explains.


MEYER

The entire outpatient procedure takes just a few hours and provides a lifetime of benefits to patients.

"I wanted women who have inoperable cancer that is limited to the gynecologic area to be cured of this cancer," she says.


WRIGHT

Women who have surgery for cancer often lose their entire gynecologic tract, including the cervix, she explains. Brachytherapy preserves these organs, which is particularly important for young women.

The types of MR technology she uses are unique. Working with the team of physicists who write special codes to direct the MRI scanner, she can look inside a tumor and provide a variety of details not available with traditional MRI. Outcomes are excellent for cervical cancer and recurrent uterine vulvar and vaginal cancers, Viswanathan says, with published data showing MR-guided brachytherapy survival rates of over 90%. As a result, Viswanathan is in demand, seeing about 300 patients a year from all over the world. She is training other radiation oncologists to perform the procedure, which she recently expanded to the Kimmel Cancer Center at Sibley Memorial Hospital.


POMPER

## THERANOSTICS

A new approach dubbed "theranostics," because it combines the diagnostic properties of molecular imaging with cancer therapy was developed at the Kimmel Cancer Center.


BHUJWALLA

Led by imaging experts **Martin Pomper** and **Zaver Bhujwalla**, and radiation oncologist **Ana Kiess**, the novel approach takes advantage of important molecular components of cancer and allows researchers and clinicians to see inside the cancer cell and view them as they are being treated.


KIESS

The team developed ultra-tiny structures called nanoparticles filled with a drug that kills cancer cells and sensitizes them to radiation and a radiopharmaceutical or cell imaging agent. The nanoparticle is targeted to PSMA, which is present at high levels in prostate cancer, so that it zeroes in on and delivers its anticancer payload specifically to prostate tumors. The particle is labeled with a radioactive isotope which can be imaged or used to treat cancer. It is given intravenously so that it can attack cells growing anywhere in the body.

Kiess and Pomper worked with chemists to modify a drug called LU-PSMA-12, to make it specific to cancer cells and less likely to go into normal cells. The drug is being studied in multicenter clinical trials of advanced prostate cancer.

## LESS IS MORE

The ability to shorten the several week course of radiation therapy is a new area of research Radiation oncologist and colorectal cancer specialist **Jeffrey Meyer** is studying—whether abbreviating a typical five-week course of radiation therapy to five days, followed by chemotherapy two months later and then surgery. The regimen is easier for patients, with far less interruptions to their normal routines.

In early studies, long-term outcomes appear to be as good as the traditional, longer courses of radiation therapy, Dr. Meyer says, but adds that the research continues.

**Jean Wright**, Director of the Breast Cancer Program's Radiation Oncology service, is studying a similar approach for breast cancer.

In the 2000s radiation therapy was delivered over five to seven weeks for almost all patients needing breast radiation, Wright says. About 15 years ago, studies found that shorter, three to four week courses were as effective for patients at lower risk for breast cancer recurrence, and, she says, they have moved to these shorter courses for many patients.

She is also exploring the benefits of an even shorter, one-week, high-dose whole breast radiation approach. The very convenient course has to be weighted for each patient, depending on their breast cancer risk as well as personal preferences and priorities, Wright says.

"This is another great example of how our field is evolving toward patient-centric, tailored treatments," says Wright.

## PROTON THERAPY

Proton therapy uses charged particles, rather than photon therapies' high-powered X-rays beams, to kill cancer. Proton does not replace photon radiation therapy but is another important tool our experts have to treat cancer.

The Johns Hopkins Proton Therapy Center opened in 2019 at Johns Hopkins Sibley Memorial Hospital. It is one of only about 40 centers in the U.S. and one of a few with dedicated proton beams for research and a specialized pediatric team.

The Proton Therapy Center is one of the most comprehensive in the world with technology to deliver the most advanced and patient-centered care. It combines cancer treatment excellence across all disciplines with proton therapy excellence, building upon a lengthy history and strong foundation of pioneering discoveries in radiation therapy.

*See section 6, page 128 to read more about the Johns Hopkins Proton Therapy Center.*

## MILESTONES IN RADIATION ONCOLOGY AND MOLECULAR RADIATION SCIENCES

**1973**: **Stanley Order** is appointed director of the Division of Radiation Oncology for the newly approved comprehensive cancer center at Johns Hopkins

**1985**: Radiolabeled antibodies prove effective against liver cancer

**1990:** World-renowned pediatric radiation oncologist, **Moody Wharam**, is appointed director of Division of Radiation Oncology

**2003**: Department of Radiation Oncology and Molecular Radiation Sciences is established, with **Theodore DeWeese** as director

Molecular Radiation Sciences division established

**2004: John Wong** is named chief of physics, bringing with him his earlier inventions of cone beam CT and his small-animal radiation research platform

**2007:** The stereotactic body radiation surgery program begins, knifeless surgery that uses focused beams of radiation to kill tumors

**Marikki Laiho** recruited to direct Molecular Radiation Sciences division

**2008:** Molecular radiation sciences research deciphers the biology of DNA damage response to radiation therapy and how cells sense and repair this damage

CT-guided miniature versions of the equipment used to treat patients are invented and used to perform first-of-its-kind research, allowing scientists to study the best ways to target radiation-based treatments to tumors and at the same time prevent damage to normal cells

Early gene editing method demonstrates how Chk1, a prototypical therapeutic target, functions in normal cell growth and in cells under stress

**2009:** A computer-assisted version of brachytherapy, a prostate cancer therapy that uses radioactive seeds inserted into the prostate to kill cancer cells, is developed, allowing for more precise placement of seeds

Molecular Radiation Sciences hosts first symposium on DNA damage repair

Magnetic hyperthermia program established, directed by **Robert Ivkov**, to exploit magnetic nanoparticles for cancer hyperthermia in alternating magnetic fields

**2010:** Oncospace, a computerized data-mining system, analyzes data from prior patients to improve the treatment of new patients

Human prostate tissues cultured in dish to investigate response to DNA damage

The Johns Hopkins Kimmel Cancer Center at Sibley Memorial Hospital opens, and includes radiation oncology services

**2011:** RNA aptamers developed to block DNA repair as a method to augment radiation response

**2012:** A drug that protects radiosensitive mice from low-dose-rate radiation identified

**2013:** Small animal radiation research platform used for targeted radiation delivery to glioblastoma to investigate new combined treatment strategies with immune checkpoint inhibitors

**2014:** Novel inhibitors of RNA Pol I, necessary for cancer growth, identified as a potential anticancer strategy

Discovery of new pathway by which p53 suppresses tumor development

First FDA-approved, real-time prostate cancer brachytherapy treatment, planning and guidance system implemented

**2015:** The Kimmel Cancer Center partners with United Medical Center and Howard University to bring cancer care to the most underserved communities in Washington, D.C.

Magnetic hyperthermia enhances therapeutic response to radiation in mouse prostate cancer models

**2016: Akila Viswanathan** is appointed director of the Department of Radiation Oncology and Molecular Radiation Sciences, and brings her pioneering therapies using CT- and MRI-guided brachytherapy to the treatment of cervical and other gynecological cancers

Minibrains grown in dish to aid research and individualized therapy

**2019:** The first phase of the Johns Hopkins Proton Therapy Center opens, with phases two and three opening in 2020

**2021:** First canine clinical trial using magnetic nanoparticles initiated

**2022: Xun Jia** is appointed chief of medical physics division in radiation oncology

**2023:** Palliative care program launches, managed by **Annie LaVigne**

Kimmel Cancer Center radiation oncology program at Sibley Memorial Hospital builds high dose rate prostate brachytherapy program

Pluvicto treatment program launches following several radiopharmaceutical trials

# A Model Clinic

AT MOST HOSPITALS around the country, diagnosis and treatment revolved around the care team, with a series of visits with medical, surgical, and radiation oncologists and other specialists at different locations. Numerous appointments for tests, care decisions, and treatments were spread out over time. At the Kimmel Cancer Center, our experts followed an opposing model in which the care team revolved around the patient in one central location.

The Johns Hopkins Multidisciplinary Clinics—the MultiDs as they are known—were born out of the desire for the Center's clinical programs to match the strength of its basic science research programs. They have played a vital role in improving the treatment of difficult cancers, such as pancreatic, liver, lung cancers, and more.

"I can't think of another place like this, with this level of interaction," says **Bert Vogelstein**, Clayton Professor of Oncology and Co-Director of Ludwig Center for Molecular therapeutics, whose genetic discoveries were and example of the basic science woven throughout the Multi-Ds, informing and improving cancer diagnostics and treatment. "You can't manufacture that kind of environment. It has to be built from the ground up, and we're very fortunate to have it here."

Our experts envisioned a clinic in which patients could come to the Kimmel Cancer Center, and after a single day's visit, receive an integrated treatment plan representing the multispecialty expertise of all experts involved in the treatment of each cancer type. The multidisciplinary care model ensured that every expert involved in the treatment of a particular cancer literally has a seat at the table when recommending a treatment plan to the patient. The clinic seamlessly incorporated all elements of cancer care, including diagnosis, therapy, follow up care and surveillance, palliative medicine, and survivorship.

"We're not just discussing the treatments that patients will need for their particular cancer but what other resources we will need to enlist for each patient based on what we know about them, their medical history, social history, and their life circumstances, because treatment isn't just about the cancer itself," says **Joy Feliciano,** thoracic cancer expert and Cancer Diagnostic Clinic Medical Director. "It's about how this patient might need rides to chemo or that one might need us to coordinate care with their cardiologist because they have a pacemaker."


FELICIANO

The clinics marked a major step forward from the early days of the Center when cancer care was often a singular approach. If a tumor could be removed with surgery, the patient was treated first by a surgeon and handed off to medical and radiation oncologists for chemotherapy and radiation therapy.

A radiologist would image the tumor and send a report to the oncologist. All of the experts would perform their tasks well, but there was no concerted effort.

"Cancer therapy transcends the boundaries of medical and surgical disciplines, so it was important to have all of the key players involved in the plan and execution of therapy from the onset," says **Elizabeth Jaffee**, Deputy Director of the Kimmel Cancer Center and co-director of the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care. "By the end of their visit they have received a rapid, wholistic treatment plan, including available clinical trials of the most novel new therapies."

This single-day approach is highly unusual in cancer care, says **Russell Hales,** radiation oncologist and Director of the Thoracic Oncology Multidisciplinary Clinic. His research has helped prove its benefits.

Although he knew patients liked the Multi-Ds, he wanted to be sure, by examining objective data, that it was the best approach for them. In 2017, he compared outcomes of lung cancer patients who received care through the Multidisciplinary Clinic with patients who received their care outside of the Clinic with individual providers through a more traditional care model.

Their findings showed that one year survival at the clinic was 82% compared with 64% for patients treated outside the clinic. The next year, Kimmel Cancer Center radiation oncologist **Ranh Voong** presented additional findings showing that the clinic provides a costs savings of 30% over traditional care, presumably because patients receive more streamlined planning and treatment, avoiding unnecessary appointments and tests.

"You don't see this magnitude of improvement in some of the newer drugs coming out, and it's even more significant because patients in the healthcare system are saving money," says Hales.

The Kimmel Cancer Center has a Multidisciplinary clinic for every cancer type.

Patients travel from around the country, across the U.S., and throughout the state and region.

"This kind of care is in the DNA of the Kimmel Cancer Center," says its Director **William Nelson**. "The collaboration across disciplines is part of our history and it continues today. We never forget the science, and that puts us at the forefront of clinical breakthroughs."


WOLFF


HOLDHOLF


VOONG


LAHERU


SHARFMAN

## *A snapshot of our many specialty centers and clinics emerging from this multidisciplinary model of care and the generosity of donors who make them possible:*

***Blood and Bone Marrow Cancers (Hematologic Malignancies) and Bone Marrow Transplant***
Directed by **Richard Jones** and **Richard Ambinder**

***Brain Cancer Disease Group and Brain Tumor Specialty Center***
Directed by **Matthias Holdhoff** and **John Laterra**

***Colorectal Cancer Research Center of Excellence***
Directed by **Nilofer Azad**

***The Greenberg Bladder Cancer Institute***
Directed by **David McConkey**

***Liver Cancer Multidisciplinary Clinic***
Directed by **Mark Yarchoan**

***Melanoma and Skin Cancer Multidisciplinary Program***
Directed by **Suzanne Topalian**, Bloomberg-Kimmel Professor of Cancer Immunotherapy, and **William Sharfman**, Mary Jo Rogers Professor of Cancer Immunology and Melanoma Research. Clinical co-directors are **Julie Lange** and **Elise Ng**.

***Head and Neck Cancer Center***
Directed by **Carole Fakhry**. Otolaryngology-Head and Neck Surgery is directed by **David Eisele**. The Head and Neck Cancer disease group is directed by **Tanguy Lim-Seiwert**, and **Harry Quon** co-directs the Head and Neck Cancer Multidisciplinary Clinic.

***Prostate Cancer Multidisciplinary Clinics, Precision Medicine Center of Excellence for Prostate Cancer, and Prostate/Genitourinary Cancer Program***
Directed by **Sam Denmeade** and **Sean Lupold**. Clinical research is directed by **Channing Paller**. Co-leaders of the Multidisciplinary Clinic are **Eugene Shenderov**, **Christian Pavlovich**, and **Danny Song**, and co-leaders of the Multidisciplinary Clinic in the National Capital Region are **Curt Deville**, **Channing Paller**, and **Armine Smith**. **Mark Markowski** is the leader of genitorurinary medical oncology in the National Capital Region.

***The Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care***
Co-directed by **Elizabeth Jaffee**, the Dana and Albert "Cubby" Broccoli Professor of Oncology, and **Daniel Laheru**, Ian T. MacMillan Professor of Pancreatic Cancer Research.

***Precision Medicine Center of Excellence for Pancreatic Cancer***
Directed by **Lei Zheng**

***Thoracic Cancer Center of Excellence and Precision Medicine Center of Excellence for Lung Cancer***
The Thoracic Oncology Program is directed by **Julie Brahmer**, and the Thoracic Oncology Multidisciplinary Program is directed by **Russell Hales**. The Precision Medicine Center is directed by **Valsamo "Elsa" Anagnostou**, and **Joseph Murray**. The Esophageal Cancer Research Program is directed by **Vincent Lam**. **Stephen Greco** is clinical director of radiation oncology at Suburban Hospital. Surgeon **Stephen Broderick** directs the Cardiothoracic Residency program.

***Under Armour Breast Health Innovation Center and Women's Malignancies***
**Antonio Wolff** is acting director. **Jean Wright** is director of the radiation oncology breast cancer program.

# Beating Pancreatic Cancer

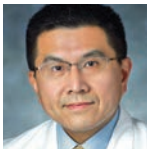

KATHLEEN

IN 1997, DARK urine and annoying itching all over her body, drove Kathleen, then 50, to see her doctor.

Her doctor suspected a gall stone. However, when routine surgery at a community hospital near her home to remove the gall bladder resulted in complications with her small intestine, pancreatic cancer was detected.


JAFFEE


DONEHOWER


ZHENG


CAMERON

The surgeon broke the devastating news to Kathleen's husband and 25- and 21-year-old daughters. He recommended Kathleen go to Johns Hopkins for surgery. The surgeon told the family that "Hopkins surgeons have the most expertise in doing this surgery," recalls Kathleen.

The next day, she was transferred by ambulance to Johns Hopkins and met with world-famous surgeon **John Cameron**. In a surgical procedure known as the Whipple, he removed Kathleen's pancreas, part of her stomach, and several lymph nodes.

The Whipple is the primary surgical treatment for pancreatic cancer, and Cameron pioneered significant improvements to the surgery. Under his direction, Johns Hopkins earned the reputation as the best in the world for pancreatic cancer surgery and for training the next generation of surgeons. These improvements made the complex surgery safe and dramatically reduced complications.

The lymph nodes are small glands that are part of the immune system and carry cells and fluid to other parts of the body. They provide a means for cancer cells to spread from the original tumor to other organs. Examination of the lymph nodes removed during Kathleen's surgery revealed that they contained cancer cells, meaning the cancer had begun to spread and would not be cured by surgery alone.

"I wasn't familiar with pancreatic cancer. I didn't know anyone who had it, so I really didn't understand how bad it was," says Kathleen. "I was shocked when I learned the statistics."

She still recalls the day she asked Cameron if the dismal pancreatic cancer survival rates she read about were true. He told her they were, but he also told her she could be the one to beat the odds.

She received chemotherapy to help mop up any remaining cancer cells. Gastrointestinal cancer expert **Ross Donehower** also told Kathleen about a clinical trial of a new cancer vaccine developed at the Kimmel Cancer by leading pancreatic cancer researcher **Elizabeth Jaffee**, co-director of the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care.

**"I wasn't familiar with pancreatic cancer. I didn't know anyone who had it, so I really didn't understand how bad it was. I was shocked when I learned the statistics."**

"He said it might keep my cancer from coming back," says Kathleen. Given the statistics she read, she wanted to give it a try. She was the eighth patient to receive the vaccine.

The pancreatic cancer vaccine works by supercharging the immune system, causing cancer cells to seek out and kill cancer cells, including hunting down and cleaning up surviving cancer cells or newly appearing cells anywhere in the body. With few treatments for advanced pancreatic cancer, the vaccine attracted worldwide attention when it was developed in the early 2000s. The clinic received more than 60 inquiries each month from patients hoping to receive the vaccine. After Dr. Jaffee appeared on the *Dr. Oz* show in 2011, the clinic was flooded with more than 1,000 inquiries.

"We were the only Cancer Center at the time doing this kind of work," says **Lei Zheng**, who works with Jaffee on pancreatic cancer vaccines and other treatments for the cancer. He is also co-director of the Pancreatic Cancer Precision Medicine Center of Excellence, aimed at the quick translation of the latest research on vaccines and immunotherapy, molecularly targeted therapy, chemotherapy, radiation, and surgical techniques to patients.

After receiving two doses of the vaccine, Kathleen developed a condition called TTP that causes blood clots to form throughout the body. It was not caused by the vaccine, but it meant she would not be able to receive additional doses of the vaccine.

Remarkably, the two doses Kathleen received were enough, and 26 years later, she remains cancer free.

"I remember the doctors telling me I had the strongest immune response of anyone in the clinical trial," says Kathleen.

It is a complex process to activate the immune system to recognize pancreas cancer cells and simultaneously suppress mechanisms Kimmel Cancer Center researchers have revealed are co-opted by tumor cells to shut down the immune response. Jaffe, Zheng and the Skip Viragh Center team continue to study new approaches,

including combining the vaccine with drug therapy or radiation therapy, and creating vaccines individualized to the unique molecular characteristics of a patient's cancer.

Today at 75, Kathleen is retired and enjoying her four grandchildren. She had one grandchild when she was diagnosed. "I didn't think I'd live to see her grow up," says Kathleen.


ONNERS

She started making bunnies, cladding them in fancy dresses. She thought it would be a way for her granddaughter to remember her. Now, they have are a lasting testament to her survival. Kathleen has made one for each of her grandchildren.

It wasn't an easy journey, and there have been a few scares along the way, such as a spot that showed up on a CT.

"They never amounted to anything," she says.

She is grateful to her doctor **Dan Laheru**, co-director of the Skip Viragh Center for being so thorough. After all these years, Kathleen still gets emotional when she thinks about her cancer battle. She has great respect for her doctors and nurses.

"Dr. Jaffee, Dr. Laheru, my nurse **Beth Onners**, I can't say enough about them," says Kathleen. "They are wonderful; top notch."

# Scientist Becomes Patient

KIMMEL CANCER CENTER researcher **Christopher Umbricht** understands the power of translational research. In 2000, he found himself simultaneously a scientist working to understand an enzyme called telomerase and a patient, applying his research to thyroid cancer.


ZEIGER

Umbricht and cancer surgeon **Martha Zeiger** had been studying telomerase for several years as a potential biomarker for the detection of certain types of cancer, including breast cancer and thyroid cancer.

In a serendipitous twist of fate, Umbricht was among the early researchers to test telomerase in the lab, and he became the first patient at Johns Hopkins to have his tumor tested for this marker.


UMBRICHT

When a needle biopsy, removing a sampling of cells from a small lump on his neck, revealed a follicular thyroid tumor, he was shocked that his research was now becoming his personal reality.

The treatment of follicular thyroid tumors is a medical challenge. Unlike other tumors that display obvious signs of being either a cancer or a harmless benign tumor, follicular thyroid tumors are not so clear cut. The entire tumor must be removed surgically and examined under a microscope to determine if the tumor is cancer, and until recently, this was done by performing a complete removal of the thyroid gland, requiring lifelong treatment with oral medications to replace the natural hormone. "Without a sure way to know, we could not risk leaving the gland in when it might be cancerous," says Zeiger.

Yet, the majority of tumors — about 80% — are benign, and would not have required surgery if there was a nonsurgical way to distinguish cancer from noncancer.

If they could figure out a way to identify the cancerous tumors requiring surgery to remove the whole thyroid, they could spare 15,000 people each year unnecessarily invasive surgeries and the need for lifelong medication, she says.

The thyroid is a small, butterfly-shaped organ in the front of the neck that performs a mighty job. It produces hormones that are carried throughout the bloodstream to every cell in the body. All of a person's organs — the heart, brain, liver, kidneys and skin — require the right amount of thyroid hormone to function correctly. Body temperature, cholesterol levels, moods and memory are all affected by the thyroid hormone.

Umbricht was confident enough in their telomerase research that he wanted to use the biomarker to guide his treatment. Zeiger was not convinced.

Despite persuasive laboratory studies on human tumors, the findings had not been used to alter therapy. The use of telomerase as a tumor marker was still in the research phase, and she advised Umbricht to have the surgery.

The cells removed from Umbricht's tumor during the needle biopsy did not show signs of telomerase, indicating the tumor was benign.

Therefore, Umbricht opted for more limited surgery, removing just the thyroid lobe containing the tumor. Fortunately, the microscopic exam confirmed the absence of cancer tissue.

As the research advanced and technologies improved and they delved deeper into the research, as is often the case with cancer, it proved to be more complicated.

With their ongoing research, the initial success in using the telomerase enzyme to distinguish thyroid cancer from benign thyroid tumors revealed some problems. Their initial biomarker lacked the sensitivity (ability of a test to correctly find disease in the person tested) and specificity (ability of a test to correctly determine the person tested is disease-free) to be a viable cancer test.

The precision medicine goal of directing treatment to the patients who need it and away from those who could be safely spared surgery and lifelong medication remains an important area of research, however, and progress has been made.

Zeiger, Umbricht and collaborators have now shifted their focus to the role of easily detectable genetic mutations in telomerase genes as a more reliable biomarker, and one that seems to mark aggressive tumors that are most likely to spread to other parts of the body. They continue to study the biomarker in samples of follicular thyroid tumors removed during surgery as they work toward a test that could reliably guide therapy.

## PIONEERING THE WHIPPLE

Surgeons, like **John Cameron**, have made significant improvements to the Whipple procedure, the primary surgical treatment for pancreatic cancer that occurs within the head of the gland (also called a pancreaticoduodenectomy). Today, our surgeons perform a high volume of these procedures and have lessened the complications during and after surgery.

Pancreatic surgery, once associated with a very high risk of surgically related death, has since dropped to 2% — when performed by an experienced surgeon — because of improvements made to the Whipple by Cameron and his trainees.

Cameron performed more than 2,000 Whipple procedures — more than anyone in the world — and trained a team of pancreatic surgeons to carry on his legacy.

## TITANS OF PROSTATE CANCER

Urologist **Patrick Walsh** is perhaps the most famous and revered figure in the world of prostate cancer. For 30 years, he served as Director of the internationally renowned Brady Urologic Institute at Johns Hopkins. He transformed prostate surgery by developing an anatomical approach to remove the cancerous prostate without causing the life-changing side effects and taught the procedure to hundreds of urologists-in-training.

Forward thinking, Walsh compiled an extensive database of thousands of patients and followed them for 30 years, which **Donald Coffey** and others who trained with Coffey used to decipher some of the first insights into the basic biology of prostate cancer.

In June 2011, he performed the procedure he pioneered for the last time. It was his 4,569th prostatectomy.

**Alan Partin**, the Jakurski Director of the Brady Urologic Institute, from 2004-2022, passed away in 2023, but his impact on prostate and other urological cancers lives on. A noted physician-scientist and prostate surgeon,Partin developed a method to predict the prognosis of prostate cancer. He pursued science with creative vigor, cared for thousands of patients with kind expertise and led the urology department through strategic growth, broadening its sphere of influence while maintaining the depth of scientific understanding that continues to inform patient care.

Under Partin's leadership, the Brady Urological Institute doubled its research space and enjoyed significant expansion with projects, such as the world-renowned Greenberg Bladder Cancer Institute and new clinical space at Green Spring Station Pavilion III.

He is known for developing the Partin Tables, which are used for predicting the prognosis for prostate cancer, and for his work developing several innovative tests to identify and track prostate cancer, including the Prostate Health Index.

Throughout his 40-year career as a researcher, a clinician and a leader, Partin was consistently at the heart of discovery and innovation in the field of urology, always keeping a singular focus on improving outcomes for our patients. He embodied the best of Johns Hopkins.

He earned his doctorate in pharmacology and molecular sciences in 1988 and his M.D. 1989 at the Johns Hopkins University School of Medicine. After completing his residency at Johns Hopkins, he joined The Brady Urological Institute as an associate professor in 1995.

In December 2022, the Alan W. Partin, M.D., Ph.D., Professorship in Urology was established to support research to develop diagnostic tools, treatments and cures for prostate cancer.

In more than 50 years at Johns Hopkins, **Donald Coffey**, the Catherine Iola and J. Smith Michael Distinguished Professor of Urology and professor of oncology, pharmacology and molecular sciences, and pathology, racked up a long list of accomplishments. Many of his accolades are as unconventional as the man. He served as acting chair of the Department of Pharmacology without every taking a course in pharmacology. With no medical degree, he helped found the Cancer Center in 1973 with its first director **Albert Owens**, and then ran it in 1987. He described himself as one of academia's worst students, but he was an astute learner and an even better teacher and was one of the foremost experts in prostate cancer.


COFFEY

The early research of Coffey was, in many ways, the bedrock on which modern genetic and epigenetic discoveries at Johns Hopkins were built. In 1974, he turned the research world upside down, challenging the popular thought on how DNA was copied. The prevailing thought of the time was that there was no single place in the cell where DNA was copied. Coffey disagreed. He believed the core of the nucleus was where DNA was copied, and the tape-like strands — a yard long — were coiled tightly inside the cell nucleus.

"The nucleus has a skeleton to it. That's the nuclear matrix," explained Coffey. He believed, however, that people would have to see it to believe it.

"**Ken Pienta** and I went to Sears and bought a jigsaw, and we built an award-winning scaled model, 175 feet long, of a relaxed single loop of DNA magnified 25 million times," recalled Coffey. Another model, this one just four feet long, was constructed to illustrate the super-coiled loops of DNA.

Coffey explained that cancer was like the body's genetic tape playing the wrong song at the wrong time. "The tape is all mixed up and contains errors," he said.

Understanding what is on the tape and how it is played in cancer has been one of the greatest scientific contributions of Johns Hopkins and its Kimmel Cancer Center. He also planted the seeds for the future multidisciplinary clinics. He believed that much could be learned if people from different specialties could just get together and talk about a problem.

A consummate teacher, Coffey continued to use models, Slinkys, soap bubbles, soda cans, and more to train the next generation of cancer researchers, which included **Ted DeWeese**, Interim Dean of the Johns Hopkins School of Medicine, **William Nelson**, Kimmel Cancer Center Director, **Bert Vogelstein**, Co-Director of the Ludwig Center for Cancer Genetics and Molecular Therapeutics, and **Drew Pardoll**, Director of the Bloomberg~Kimmel Institute for Cancer Immunotherapy.

The classroom and the laboratory never closed for Coffey. In the hallways of the Brady and the Kimmel Cancer Center, in his office over high tea, or in a conference room, he could be found fostering collaborations and inspiring new ideas about cancer.

Coffey trained some of the greatest minds in the Kimmel Cancer Center, and although he passed in 2017, his lessons are timeless:

**Don't assume anything you can't prove.**

**The experiment that doesn't come out the way you think it should is the only experiment that is really going to teach you something new.**

**If you find something to be true, what does it imply?** *Often we don't need more experiments we need more critical thinking about the results.*

**Generate more than one concept to explain your data, then give all the possibilities your equal attention and effort.** *Your pet idea will usually turn out to be just that.*

**When discoveries are made give everyone credit.** *You were probably not the first one to study the problem, nor will you be the last.*

## MORE TITANS AND PIONEERS

The Kimmel Cancer Center also recognizes these Cancer Center titans and pioneers:
Prostate cancer: **Michael Carducci, Mario Eisenberger**, **John Isaacs**, **William Isaacs**, **Ken Pienta**, and **Hugh Jewett**; Cancer pathology: **Ralph Hruban** and **Robert Kurman**; Cancer research: **Scott Kaufman** and **Strat May**; Viral oncology: **John Nicholas** and **Prashant Desai**; Head and Neck Cancer: **Wayne Koch** and **Joseph Califano**; Cancer surgery: **John Niederhuber** and **Rick Schulick**; Solid tumors: **Skip Trump**.

# CANCER RESEARCH | ADVANCES

## A HISTORY OF PROGRESS AGAINST PROSTATE CANCER

Performed the first prostatectomy in 1904 and later pioneered the atomical nerve sparing approach

Developed some of the first therapeutic approaches and clinical models for prostate cancer, including the earliest form of brachytherapy, and were the first to culture human prostate cancer cells to study therapeutic targets

Developed the first animal models to characterize the properties and types of prostate cancer

Discovered the first human gene mutation in prostate cancer

Deciphered the mechanisms for prostate cancer metastasis

Provided the first description of the basic cellular and molecular properties of prostate cancer

Were the first to describe the importance of stem cells in prostate cancer

Deciphered how prostate cancer growth is regulated

Defined hereditary prostate cancer

Performed the first DNA methylation studies in prostate cancer

Developed an animal model of prostate inflammation and defined proliferative inflammatory atrophy, a new model for what causes prostate cancer

Pioneered quantitative pathology to refine staging and prognostic markers

Developed the Partin Tables, Pound Tables, and Han Tables to predict localized cancers, relapse time, metastasis, and survival

Used PSA velocity to define lethal types of prostate cancer

Developed and clinically tested the first prostate specific adenovirus to treat recurrent and metastatic prostate cancer

Performed the first protein analysis of normal prostate and prostate cancer

Developed new biomarker tests for prostate cancer

Led the work in robotics for prostate cancer treatment

Pioneered tumor immunology studies and developed GVAX, the first therapeutic vaccine for prostate cancer

Identified new drug targets, PSA negative activated pro drugs and other agents

## NEWS THAT BROKE IN THE 2000s

**2001**
On September 14, 2001, Kimmel Cancer Center patients, faculty and staff members joined together in a healing service following the tragic terrorist attacks of September 11, 2001.

**2002**
*Baltimore* Magazine's "Best Doctors" issue included Kimmel Cancer Center oncologists **Martin Abeloff**, **Nancy Davidson**, **Ross Donehower**, **Mario Eisenberger**, **David Ettinger**, **Stuart Grossman** and **Georgia Vogelsang**.

**2003**
**Scott Kern** links three genes associated with a rare disease known as Fanconi's anemia to a subset of pancreatic cancers.

**Joel Shaper** was selected to serve on the National Institutes of Health Pathobiochemistry Study Section.

**2004**
**Sauk Sharkis** finds that bone marrow stems cells exposed to damaged liver tissue converted into healthy liver cells and helped repair the damaged organ.

**Angelo De Marzo** and **Alan Meeker** find that abnormal telomeres, the protective end caps on chromosomes, play a causal role in cancer development.

**2006**
**Saraswati Sukumar** uses a tiny catheter inserted through the nipple to deliver anticancer drugs directly into the breast ducts.

**Deborah Armstrong** revives a 50-year-old method for delivering chemotherapy directly into the abdomen for patients with ovarian cancer.

**Akilesh Pandy** and colleagues at the Institute for Bioinformatics in Bangalore, India, create the Human Protein Reference Database of more than 25,000 human protein-to-protein interactions.

**Victor Velculsecu** reports that the PIK3CA gene is one of the two most highly mutated oncogenes (tumor promoting gene) discovered in human tumors.

**William Nelson** and **Angelo De Marzo** find that PhIP, a compound found in meats cooked at very high temperatures, such as open flames, could be linked to prostate precancers.

**Paula Pitha-Rowe** identifies a gene, ISG15, as an inhibitor of a cellular pathway used by HIV-1, the AIDS causing human immunodeficiency virus.

**2007**
**Chi Dang** finds that the role of antioxidants may be to destabilize a tumor's ability to grow in oxygen-starved conditions.

**Rhoda Alani**, identifies a gene expression pattern that could help pinpoint deadly melanoma skin cancers.

**Allison Klein**, develops PancPRO, a risk calculator for pancreatic cancer.

**2009**
For the 19th consecutive year, the Johns Hopkins Hospital earns the *U.S. News and World Report*'s top spot in its annual rankings of America's hospitals. The Kimmel Cancer Center ranks among the top three cancer centers in the nation.

**G. Steven Bova** works from the autopsies of 33 men who died of prostate cancer, examining 150,000 slides and 30,000 blocks of tissue and traces the origin of each person's cancer to a single cell source.

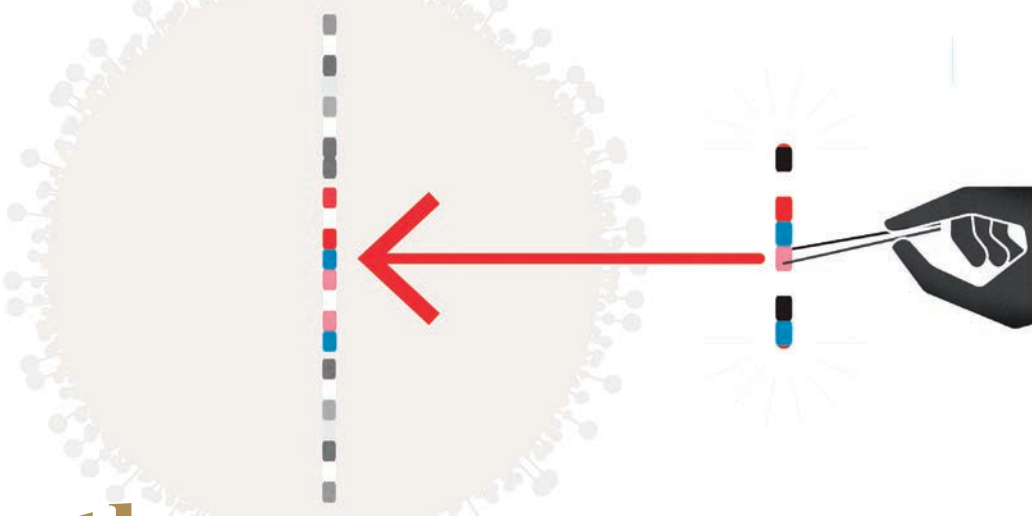
**Charles Rudin** finds that lung cancers in never smokers have more mutations of the EFGR gene, making these patients candidates for therapies that block EGFR signaling.

The Kimmel Cancer Center's Next Generation Sequencing Lab opens under the direction of **Vasan Yegnasubramanian** and **Sarah Wheelan**, allowing researchers to see inside the cancer cell in ways never before possible and speeding the pace of discovery.

**Carol Greider** wins the Nobel Prize in Physiology or Medicine for her discovery of telomerase, an enzyme that restores telomeres, protective caps that protect the ends of chromosomes. The connection of telomeres and telomerase to cancer development is a major area of cancer research.

## 2010s

Cancer care moves primarily to the outpatient setting, and the Kimmel Cancer Center expands, occupying the largest footprint at Johns Hopkins. Breakthroughs in immunotherapy, using drugs and vaccines to unleash the natural killing power of the immune system against cancer, are a key clinical advance. Multidisciplinary Clinics, with specialists from all fields related to cancer care working together, become the standard, leading to improved therapies and survival.



# Immunotherapy

## *A Game Changer*

Therapies that empower the body's own natural defenses became a reality in the mid 2010s, providing unparalleled, long-lasting responses across many cancer types, and even in the most advanced and treatment-resistant cancers.

These discoveries led to the launching of the Bloomberg-Kimmel Institute for Cancer Immunotherapy (BKI) in 2016, started with lead gifts of $50 million each from **Michael Bloomberg** and **Sidney Kimmel**.

As long as cancer has been a recognized disease, doctors have believed the power to eliminate it existed within the immune system.

### A VACCINE

**Drew Pardoll**, BKI director, **Elizabeth Jaffee**, BKI associate director, and former faculty member **Hyam Levitsky**, began in the 1980s 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, Levitsky, and collaborators understood that it should be the perfect anticancer weapon, but if the cancer cell was complex in its molecular construction, the intricacies of the immune system were equally complicated.

PARDOLL

JAFFEE

LEVITSKY

"IMMUNE THERAPY IS A GAME CHANGER... WE DON'T THINK THERE IS A SINGLE CANCER THAT THE PATIENT'S OWN IMMUNE SYSTEM ULTIMATELY CAN'T BEAT."

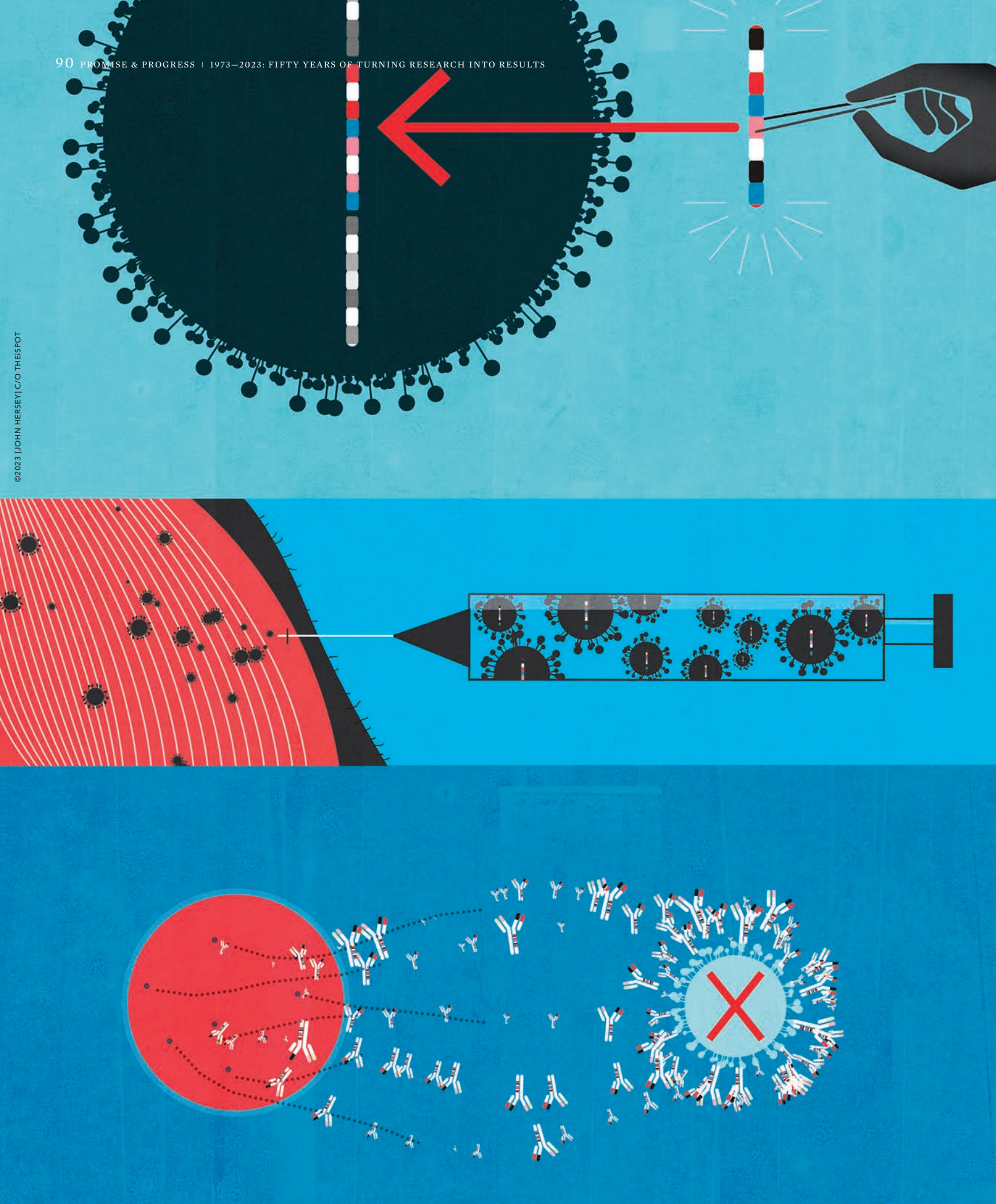
Immune-based therapies reflect a different approach to treatment. Instead of targeting cancer cells, the new therapies target immune cells in and around cancers. Some treatments increase the number of immune cells summoned to the tumor, and others unleash the commands that send the immune cells to work against the cancer. These types of immune therapies have had success alone, but perhaps their greatest power is coming in combining them and, through precision medicine, using the biological clues within each patient's cancer to guide treatment.

One of the first immunotherapies developed at the Kimmel Cancer Center was a therapeutic cancer vaccine called GVAX, the first genetically engineered vaccine in history to be tested in patients. The novel vaccine supercharged immune cells, which tend to be tolerant of cancer, to seek out and destroy cancer cells throughout the body.

Pardoll, Jaffee, Kimmel Cancer Center Director **William Nelson**, and former faculty member **Jonathan Simons** first tested GVAX in kidney cancer.

It's greatest success, however, came in pancreatic cancer, leading to several long-term sur-

SIMONS



vivors (see story on page 84) of this often lethal diagnosis. Jaffee, who originally created the pancreatic cancer GVAX in her laboratory and led the pancreatic cancer studies, even opened a GMP (Good Manufacturing Practice) facility at the Kimmel Cancer Center to produce the vaccine for clinical studies.

Jaffee continues to work with young faculty members to develop and study better iterations of the vaccine, adding gene mutation-directed components, combining the vaccine with other immunotherapies, and using modified bacteria to augment the immune response.

### MORE POWER

Researchers believed there was still much more power in the immune response that remained untapped and could be used against cancer.

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

**Center team of multispecialty collaborators— seasoned investigators and young clinician-scientists— figured out how to reset the cellular controls hijacked by the cancer cell and restore power to the immune system.**

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. A Kimmel Cancer

Center team of multispecialty collaborators—seasoned investigators and young clinician-scientists— figured out how to reset the cellular controls hijacked by the cancer cell and restore power to the immune system.

As the therapies began to unfold, the results were unparalleled. Some patients who were months, even weeks, from dying survived, some five years and longer after treatment.

### IMMUNE CHECKPOINT BLOCKADES

TOPALIAN

In 2012, **Suzanne Topalian,** BKI associate director, saw more than 8,000 practicing oncologists and clinical cancer scientists from all over the world fill the lecture hall at the 2012 annual meeting of the American Society of Clinical Oncology (ASCO) to hear her speak.

BRAHMER

It was not the first time a standing-room only crowd had come to hear a Kimmel Cancer Center researcher discuss this new type of immune therapy. Just a day before, Thoracic Oncology Program director **Julie Brahmer**, presented findings on an immune checkpoint blockade study in lung cancer. It marked a changing tide in clinical cancer research. Immunology studies had never before received this level of attention at ASCO meetings. "The session chair announced Brahmer's presentation saying, 'Nobody in this room ever before believed immunotherapy could make a difference in lung cancer. Today, that is all going to change,'" recalls Pardoll.

With remarkable and lasting results in about 20% to 50% 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 were new, first tested in patients in 2006.

These long-lasting responses that continued even after therapy was stopped and did not cause the side effects of nausea, vomiting, hair loss, and low blood counts, that had become so characteristic of cancer chemotherapy, are the reason the ASCO meeting auditoriums were filled to capacity. Doctors were anxious to learn how and when they could get this new therapy for their patients.

### CHECKPOINTS

The source of the excitement was an immune target called PD-1. It is what immunology experts call an immune checkpoint. The results in laboratory research and these early clinical trials showed it to be one of the strongest influencers of an immune response to cancer identified. It—and other similar proteins—are responsible for cancer's ability to avert an immune attack.

One of the primary functions of the immune system is to distinguish organisms that are foreign to our bodies from our own cells. "Our cells are constantly presenting our own proteins to our own immune system," explains pathologist **Bob Anders**, and the immune system must leave them alone.

ANDERS

In the same way it recognizes bacteria and viruses as foreign, the patrolling immune system can recognize abnormal cells that have a mutation

in their DNA. The mutation confers a subtle biochemical mark that the immune system can distinguish from the normal protein.

"When immune cells come upon something that shouldn't be there, they generate an immune reaction," says Anders. "This is the go signal. When the job is done and the invading cells are taken care of, theimmune 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, even though they have lots of mutations that allow the immune system to easily distinguish them from their normal counterparts. 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.


TAUBE

"Essentially, they're told to go home. There is nothing to see here," says pathologist **Janis Taube**.

Drugs that block PD-1 release these restraints, unharnessing the power of the immune system against the cancer.

The first clinical reports of checkpoint inhibitors in melanoma were exciting and peaked interest, but there was skepticism about how applicable they would be in other cancers. The anecdotal successes in immune therapy over the last three decades had largely been in melanoma and kidney cancer. There have been rare 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. Yet even in melanoma and kidney cancer, earlier immunotherapies led to remission of the cancer less than 10% of the time. No other type of cancer was considered to be responsive to immune interventions, so 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 that induced remissions in 25% of melanomas and, surprisingly, in lung cancer patients too. 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 cancer immunologists long believed—if understood, the immune system could be used to fight any cancer. These early trials tested the anti-PD-1 drug in patients who had already received many previous therapies and had exhausted all standard therapies.

"Anti-PD-1 has become a cancer juggernaut," says Pardoll. "There are now seven FDA-approved antibodies that block this checkpoint pathway. It is the most commonly targeted in all of cancer therapy."

## DEVELOPED FROM SCRATCH


CHEN

Pardoll first became interested in the PD-1 in 2000, when he came upon a partner protein, called PD-L2. **Lieping Chen**, a collaborator of Pardoll's at the Kimmel Cancer Center, and now at Yale, had just discovered PD-L1, the other partner protein to PD-1, and showed that it's expression in many types of cancer, including lung cancer, was 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.

"We developed this idea from scratch at the Kimmel Cancer Center," says Pardoll.

As soon as the components of the PD-1 pathway were discovered in 2000, Pardoll and Chen saw the potential of blocking it. They began working to develop the first anti-PD-1 antibody. Topalian, Brahmer, immunology and genitourinary cancer expert **Chuck Drake**, now cancer immunology leader at Johnson & Johnson, and research nurse **Alice Pons** took it to patients. They found stronger and more frequent responses in melanoma and kidney cancer than previous immunotherapies, but it was Brahmer's lung cancer patients that were game changers. The most common cancer killer had never previously responded to any immunotherapy.


DRAKE

It was the moment Pardoll staked his career on when he left the laboratory of world renowned cancer genetics researcher and pioneer **Bert Vogelstein** in the 1970s to branch out on his own and start his cancer immunology lab.

For Topalian, it felt like redemption. She worked with **Steven Rosenberg** at the National Cancer Institute for 20 years, exploring interferons and interleukins, cellular messengers critical to immune responses. In the 1980s, they had garnered similar excitement 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" was announced in 1971—the field of cancer immunology was nearly crushed.

Topalian saw it differently, however. Interferon wasn't the blockbuster immunotherapy people had hoped for, but 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 impor-

tant because it told us we were on the right track with immunotherapy and needed to keep working on this."

Unfortunately, others 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. In true Kimmel Cancer Center fashion, the immunology research team remained undeterred.

### A MILESTONE

As they began to dig deeper into the responses of lung cancer and other cancer patients in the PD-1 clinical trials, they began to learn more about what drives an immune response.

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," said 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 with platforms like ASTRO-PATH and MANAFEST, developed by Bloomberg~Kimmel Institute investigators.

Remarkable responses were occurring in a significant number of patients, putting the framework for a potentially broad-based treatment for cancer in place. What started in melanoma, kidney cancer, and lung cancer was expanded across all cancer types and has spurred over 10,000 new clinical trials among collaborators across the country and around the world.

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 clinical studies provided clear evidence that for lung cancer patients whose infiltrating T 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, and roughly 15% appear to be cured.

"In my 20 years in practice, I have never seen anything like this. We're reporting many year survival rates in lung cancer patients who honestly would not typically be around," says Brahmer. "This is truly a milestone in cancer medicine."

### A GAME CHANGER

One of the ways cancer immunology experts improved response was by combining immunotherapy drugs, and the findings have since led to FDA approvals for immunotherapy/chemotherapy combinations in several cancer types, including lung cancer, melanoma, gastric cancer, liver, and breast cancer.

"These drugs and drug combinations are turning clinical therapeutics on its head," says Pardoll. "This is a game changer."


POWELL

One of the recently-approved immunotherapy combinations is anti-LAG-3 and anti-PD-1. LAG-3 was shown by Drake, **Jonathan Powell** and other Bloomberg~Kimmel Institute collaborators to shut down immune responses to cancer cells, similar to PD-1. Unlike PD-1, however, inhibiting LAG-3 by itself did not create the same robust response that occurred with anti-PD-1 therapies. However, the researchers 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.

Nearly two decades after the discovery of LAG-3 as an immune checkpoint, **Evan Lipson**, a clinical researcher who trained with Topalian and skin cancer expert **William Sharfman**, completed a five-year clinical trial that showed combined anti-LAG-3 and anti-PD-1 immunotherapy improved melanoma responses, compared to anti-PD-1 alone, resulting in a 2022 FDA approval of the combination.

Combined approaches using another checkpoint inhibitor, known as anti-CTLA-4, and anti-PD-1 drugs also have been studied, and Pardoll believes that as more immune regulatory genes are identified, more combinations will be revealed. In some cancers, they say, it may be necessary to block multiple immune checkpoints to control a cancer.

"Immune therapy is a game changer, but we have only just scratched the surface," says Pardoll. "We continue the 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."

## MAJOR MILESTONES OF THE BLOOMBERG~KIMMEL INSTITUTE FOR CANCER IMMUNOTHERAPY

### HISTORIC FDA APPROVALS

• Nivolumab (anti-PD-1) was approved for lung cancer, after a BKI-led clinical trial showed the drug quadrupled the survival rates of lung cancer patients when compared to chemotherapy. Pembrolizumab was also approved for lung cancer patients based on BKI research.

• The FDA approved two immunotherapy treatments based on the results of clinical studies led by the Bloomberg~Kimmel Institute for Cancer Immunotherapy. Coming just weeks apart, the approvals marked the culmination of years of research starting with laboratory discoveries by BKI scientists that were later transferred to patients in clinical trials led by its clinical investigators. A nivolumab/chemotherapy combination was approved for early non-small cell lung cancer (NSCLC), the leading cancer killer in the U.S. It marked the first FDA approval for neoadjuvant (before surgery) therapy for early stage lung cancer. An immunotherapy combination of nivolumab and relatlimab — a new immunotherapy drug targeting the LAG-3 immune checkpoint discovered by Bloomberg~ Kimmel Institute scientists — was approved for the treatment of advanced melanoma, an aggressive and deadly type of skin cancer.

• The historic 2017 approval of pembrolizumab (anti-PD-1) for all cancers that have mismatch repair deficiency/microsatellite instability — a genetic alteration and biomarkers for response to immunotherapy discovered at the Kimmel Cancer Center and BKI in a clinical trial led by **Dung Le** and **Luis Diaz**—was the first ever drug approval not tied to a specific cancer type.

• Based on this approval, pembrolizumab was also approved for the first line treatment of patients with inoperable advanced colorectal cancer that has spread to the other places of the body and has mismatch repair deficiency/microsatellite instability. It marked the first major change in colorectal cancer for the first line of treatment in decades and the first that does not also require patients get chemotherapy.

• Pembrolizumab was approved as the initial treatment for people with advanced Merkel-cell carcinomas, a type of skin cancer, based on a multi-center trial led by **Suzanne Topalian**.

• A BKI-led discovery revealed Lag-3 as an immune checkpoint. A new immunotherapy drug developed by BKI researchers, in collaboration with Bristol Myers Squibb, was shown in clinical trials to stop the progression of advanced melanoma skin cancer and improve survival rates in patients. Based on the results of these clinical trials, the FDA approved the immunotherapy as standard of care for melanoma.

• Another groundbreaking FDA decision came when pembrolizumab was approved to treat patients with recurrent or metastatic Merkel cell carcinoma. The approval was the result of a clinical study co-led by **Suzanne Topalian**, and other investigators at the BKI, Fred Hutchinson Cancer Research Center in Seattle and 11 other U.S. medical centers. Topalian also led a study using immunotherapy before surgery against Merkel cell carcinoma, reporting that the therapy eliminated the cancer in nearly half of the 39 patients treated.

### IMMUNOTHERAPY BEFORE LUNG CANCER SURGERY

In 2016, a national clinical trial led by BKI lung cancer expert **Patrick Forde** showed that giving anti-PD-1 immunotherapy before surgery for patients with non-small cell lung cancer gets ahead of the cancer, killing more of the cancer and stopping it from spreading and coming back, extending survival. The treatment worked so well, that by the time of surgery, the tumors in many patients had nearly or completely disappeared. Two years after the study, all but one of the lung cancer patients continued to do well. With surgery alone, about half of patients usually relapse within two years.

Forde predicted the findings would be practice changing, and he was right, as FDA approvals soon followed. The work has inspired more than 70 similar clinical trials across the U.S., exploring the benefits of earlier use of immunotherapy in lung and other cancers.

Forde's findings were published in the prestigious *New England Journal of Medicine* in 2016 and at the 2017 annual meeting of the American Association for Cancer Research.

### MICROBIOME

The gut microbiome, made up of more than 100 trillion organisms, traditionally aids in digestion and metabolism functions, but as BKI researcher and microbiome researcher **Cindy Sears** discovered, it also has an impact on the body's response to cancer immunotherapy.

Sears uncovered two bugs, that when present together, drive colon cancer development through an unexpected cancer-promoting type of immune response. This finding has underpinned a 2000-patient public health initiative that uses a simple stool test to find out if colon polyps, a precursor to cancer, are more common when these two types of bacteria are detected together.

In other research, Sears and **Fyza Shaikh** reported that microbes in the stool of patients who respond to immune checkpoint blockade reveal a heightened immune response against primary tumors and metastatic tumors. The constant recirculation of immune lymphocytes through the gut and lymph tissue amplifies immunity throughout the body in patients through cytokine production, substances secreted by immune cells.

A big data analysis led by Sears also found ties between antibiotics and a slightly increased risk of colon cancer. Because antibiotics could kill beneficial bacteria and allow dangerous ones to thrive, some of the surviving bacteria could be encouraging benign polyps to grow and transform more quickly into malignant tumors, Sears explains. She and her colleagues concluded that a single course of antibiotics could boost the risk of colon cancer a decade later. Half a month or more of lifetime antibiotic exposure was associated with a nearly 8% increased risk of colon cancer, and the risk increased to 15% at the 30-day mark.

The study emphasizes the need for more judicious use of antibiotics, which Sears says are often improperly prescribed or over-prescribed. Decreasing antibiotic exposure could mean 50,000 – 100,000 fewer people a year die from colon cancer around the world, she said.

### BIG DATA

**AstroPath:** A cancer-imaging platform, called Astropath, developed by BKI researcher **Janis Taube** and astrophysicist **Alexander Szalay**, a Bloomberg Distinguished Professor of Physics and Astronomy, is at the center of ongoing research that applies the technology to the spatial relations in the tumor microenvironment. AstroPath's groundbreaking celestial mapping algorithms can analyze hundreds of millions of cells, so researchers receive a detailed picture of the tumor's location in the body and how it reacts with surrounding tissues.

**MANAFEST:** BKI researcher **Kellie Smith** was the developer of MANAFEST (Mutation Associated NeoAntigen Functional Expansion of Specific T cells) technology, which helps identify immune cells that recognize proteins produced by cancer-

ous mutations. Smith used MANAFEST to learn about the difference between cancer-fighting immune cells in patients with lung cancer whose tumors do respond to immunotherapies vs. those whose tumors do not respond. In patients whose lung cancers responded to immunotherapy, immune T cells had been completely reprogrammed to be effective cancer killers. In non-responders, though, she found the same T cells were sluggish and sent signals to block the immune response.

**Immunotherapy Before Surgery Could Advance Care of Merkel Cell Skin Cancer**
In what is believed to be a first-of-its-kind study, BKI researchers evaluated the safety of a type of immunotherapy before surgery in patients with Merkel cell carcinoma. **Suzanne Topalian**, Bloomberg~Kimmel Professor of Cancer Immunology, **William Sharfman**, the Mary Jo Rogers Professor of Cancer Immunology and Melanoma Research, and **Janis Taube** reported that the treatment eliminated pathologic evidence of cancer in nearly half of the study participants undergoing surgery. In patients whose tumors responded, this treatment approach offers the potential to reduce the extent of surgery and may also slow or eliminate tumor relapses that often occur after surgery.

## A DRUG NAMED DON

**Jonathan Powell**, former BKI researcher, and Johns Hopkins Drug Discovery director **Barbara Slusher**, developed a drug called DON 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.

Tumor cell metabolism can be considered a kind of immune checkpoint because it creates an environment that turns off the immune response, the researchers said. 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. 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.

The drug was licensed to Dracen Pharmaceuticals and is currently being studied in clinical trials.

## DRUG COMBINATION FOR ADVANCED LIVER CANCER

For years, a vast majority of liver cancer patients were not considered candidates for surgery to remove tumors. That may be changing, due to a study by BKI researchers that led to a new immunotherapy/targeted drug combination that makes potentially curative surgery possible for many liver cancer patients.

The treatment combines the immune response-boosting anti-PD-1 immune checkpoint blocker nivolumab and cabozantinib, a drug that blocks specific proteins that help cancer cells grow. The two drugs have been used separately and in combination to treat advanced liver cancer before, but the BKI research was the first time they were studied for their ability to get patients to potentially curative surgery.

In a small study, 75% of the patients treated were able to have their cancer successfully removed after receiving the new therapy, and 1/3 of the patients had 10% or less of their tumor remaining after receiving the drug treatment.

## ADDING IMMUNOTHERAPY IMPROVES MESOTHELIOMA SURVIVAL

An international, multicenter study led by BKI researchers found that combining the immunotherapy drug durvalumab with two chemotherapy drugs, pemetrexed and either cisplatin or carboplatin, extended survival. This provides a new treatment option for patients who have inoperable pleural mesothelioma, a cancer of the tissues lining the lungs.

## MARK FOUNDATION CENTER FOR ADVANCED GENOMICS LAUNCHED

The Mark Foundation for Cancer Research and BKI announced a $10 million commitment to fund novel work to advance immunotherapy research and provide lifesaving breakthroughs for cancer patients. The Mark Foundation Center for Advanced Genomics and Imaging is co-led by **Janis Taube**, professor of dermatology and pathology and co-director of the Tumor Microenvironment Technology Center and BKI director **Drew Pardoll**.

## BLOOMBERG~KIMMEL PROFESSORS OF CANCER IMMUNOTHERAPY ANNOUNCED

The BKI named three inaugural Bloomberg Professors of Cancer Immunotherapy:

- **Jonathan Powell** developed a drug that simultaneously strengthens immune cells within tumors and weakens cancer cells. He has since gone on to continue his research in the biotech industry.
- **Cynthia Sears** linked the collusion of two types of gut bacteria to a cancer causing immune response in colon cancer.
- **Suzanne Topalian** was at the center of the groundbreaking studies that led to anti-PD-1 and anti-PD-L1 immunotherapies.
- **Dung Le** is the newest Professor. She is a gastrointestinal cancer expert who led the clinical trials that established a genetic defect called mismatch repair deficiency/microsatellite instability as predictor of response to immunotherapy with drugs that block the PD-1 immune checkpoint.

## INTERNATIONAL IMMUNOLOGY LEADERS JOIN BKI

World-renowned immunology researchers **Erika Pearce**, a molecular biologist, and immunologist **Edward Pearce**, joined the Bloomberg~Kimmel Institute for Cancer Immunotherapy as Bloomberg Distinguished Scholars. They will continue their promising path of research, providing important information about how the human immune system is activated, evaded and reprogrammed.

As Bloomberg Distinguished Professors, Edward and Erika Pearce join an interdisciplinary cohort of scholars working to address major world problems and teach the next generation.

## CHI VAN DANG RETURNS TO JOHNS HOPKINS

**Chi Dang** returned to Johns Hopkins, with primary appointments in the Kimmel Cancer Center's Bloomberg~Kimmel Institute for Cancer Immunotherapy and the Department of Biochemistry and Molecular Biology.

Dang is best known for defining the function of MYC, the first cancer gene known to act as a switch, turning on metabolic pathways and mechanisms that are advantageous for cancer cells. He showed that MYC alters the metabolic pathways in cancer cells, and tumor cells become addicted to certain nutrients. This landmark research from 1997 opened up the field of cancer metabolism, a major area of study in the BKI.

# An Immunotherapy Pioneer

## *Research nurse Alice Pons recalls the first clinical trials of immunotherapy drugs*


PONS

**Alice Pons** is a pioneer in cancer immunotherapy. In 2007, she administered some of the first treatments in clinical trials of anti-PD-1 and anti-PD-L1 immunotherapies.

These new cancer therapies were developed based on research at the Johns Hopkins Kimmel Cancer Center that showed cancer cells co-opted natural on/off switches of the immune system, called immune checkpoints, to shut down the immune response to cancer. The new drugs, researchers believed, had the power to re-ignite the immune response.

Ultimately, they transformed the cancer treatment paradigm, mainstreaming immunotherapy as a cancer medicine. However, in 2007, they were trailblazers, as phase I clinical trials began to evaluate the safety and determine the dosing for these promising new drugs that were about to be given for the first time to patients.

**New therapies showed that cancer cells co-opted natural on/off switches of the immune system, called immune checkpoints, to shut down the immune response to cancer. The new drugs, researchers believed, had the power to re-ignite the immune response.**

Pons recalls administering the first doses of the drugs in patients with advanced cancers who were out of options. Many of them were near death, she recalls.

"Desperation," is the word that best describes the mood, she says. "These patients had tried a lot of therapies that did not work against their cancers. This was their last chance."

They wanted the drug to be the thing that finally worked for them, but if it didn't, maybe what the nurses, doctors and researchers learned from them would help others in the future. Patients wanted to find a greater meaning in their battle against cancer, for them and for their families, says Pons.

The anti-PD-1 and anti-PD-L1 immunotherapies were different than the chemotherapies that had led to the dreadfully common characteristics that grew to define cancer, and the fear associated with the disease. The treatments, while lifesaving for many, often came with debilitating side effects. Essentially, they worked by poisoning rapidly reproducing cells, which meant they killed cancer cells, hair cells, gut cells and more, causing patients to lose their hair and suffer from nausea and vomiting. It is not an overstatement to say many patients feared treatment as much as the disease.

The patients Pons was treating in these immunotherapy clinical trials had already received many rounds of chemotherapy. "They were worn out," she says. "When we told them these drugs did not usually cause hair loss or nausea and vomiting, they were ready to give it a try."

From the very first infusion, it was clear this treatment was different, Pons says. It truly was a new frontier. They didn't know what to expect, so they were hyper-vigilant.

"We took vital signs every 15 minutes," says Pons. "Almost immediately, we could see this was not like chemo. When you give chemo, patients get sick. With this, they did not.

It took a year before they began to see responders. The immunotherapy drugs worked best against melanoma, a type of lung cancer called non-small cell lung cancer, and kidney cancer.

Pons says they were elated when some patients began to respond to the immunotherapy. "I would be sitting with the different doctors when they got the results that it was working. They couldn't wait to tell the patient. Of course, the patients were very happy," she says.

Then, she says, trepidation set in, and they began to worry about how long it would last. Would they get to the next scan and find the cancer had come back?

Pons worked so closely with patients and families, it was impossible not to become emotionally invested. She was beyond excited about the responses but admits she remained skeptical.

For Pons, it wasn't about the science, the proof was in the patient standing in front of her.

"We didn't know why it worked in melanoma and a few kidney cancer and lung cancer patients but not in other cancers. I was stoked for the mela-

noma patients because they had been striking out for so long," says Pons. "I was so deep in the trenches with the patients that sometimes the broader picture eluded me. The doctors were confident. They would tell me it was going to work, but I found it hard to believe until it a happened a couple of times over a couple of scans."

As more responses to the treatment became long-lasting, extending years, her relationships with the patients and families did as well. This was unusual because most patients with advanced cancers died within months. She was invested.

"Every time a patient came back for a scan, I would get a pit in my stomach. 'What if it comes back?' I'd think to myself, and I knew the patient had the same worry."

Her thoughts immediately turn to a patient whose cancer came back after two years. "It was heartbreaking. I had let my guard down and believed the immunotherapy would make it a lasting remission," she says.

Fortunately, for many patients, there have been long remissions. In fact, some have lasted 15 years and are considered cured, says **Drew Pardoll**, director of the Bloomberg~Kimmel Institute for Cancer Immunotherapy.

Still, one of the key areas of research remains focused on figuring out who will respond and then among responders what makes the treatment stop working.

"There is much left to learn," says Dr. Pardoll. "We're getting better at predicting who will respond in the first place, but we still don't know why some people who respond relapse years later."

Another area of major focus, and again one where the Bloomberg~Kimmel Institute for Cancer Immunotherapy led the way, was in detecting and managing side effects. The immunotherapy drugs worked by unleashing the immense power of the immune system, and sometimes the immune system attacked healthy tissue and organs in addition to cancer cells.

Just as this type of immunotherapy was new, so were its side effects. They were not as obvious as chemotherapy side effects.

"They crept up and were harder to detect," says Pons. "They were outside of my realm of experience having done chemo for so long."

"We can't minimize the autoimmune side effects because there were people who sacrificed their lives on the way because they were already suffering from toxicities caused by chemotherapy, and now on top of that, they had autoimmune side effects," she adds. "We got hit pretty quickly with what worked and didn't work and with warning signs about something coming and heading it off at the path. It was hard in the beginning, but we figured out fast how to recognize warning signs and how to manage them."

When the Bloomberg~Kimmel Institute-developed therapies were proven in clinical trials, received FDA approval, and now were being administered by community practices, the importance of recognizing and managing side effects became even more evident.

"We had patients coming to us because their immunotherapy was poorly managed in the community."

Managing side effects was a science of its own that many beyond the walls of the Bloomberg~Kimmel Institute did not appreciate. Our experts engaged a broad range of specialists—endocrinologists, rheumatologists, dermatologists, and more—to develop the standard of care and ensure doctors and patients recognized the warning signs, which to an untrained eye could be easy to miss.

In general, serious side effects occur in about 20% of patients, but at the Bloomberg~Kimmel Institute, it's much lower at 5% to 10%. Pons says it is the expertise here that makes the difference.

Pons credits the doctors and scientists who developed the treatment protocols for making Johns Hopkins a standout.

"Had I not been on this team, with **Suzanne Topalian** at the helm, it would have been a lot different. She kept our noses to the grindstone and instilled in all of us the importance of focus and attention to detail. I am very thankful for that. This strong leadership and commitment to patient care is what makes the Kimmel Cancer Center and the Bloomberg~Kimmel Institute special."

"On a clinical trial, we're giving them concierge nursing. I'm responsible for my patients. I want to know; I have to know. I go through the side effects from head to toe with each patient. We're calling, emailing. That accessibility translates into patients being treated for their side effects more quickly. Our goal is to keep everyone safe," she says.

Fast forward to 2023, and now combination therapies of different immunotherapies, and even chemotherapy, given together are improving response rates. Research at the Bloomberg~Kimmel Institute has led to multiple FDA approvals and immunotherapy as a first line treatment for many types of cancer.

Pons becomes emotional when she thinks of the journey from the very first patient she treated to the continuing progress still being made today.

"It was exhilarating. I imagine it is how skydiving feels. In a way, that's what we were doing," she says, referring to all of the unknowns of the first clinical trials. "It achieved one of my objectives in life, to contribute to mankind. This allowed me to do it, and I am forever thankful."

# A Historic Decline in Cancer Deaths

*Cancer death rates in the U.S. took the "biggest single year drop ever," between 2016 and 2017, according to a January 2020 report by the American Cancer Society.*

IMPROVEMENTS IN the screening and treatment of lung cancer, the 2nd most common cancer and leading cancer killer, are a main contributor to this positive trend. **Julie Brahmer**, Director of the Kimmel Cancer Center Thoracic Center of Excellence and Director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy Lung Cancer Program, attributes the improved lung cancer survival to screening programs aimed at people at highest risk of developing lung cancer and new immunotherapies and targeted therapies.

The Kimmel Cancer Center participated in a national lung cancer screening study that showed screening those at high risk leads to early detection of lung cancer and improved survival, Brahmer explains. As a leader of a SU2C-LUNGevity Foundation-American Lung Association Lung Cancer Interception Dream Team, Brahmer is collaborating with scientists and clinicians throughout the country who are working in many fields of lung cancer research, from prevention through early detection and treatment, to develop new ways to stop lung cancer before it progresses to an advanced stage

"There is plenty of opportunity to see these rates decline further," she says. "We may just be seeing the tip of the iceberg."

Brahmer says new treatments that have become available over the last couple of years, particularly new immunotherapies and targeted therapies, also played a key role in the decline in lung cancer deaths. She led the landmark clinical trials that helped earn FDA approval for the immunotherapy drugs nivolumab and pembrolizumab in lung cancer. In some patients, these treatments ignite the body's own natural defenses to attack cancer cells, even advanced cancers that have spread from the lung to other parts of the body.

A clinical trial led by Kimmel Cancer Center lung cancer expert **Patrick Forde** in collaboration with thoracic surgeons **Richard Battafarano**, **Stephen Broderick** and **Stephen Yang** found that, for some patients, giving immunotherapy before surgery can decrease the cancer size in hopes of improving survival.

FORDE

BATTAFARANO

BRODERICK

Brahmer says follow-up data on immunotherapy supports their findings. The immunotherapy drug nivolumab has the longest follow-up to date of these drugs. "Five-year overall survival quadrupled in non-small cell lung cancer, compared with what we would expect from chemotherapy," she says.

Other therapies, known as targeted treatments because they zero in on features of the cancer that drive its growth and spread—such as an EFGR gene mutation or the presence of a cancer-promoting ALK fusion gene in the cancer—are also leading to improved survival, says Brahmer

Although the greatest strides have been made against non-small cell lung cancer, the most common type of lung cancer, Brahmer says there are also promising new treatments for small cell lung cancer, an aggressive and treatment-resistant type of lung cancer. A new treatment combining immunotherapy and chemotherapy for patients with advanced small cell lung cancer received FDA approval last year, she says.

"This is the power of precision medicine," says Brahmer. "There is no longer one-size-fits-all therapy for cancer. We look at each individual patient's cancer and determine the treatment that will best attack the unique characteristics of the cancer."

# From Metastic Cancer Survivor to Marathon Runner

## *A Bloomberg~Kimmel Institute Treatment Saves Another Life*

As 37-year-old **Kristina** laced up her running shoes to begin the grueling 26.2-mile New York City Marathon in 2019, she knew where to find the grit, tenacity and determination it would take to make it to the finish line. Baum drew her inspiration from her 7-year battle with metastatic melanoma, a deadly skin cancer.

Her survival—and the ability to take on a marathon—are a testimony to Baum's strength and the power of discoveries at the Kimmel Cancer Center's Bloomberg~Kimmel Institute for Cancer Immunotherapy. Experts there researched and developed the treatment plans that saved Kristina's life—twice.

Baum's cancer story began in 2012 when she noticed a raised bump on her arm. At 30, cancer was the last thing on her mind.

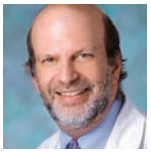
"I thought cancer was an old person's disease," she said.

A biopsy of the bump revealed it was melanoma, and worse yet, it had already spread to nearby lymph nodes. At the time, there were not many effective treatments for patients with melanoma. It was a grim diagnosis.

> **"I thought cancer was an old person's disease."**

She received initial treatment at a hospital near her home in Washington, D.C., with a drug called interferon, a version of the body's own natural protein that works by stimulating the immune system. Melanoma and other cancers sometimes respond to the treatment, but there


LIPSON


KLEINBERG

are many side effects, such as flu-like symptoms and severe fatigue.

Interferon might have been tolerable if it kept her melanoma in check, but in 2016, Kristina learned the cancer had spread to her kidney. She came to the Kimmel Cancer Center to see melanoma expert **Evan Lipson**.

"Learning you have metastatic cancer is not just life-altering, it's life-shattering," says Kristina

She didn't believe she had many options, but Lipson told her about a clinical trial testing a new combination of medicines called immune checkpoint inhibitors. When cancer cells turn off natural immune regulators to avoid recognition by the immune system, these drugs re-ignite the immune response to the cancer.

The combination Lipson had in mind was based on research from the Kimmel Cancer Center's Bloomberg~Kimmel Institute for Cancer Immunotherapy, demonstrating that blocking two of these immune checkpoints, called PD-1 and LAG-3, could work in synergy to boost the immune response.

**Research at the Kimmel Cancer Center suggested that radiation therapy might prime the body's immune system to respond better to immunotherapy and more easily recognize and attack cancer.**

After two infusions, she was hospitalized with autoimmune meningitis—her own immune system was attacking and inflaming tissues surrounding her brain. Her skin felt like it was on fire. She was weak and had no energy. To add insult to injury, the prednisone given to control the side effects caused her to gain weight. The good news was that the tumor in her kidney was going away.

Kristina longed to feel well again. She started with long walks, gradually building her strength back. She wanted to try a triathlon, and she made that her goal.

By 2017, she was running five miles a day and was finally beginning to feel like herself again, so in December 2018, when she began experiencing extreme fatigue and vertigo, she chalked it up to over-training.

As part of her follow-up care for her cancer, she had an imaging test called an MRI. Lipson called her with the results.

"I knew it wasn't good. I could hear it in his voice," Kristina recalls.

She learned that the cause of her symptoms was her melanoma, which had appeared again and, this time, it was in her brain. The news was crushing.

"No matter how many times you go through it. It's traumatic. It makes you emotional," says Kristina.

Lipson had another clinical trial in mind for Kristina. This time, in collaboration with radiation oncologist **Lawrence Kleinberg**, he prescribed a treatment that included a course of immunotherapy given in combination with focused beams of radiation aimed at the brain tumor. Research at the Kimmel Cancer Center suggested that radiation therapy might prime the body's immune system to respond better to immunotherapy and more easily recognize and attack cancer.

Less than a year later, after finishing treatment for cancer that had spread to her brain, Kristina was about to realize the goal she set for herself a few years earlier. As she approached the starting line of the New York City Marathon and joined a field of 55,000 other runners, she had a unique driving force, harnessing inspiration from her hard-fought battle against cancer.

"It was one of the hardest things I've ever done. You have to dig deep," says Baum. "That's where you find the reason to keep putting one foot in front of the other."

Kristina, now in her forties, purchased her first home, finished her fifth marathon, and started a new job, leading strategic communications for the American Veterinary Medical Association. She also joined the board of directors of the Melanoma Research Foundation.

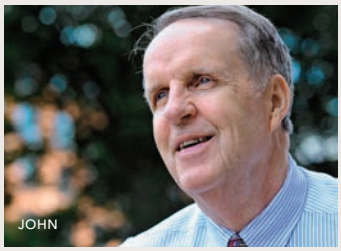
"I wanted to be an advocate for others in the trenches," she says. "As a patient being able to have access to top research is so important. You want to be closer to advancements."

Kristina says she has a special place in her heart for the physicians and nurses doing translational research.

"Being part of a clinical trial and playing an active role in advancing medicine felt very empowering for me," says Kristina. "I want to help make a better journey for others."

# "I gained 100 months of quality life..."

## *One Patient's Journey in this History-Making Clinical Trial*


JOHN

**John** was one of the lung cancer patients who benefitted from the historic clinical trials of anti-PD1 immunotherapy in lung cancer.

In 2015, John, then 68, began coughing 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.

"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," John recalls.

The first treatment he received was chemotherapy, and for a time, it 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. He thought he might be out of options.

It was then that his doctor suggested he go meet with **Julie Brahmer**, who was one of the lead investigators on an experimental clinical study of anti-PD-1 immunotherapy in a variety of advanced cancers. John's form of lung cancer was among the cancers that showed unprecedented responses.

The anti-PD-1 drug, called nivolumab, interfered with cancer cell's ability to shut down the immune response to cancer, unharnessing the immune response against cancer.

"I had struggled to sit at my kitchen table. After just four treatments, the tumor shrunk by 65%, and I felt like a human being again," says John. A few more treatments and his rapidly growing lung cancer was nearly gone, and the cancer that spread to his rib was eliminated.

About one-quarter of the lung cancer patients in the study responded to the treatment. The numbers were even higher for melanoma and kidney cancer patients, but it was the lung cancer responses that garnered the most attention.

Anti-PD-1 was the first checkpoint inhibitor to work against lung cancer—and as many as 14 other cancer types —and that's the pivotal difference that excited the cancer world.

Despite the great success, Brahmer and her Kimmel Cancer Center colleagues began to observe that, in some patients, the immune response did not stop at the cancer but rather continued to attack and inflame the lung, skin, gut or other organs. John was among them.

In March 2022, he began having trouble breathing. The immunotherapy, that kept his advanced lung cancer in check for more than eight years was now triggering his immune system to attack his lungs. The persistent inflammation, called pneumonitis, caused scarring in the lungs, leading to significant shortness of breath.

John was not the only patient to experience this side effect. The Kimmel Cancer Center and its Bloomberg-Kimmel Institute for Cancer Immunotherapy (BKI) led the way in research and addressing the challenge, launching a new dedicated initiative for managing side effects of immunotherapy, led by **Jaruska Naidoo**.


NAIDOO

BKI researchers and clinicians are setting the standard of care for how to recognize and treat these types of immunotherapy toxicities.

These side effects can present with a wide range of symptoms, so their management requires the cooperation of many experts. Naidoo and colleagues assembled a group of specialists in every part of the body that has the potential for adverse reactions to immunotherapy and they are on call for the BKI 24/7.

Naidoo attended national cancer meetings with a research nurse to educate other doctors and worked with organizations, like the National Comprehensive Cancer Network, to share what they have learned and to establish standards for managing immunotherapy side effects. They are also assembling a web-based course for doctors.

Despite the limiting toxicities, John continues to battle. He still believes he was in the right place at the right time. He feels fortunate that his diagnosis coincided with advances in immunotherapy. Without it, he points out, he had, at best, nine to 18-months to live.

"Having just passed the 10-year survival milestone in April 2023, I am humbled and grateful to the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and Dr. Julie Brahmer, and the team of doctors and nurses who have provided unparalleled expert medical care to me throughout this journey. I am comforted in knowing that I am with the best team of experts in the world," says John. "I gained 100 months of quality life extension. I have been there for college graduations, weddings, and the births of grandbabies. If I had to do it over again, even with the pneumonitis, I would make the same choice. The alternative would be not to be here. Immunotherapy saved my life."

# Preventing Cancer Through Discovery


PLATZ


GROOPMAN


VISVANATHAN


TALALAY


PALLER

FROM THE SANDY beaches of the Atlantic Ocean on our Eastern Shore to the Appalachian Mountains of western Maryland and everything in between, Maryland's geography is as diverse as our citizens. Our shores, mountains, the Chesapeake Bay, Baltimore's Inner Harbor and other natural resources frame our history — the agricultural and manufacturing industry that thrived, the rural and urban towns and communities that emerged — and these had a unique impact on cancer rates.

The entire Johns Hopkins enterprise is very much a part of this history. It was discoveries by our own School of Public Health in the late 19th and early 20th centuries that revealed the carcinogenic effects of asbestos in Maryland's shipbuilding industry. Decades later, other School of Public Health researchers revealed that arsenic was seeping into the groundwater supply on the Eastern Shore from chicken manure as a result of farming.

In the 1970s and early 1980s, much of the cancer prevention and control focus was on toxic exposures in the workplace. It was estimated that 20% of U.S. cancer cases were linked to toxic exposures on the job. Researchers, like **Morton Corn**, director of the School of Public Health division of environmental engineering introduced ideas, such as air cleaning systems and worker education. Cleaning up the workplace costs money, he pointed out, but not cleaning it up costs too, in the illness it causes to the workforce.

Later, researchers, including **Timothy Buckley** and **Thomas Burke** began to look at environmental toxins, such as air pollution.

In 1985, the Kimmel Cancer Center established the Cancer Prevention and Control Program and began a collaboration with the state that continues today and includes leadership positions on the Maryland State Council on Cancer Control and the Maryland Cigarette Restitution Fund. These efforts were targeted to and positively impacted cancer rates and disparities.

These efforts are making a difference as Maryland, which had the highest cancer death rates in the nation in 1985, is now ranked below the national average, at 34th among states.

**Elizabeth Platz**, co-leader of the Cancer Center's Cancer Prevention and Control Program and the Martin D. Abeloff Scholar in Cancer Prevention, explains the how and why of this kind of research.

"In population science, we try to figure out what causes cancer. We look in large groups of people. What do they do? What do they eat? How much do they exercise? We may take measurements in blood or other body fluids that tell us about exposures and risks."

Platz's own research is focused on prostate cancer prevention. Her colleague and associate director for population sciences **John Groopman** linked environmental exposures to liver cancer.

Cancer is considered a genetic disease, but Groopman points out that most of the gene mutations that characterize cancer are caused by lifestyle not heredity. Where do the bad genes come from? The societal burden is lopsided toward behavioral issues, he says. Often, it is through our own behaviors. Cigarette smoking, virus exposure, sunburns, poor and unbalanced diets, and obesity are a few of the most common culprits.

**Cancer is a genetic disease, but most of the gene mutations that characterize cancer are caused by lifestyle not heredity.**

Groopman and Platz both agree that obesity is currently the leading cancer prevention concern and, without intervention, one expected to have impact long into the future.

"Intervention is individual and societal," Platz points out. Addressing health inequities in primary prevention—identifying and eliminating cancer causing exposures and education about behavioral changes that can reduce cancer risk—early detection and diagnosis, and improving the quality of life and life expectancy of cancer survivors is also urgent, she adds.

"Calorie balance versus inactivity is likely a cause of about 14 cancers, including a higher risk of fatal prostate cancer," says Platz. Groopman, who estimates that more than 60% of Americans are overweight, calls obesity a U.S. epidemic and one of the nation's most consequential health concerns.

"The effect of this epidemic of obesity on cancer statistics over the next decades remains to be seen but it will certainly have an impact," says Groopman, but, he adds, "we can and need to do a better job of identifying and eliminating exposures earlier. There are things we can do to tilt the odds in our favor."

Looking forward into the next decades, Platz says cancer prevention science will benefit from the mountains of data that are currently being generated. Technologies to gather and mine this data will help reveal new associations to cancer that can be studied.

She says that measuring exposure and classifying people with respect to their exposures helps reveal what is causing cancer on a population level. Although, there are many opportunities to derail cancer, Platz says, things we know about—smoking, obesity and physical activity—only explain about 50% of cancers in the population. We will begin to understand the causes of the other 50% and ways to translate what we've learned about prevention into behavior changes so that we reduce the risk of cancer on a population scale and create healthier survivorship.

"Data will be powerful tool," says Platz, "and we need to start thinking about how we will analyze it and what questions we need to ask to get meaningful results that will impact cancer prevention."

*Also see, Maryland Confronts Cancer, page 105.*

## MILESTONES IN CANCER PREVENTION AND CONTROL RESEARCH

### CHEMOPREVENTION

**Paul Talalay** was an internationally renowned Johns Hopkins pharmacologist whose research on the cancer-prevention properties of a chemical abundant in broccoli sprouts, called sulforaphane, launched the still-burgeoning field of research into what he dubbed "chemoprotection." Talalay discovered that sulforaphane activated a gene signaling pathway that may protect against cancer.

When Talalay decided in 1993 to switch his laboratory's research from cancer treatment to cancer prevention, many colleagues took a dim view of his new focus. "Cancer was not a preventable disease in their eyes," he said in a 2008 interview. Funding for cancer-prevention research was scarce, and few were interested.

Sulforaphane-rich broccoli sprouts were studied by **Tom Kensler**, **Kala Visvanathan**, and other School of Public Health and Kimmel Cancer Center researchers in lung, prostate, breast, liver and skin cancers to see how it increased the activity of cancer detoxifying enzymes.

### PREVENTING LIVER CANCER

**John Groopman** studied liver cancer, a major cause of morbidity and mortality in Asia and Africa, where over 600,000 new cases occur each year. Groopman's initial biomarkers were rapidly translated into a multinational investigation of the causes of liver cancer that, for the first time, characterized the relationship between exposure to the mold-derived food contaminant, aflatoxin, and infection with hepatitis B virus. His molecular epidemiology investigations of liver cancer are considered among the most detailed sets of data that link environmental exposures to cancer outcome.

This observation led to the proposition that a chemopreventive agent such as oltipraz could be used in interventions in high-risk human populations. Further studies in China using the agent chlorophyllin found that DNA damage in people could be reduced by 55%.

### HOPKINS RAN MULTI-STATE NETWORK TO STUDY CANCER RISK

In 1999, the Cancer Center received a grant from the National Cancer Institute to establish the Mid-Atlantic Cancer Genetics Network, charged with learning more about the genetic basis of cancer susceptibility and translating the new knowledge into patient care.

The cancer risk assessment team chosen to run the Network was **Constance Griffin**, **Kathy Helzlsouer**, **Gloria Petersen** and **Karen Johnson**. They recruited the participation of dozens of community hospitals in Maryland, Virginia, Delaware, Washington, D.C., Pennsylvania, New York, and Florida. Physicians, nurses, genetic counselors, population scientists, researchers, and information specialists worked together to study high risk populations, defined as families that have at least two immediate family members who have developed the same cancers during their lifetimes, families with large numbers of cancer cases, and people who develop two or more types of cancer during their lives.

"We want to understand what is causing their high frequency of cancers," explained Constance Griffin, co-director of the project, who passed away in 2012.

The main focus of the network initially was on cancers, such as breast and colon cancer, where genetic predispositions had been discovered and were known to occur with frequency among certain families. The researchers wanted to learn how people interpret and use the information given to them during genetic counseling and see how closely they adhere to screening recommendations.

### CANCER-PREVENTING SPICE

In 2013, breast cancer researcher **Saraswati Sukumar** and former faculty member **Anirban Maitra** reported that a tiny oral dose of curcumin, a compound found in turmeric, cut breast cancer rates in rats by half. In another study, curcumin helped deter drug-resistant cancers. Prepared as minute particles for better absorption, a combination of curcumin and the cancer drug doxorubicin shrank the tumors and helped avoid the toxic side effects of the drug on heart muscles.

### PREVENTING PROSTATE CANCER

Chronic inflammation has been shown to be a risk factor for cancer development. In animal models, **William Nelson** and **Angelo De Marzo** found foods mixed with PhIP caused inflammation of the prostate. PhIP is a compound that forms when meats are cooked at very high temperatures, such as cooking over an open flame.

**Elizabeth Platz** found cholesterol-lowering drugs, called statins, could keep prostate cancer from progressing. In a 10-year study of 30,000 men, she found men taking statins were half as likely to develop advanced prostate cancer compared to men who did not take statins.

## MILESTONES IN CANCER PREVENTION AND CONTROL RESEARCH

### NATURAL PROSTATE CANCER PREVENTION

The idea for **Michael Carducci**'s clinical research of the pomegranate fruit came from the Kimmel Cancer Center's benefactor **Sidney Kimmel**. A pomegranate product manufacturer was widely touting a UCLA study that seemed to indicate the food had prostate cancer fighting properties. Kimmel wanted his Cancer Center to figure out if it was true.

Carducci, the AEGON Professor in Prostate Cancer Research, decided to look at pomegranate and muscadine grapes, another product marketed for prostate health. For his pomegranate study he used extract capsules because the product is 100% pomegranate. Carducci and team, which included **Emmanuel Anatonarakis** and **Channing Paller**, confirmed that PSA doubling time slowed, an indication but not proof that the pomegranate extract could be having an impact on the progression of disease. Moreover, they resolved the "how much is enough issue," and showed that low doses of the extract had the same effects as higher doses.

Partnering with Howard University, Carducci and Paller also explored the benefits of muscadine grapes. The skin of the large dark purple grapes contains two antioxidants—resveratrol, which is common to grapes and ellagic acid, the same antioxidant in pomegranate. They hope the studies will lead them to alternative therapies for men whose PSA begins to rise after surgery.

### FITNESS AND CANCER

**Catherine Handy Marshall** conducted one of the first, largest and most diverse looks at the impact of fitness on cancer. She found that the most fit adults have the lowest risk of developing a lung, colon or prostate cancer diagnosis. The physically fit also have a better chance of surviving a lung or colon cancer diagnosis than those with low fitness levels.

She says her findings may also apply to prostate cancer and likely many other cancer types. Marshall is designing a clinical trial of an exercise intervention in men with prostate cancer and is conducting another clinical trial of a minimally invasive weight loss procedure to see if obese patients diagnosed with prostate cancer benefit from losing excess pounds. The procedure was pioneered at Johns Hopkins, but this is the first time it has been studied in prostate cancer.

### OBESITY AND CANCER RISK

Being overweight or obese is linked to the risk of developing cancer and cancer recurrence. **Jessica Yeh** leads the ASPIRE study. ASPIRE is a free program taking remote weight loss education and coaching to overweight and obese cancer patients throughout Maryland, using technologies like smart phones, smart phone apps, and email.

Through two other studies—POWER and COIN Studies—**Jenni Sheng**, is using telephone coaching, smart phone apps and web-based weight loss plans to use as behavioral approaches to help patients with weight management. COIN has an added focus on sleep disturbances and insomnia and how they may impact weight and metabolism.

### GUM DISEASE AND CANCER

Data collected during a long-term health study, that included participants from Maryland, provided evidence for a link between increased risk of cancer in individuals with advanced gum disease, also called periodontitis. The research team, organized by **Elizabeth Platz**, used data from comprehensive dental exams performed on 7,466 participants who were followed from the late 1990s until 2012.

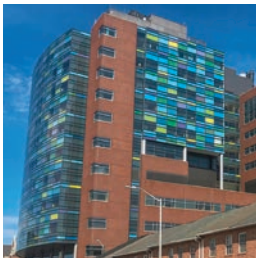
Platz and colleagues found a 24% increase in the relative risk of developing cancer among participants with severe gum disease compared with those with mild to no gum disease. The highest risk was observed in cases of lung cancer, followed by colorectal cancer. Among patients who had no teeth, which can be a sign of severe gum disease or past periodontal treatment, the increased risk was 28%. Platz notes that the association is not strong enough to recommend screening for a risk of particular cancers based on a periodontal disease diagnosis, but since the modest to moderate risk increase in cancer seems to be holding up across studies, it may be worth warning patients that there are risks related to periodontal disease.

The exact mechanism connecting the two diseases is still uncertain. Platz says one possibility is that the bacteria that cause periodontal disease go from the mouth directly into the lungs or from the mouth into the colon, causing an inflammatory response that could increase the risk of cancer formation.

### THE JOHN FETTING FUND FOR BREAST CANCER PREVENTION


FETTING

The John Fetting Fund for Breast Cancer Prevention was established with a lead gift from breast cancer survivor Leslie Ries and her husband Tom. The Fund is named in honor of **John Fetting**, a Kimmel Cancer Center breast cancer expert who has been treating patients for nearly 40 years. Fetting called for a greater investment in the science of breast cancer prevention to address worldwide increasing incidence of breast cancer and to limit the trauma caused by the invasive treatments and risk of recurrence. The Fetting Fund supports prevention research through its Scholars grants. Fetting Fund Scholars include **Kala Visvanathan**, **Sara Sukumar**, **Dipali Sharma**, and **Cynthia Zahnow**.








# Maryland Confronts Cancer

## *The Maryland Cancer Control Plan, Flight Attendant Medical Research Institute, and Cigarette Restitution Fund*

AS WE REFLECT on the 50th anniversary of the Kimmel Cancer Center, it is worth noting that the collaborative relationship between state governors, the Maryland General Assembly, and John Hopkins has always existed.

In 1985, we established the Cancer Prevention and Control Program and began a collaboration with the state that continues today and includes leadership positions on the Maryland State Council on Cancer Control and the Maryland Cigarette Restitution Fund. These efforts were targeted to and positively impacted cancer rates and disparities.

In 1989, after learning that Maryland and neighboring Washington, D.C., had the highest cancer death rates in the nation, our experts worked with then-Gov. William Donald Schaefer to form the Maryland Cancer Consortium, now called the Maryland State Council on Cancer Control, and in 1991, to establish the first Maryland Cancer Control Plan to address the causes of these high rates.

In 2001, Maryland's plan was recognized with funding from the U.S. Centers for Disease Control and Prevention (CDC).

"Maryland's plan is an example for other states. It is our goal that every state creates similar plans for cancer control and prevention," said Jim Marks, then-director of chronic disease prevention for the CDC.

The plan is now known as the Maryland Comprehensive Cancer Control Plan, and it is administered by the Maryland Cancer Collaborative, a statewide coalition of volunteers, which over the years has included many Kimmel Cancer Center faculty members. Kimmel Cancer Center co-leader of Cancer Prevention and Control, **Elizabeth Platz** was appointed to the Maryland State Council on Cancer Control and is a steering committee member and former chair of the Maryland Cancer Collaborative. Platz and **Otis Brawley**, Bloomberg Distinguished Professor and director of Community Outreach and Engagement, contributed to the 2021-2025 Maryland Comprehensive Cancer Control Plan

### THE FLIGHT ATTENDANT MEDICAL RESEARCH INSTITUTE

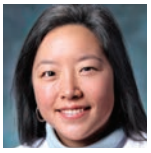
In 1997, a group of flight attendants took on Big Tobacco. These non-smoking flight attendants were suffering from cancer, emphysema and other smokers' diseases they believed were caused from years of exposure to secondhand smoke in the cabins of airplanes where they worked.

They fought a class action suit against the U.S. tobacco industry, and we're awarded $300 million in damages. They used the settlement to establish the Flight Attendant Medical Research Institute (FAMRI) to fund research of early detection and treatment of tobacco smoking-related diseases.

THE DAVID H. KOCH CANCER RESEARCH BUILDING

Today it is difficult to imagine or remember such a time, but when these courageous flight attendants waged their heroic fight, smoking was accepted and common in many public places. Although the connection between smoking and cancer and other diseases had at last been widely accepted, the effects of secondhand smoke were not yet appreciated. They stood bravely before a doubtful public as living proof of the very real dangers of secondhand smoke.

Then unselfishly, they used the money they were awarded to help others and support the science to unequivocally prove the connection between secondhand tobacco smoke and cancer as well as other diseases. FAMRI-funded research has been the impetus for cities in 25 countries, including the U.S., to adopt no-smoking policies.


HANN

At the Kimmel Cancer Center, FAMRI-supported research spanned from basic molecular mechanistic work to clinical research to population studies of tobacco related disease.

Johns Hopkins investigators funded by FAMRI included **Shyam Biswal, Christin Hann**, **Ana Navas-Acien**, **David Sidransky**, and **Cynthia Zahnow**. As a result of FAMRI support, these researchers deciphered the cellular causes of tobacco smoke-related cancers and helped develop new tobacco policies.


KANAREK

In appreciation of the Flight Attendant Medical Research Institute, the FAMRI courtyard and fountain was installed during the construction of the David H. Koch Cancer Research Building.

## MARYLAND CIGARETTE RESTITUTION FUND

In 1998, 52 state and territory attorneys general signed the Master Settlement Agreement with the four largest U.S. tobacco companies to settle dozens of lawsuits brought to recover billions of dollars in health care costs associated with treating smoking-related illnesses. We worked with then-Gov. Parris N. Glendening and the General Assembly to establish the Maryland Cigarette Restitution Fund (CRF).

Maryland was unique, named by the U.S. Congress as a national model. As most states engaged in lengthy battles over how to use the funds, Maryland got to work, investing its settlement funds to fight cancer—particularly seven CRF-targeted cancers: breast, cervical, colorectal, lung, melanoma, oral and prostate cancers, with a specific focus toward minority and underserved populations. Johns Hopkins investigators leveraged their grants, earning research funding and other support more than 10 times the CRF investment.

Sidney Kimmel, the Cancer Center's benefactor, cited the partnership between the Cancer Center and the state of Maryland to use the CRF to finance cancer research as one of the things that influenced him to make his historic $150 million gift in 2001.

Kimmel Cancer Center Director **William Nelson** and **John Groopman**, associate director of population sciences are co-principal investigators of the Maryland Cigarette Restitution Fund at Johns Hopkins. **Norma Kanarek** administers the grant.

To date, the CRF has funded 166 grants, totaling nearly $145 million.

The state's commitment to combatting cancer and years of dedicated CRF-support helped move our state from leading the U.S. in cancer deaths to 34th in the nation, and as we continue to work together, we will realize even more opportunities for unprecedented progress against cancer for all Marylanders.

# Tracking a Cancer Starter

## *HPV and Head and Neck Cancers*


GILLISON


SHAH


D'SOUZA


FAKHRY

For researcher **Maura Gillison**, the human papilloma virus (HPV) was a smoking gun. After proving that the virus was present in tumor cells of a subset of patients with head and neck cancer—primarily those of the pharynx, tonsils, and base of tongue and often those who didn't fit the risk profile for the disease—she set out to find how it could affect screening, prognosis, and treatment of head and neck cancers.

Gillison was an assistant professor of oncology at the Kimmel Cancer Center in 2002. She had been mentored by leading HPV researcher **Keerti Shah** and was intrigued by evidence of HPV DNA in head and neck cancer and wanted to find out what role the virus might be playing in this form of cancer. The fact that the virus had been detected in some head and neck cancer was no secret, but most scientists attributed it to laboratory contamination.

"I couldn't help but wonder what if it wasn't," she said.

When she began her research, Gillison truly expected the results to be negative, that she would not find HPV in the tumor cells. Instead, she became the first researcher to prove that the virus was actually driving the cancer. To her surprise, she also found that these patients typically fared better than those with non-HPV-associated head and neck tumors.

The finding presented opportunity for intervention, such as early detection of HPV infection through screening and potential prevention of the infection through HPV vaccines. The vaccines had been approved for the prevention of cervical cancers, the majority of which are also caused by HPV infection. HPV-positive cancers made up about 60% of cancers of pharynx, tonsils and base of the tongue, and those who got them were cured 85% of the time.

Her findings shifted the treatment paradigm for this cancer. Today, distinguishing head and neck cancers between HPV-positive and negative to guide treatment is standard of care.

"It suggests that HPV-positive head and neck cancers comprise a distinct molecular, clinical, and pathological disease very different from other types of the disease," said Gillison.

She suspected the HPV infection of the oral airway occurred through oral/genital contact. She set out to find exposures contributing to HPV-related oral cancers. She was particularly, interested in tonsillar cancers, which had been steadily rising since 1973.

In May 2007, Gillison's practice-changing research was published in the prestigious *New England Journal of Medicine*, with a finding that the overriding risk factor for the cancer was multiple sex partners.

Gillison collected blood samples and examined a variety of behaviors, including smoking, alcohol use, family history, poor oral hygiene, multiple sex partners, and other sexual behaviors that would expose a person to HPV. She followed participants for five years and found that people who reported more than six oral sex partners through a confidential survey had a higher than eight-fold increased risk of developing cancer.

"When you compare that to three-fold for smoking and two-fold for drinking, this is a very significant odds ratio," said Gillison.

In 2007, the American Society of Clinical Oncology named Gillison's research one of the top cancer advances of the year.

Gillison is now a professor in the department of Thoracic/Head and Neck Cancer at MD Anderson Cancer Center, but **Amber D'Souza,** Kimmel Cancer Center and Bloomberg School of Public Health investigator, who was mentored by Gillison, has built upon the research.

D'Souza is working with **Carole Fakhry**, director of the Johns Hopkins Head and Neck Cancer Center to better understand the natural history of HPV infections, how long they last, and risk factors that make them persist.

"It's not so much the infection, but that some people don't clear the infection that is the problem," says D'Souza, adding that, "Overall, the cancer risk from an oral HPV infection is low."

This aspect of the research, she says, has been in reassuring patients with HPV-positive head and neck cancers worried about putting their partners at risk. D'Souza's multicenter, pilot study revealed that spouses and long-term partners of patients with mouth and throat cancers related to HPV infection appear to have no increased prevalence of oral HPV infections.

"There are lots of people who have risk factors who don't get cancer and vice versa, so oral HPV infection alone is not very predictive as a biomarker for cancer risk, and that makes screening challenging," she says. "Screening people who have no symptoms risks overdiagnosis and causing more harm than good in someone who tests positive for HPV but were never going to get cancer."

They continue to work on ways to screen for those most at risk of developing cancer, but there is work to be done in this area, D'Souza says.

They are also interested in better understanding which patients are likely to develop treatment-resistant cancers. Despite the higher survival rates for patients with HPV-positive head and neck cancers, D'Souza says, not every patient does well.

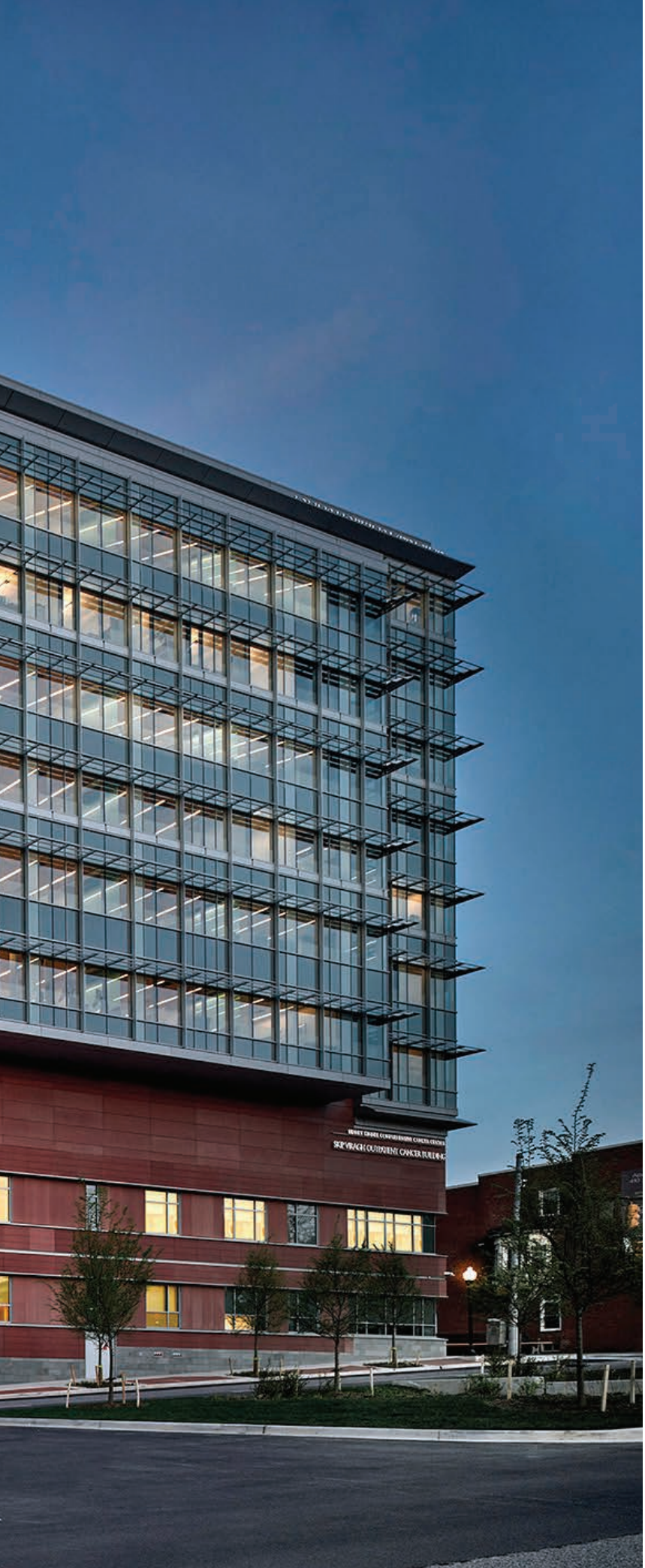
"We are trying to better stratify and understand the nuances of our patient population," she says.

Vaccines, like Gardasil, perhaps provide the greatest opportunity to prevent HPV infection, and as a result, the development of HPV-related cancers.

She suspects there are a small number of cancers being prevented in young people in their 30's now as a result of the vaccine, but with the median age of cancer being 65, the good news is coming in about ten years.

"Better uptake of the vaccine would help, but I am confident prevention is going to have a significant impact," she says.


ON JUNE 8, 2018, **THE SKIP VIRAGH OUTPATIENT CANCER BUILDING** OPENED. THE BUILDING IS NAMED FOR ALBERT P. "SKIP" VIRAGH, FULFILLING HIS COMPLETE VISION FOR CANCER CARE, CREATING A SINGLE PLACE WHERE CANCER PATIENTS COULD HAVE ACCESS TO THE BEST POSSIBLE AND MOST INNOVATIVE CANCER CARE AND SUPPORTIVE SERVICES.



# Skip Viragh Outpatient Cancer Building Opens

On June 8, 2018, the Skip Viragh Outpatient Cancer Building opened. The building is named for Albert P. "Skip" Viragh, fulfilling his complete vision for cancer care, creating a single place where cancer patients could have access to the best possible and most innovative cancer care and supportive services.

Viragh was a Maryland mutual fund investment leader, philanthropist, and pancreatic cancer patient treated at the Kimmel Cancer Center who died of the disease in 2003 at age 62. He funded pancreatic cancer research at the Kimmel Cancer Center, including the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care.

The Skip Viragh Outpatient Cancer Building represents the future of cancer medicine, said Kimmel Cancer Center Director **William Nelson**.

With an increasing amount of cancer care provided in the outpatient setting, and expected to grow over the next decade, the building became the new hub of Kimmel Cancer Center clinical services and clinical research.

> **"Here, in our Skip Viragh Outpatient Cancer Building, I believe we will begin to see the beginning of the end of cancer."**

The $100 million, ten-story 184,000-square-foot cancer care building, was funded entirely by private support, including a $65 million lead gift made possible by Skip Viragh and $10 million from Under Armour.

It provides clinical services to more than 200 patients daily, including about 80 new patient visits per week. It houses a patient welcome center, phlebotomy and pharmacy services, the Harry J. Duffey Family Patient and Family Services, the Seraph Foundation Meditation Room and Chaplaincy Suite, Imaging, diagnostic and treatment planning services for new patients and multidisciplinary clinics where patients benefit from a wide range of coordinated surgical, medical, radiation, and other consultations and services provided in one- to two-day visits.

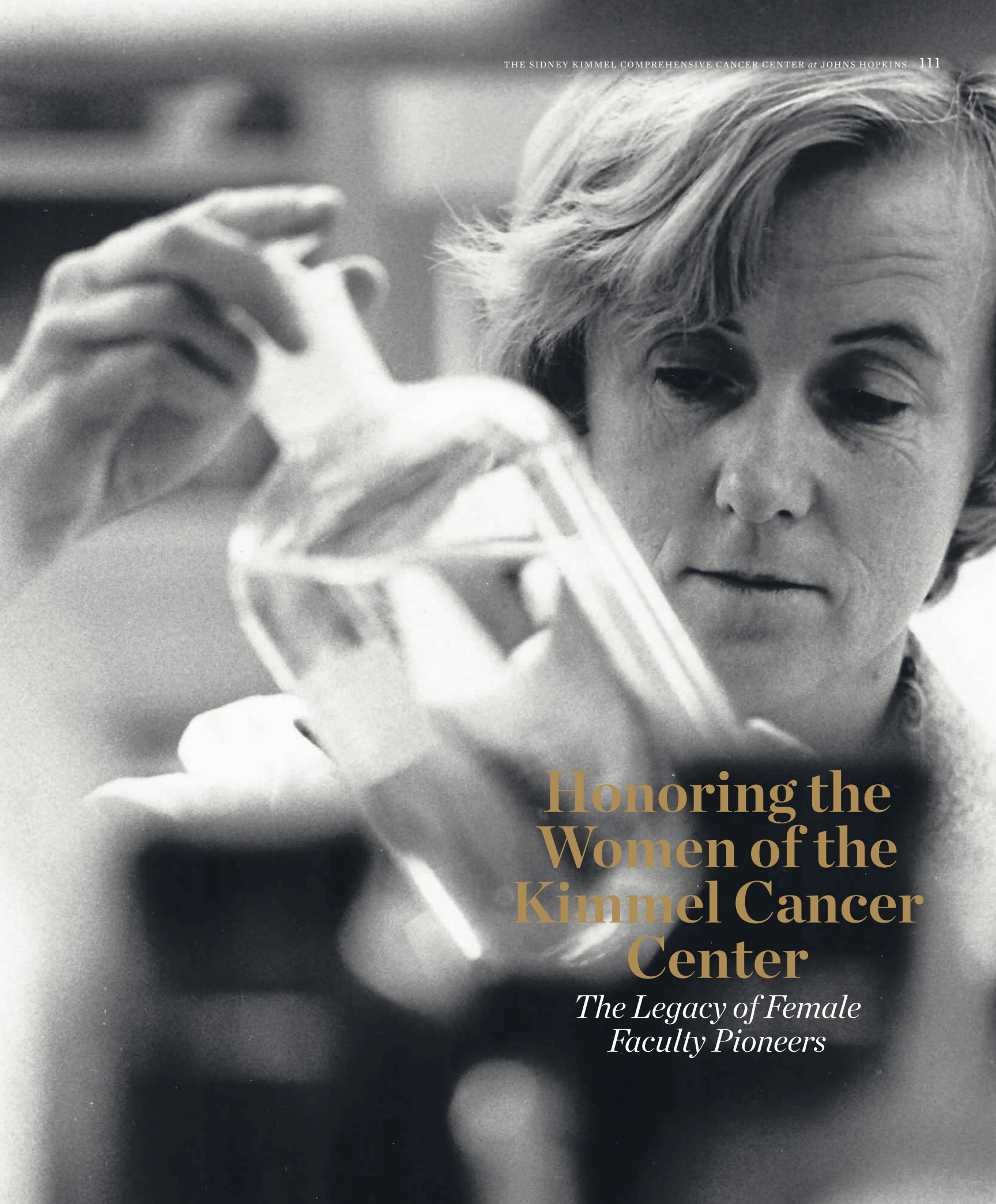
The Under Armour Breast Health Innovation Center, which includes breast health services such as nutritional counseling, fitness evaluation, and survivorship services, is located on the 10th floor along with the Skyline Café, which boasts panoramic views of the city.

The Viragh Building freed up space in the Harry and Jeanette Weinberg Building for the Kimmel Cancer Center to expand outpatient services for patients with blood and bone marrow cancers, inpatient cancer treatment, and 24-hour oncology urgent care.

Upon the building's opening, Nelson said, "Here, in our Skip Viragh Outpatient Cancer Building, I believe we will begin to see the beginning of the end of cancer."

## 2020s

Entering the digital age of cancer medicine, advanced computer technologies, such as machine learning, are making sense of the billions of data points generated in modern cancer research and medicine to predict the best treatment options for each patient, understand disparities and close gaps, improve cancer detection, and reveal novel ways to combat cancer.



# Honoring the Women of the Kimmel Cancer Center

## *The Legacy of Female Faculty Pioneers*

There is an unbreakable connection from our earliest female faculty members to our most recent recruits. Great pioneers and leaders, such as **Paula Pitha-Rowe**, who joined the Cancer Center in 1971 as its first basic scientist, **Judy Karp**, who came in 1973 as one of the first three oncology fellows, and **Brigid Leventhal**, recruited in 1976 to lead pediatric oncology, were role models and mentors who helped pave the way for our most recent female faculty members.

"These women were significantly productive in their own careers, and they helped shape our Cancer Center, creating an environment that made it better for the women who came after them. They helped us succeed," says **Elizabeth Jaffee**, deputy director of the Kimmel Cancer, the eighth woman to join the Cancer Center, and the 88th woman to earn a professorship at Johns Hopkins.

Major scientific advances typically do not come from one discovery at one moment in time. Instead, they unfold over many years. The women who pioneered technologies and advances against cancer in the early years of our Cancer Center trained many of today's leaders in cancer medicine, and they helped create a foundation upon which some of the most significant discoveries in the history of the Kimmel Cancer Center were made.


LEVENTHAL

**Brigid Leventhal** was the Kimmel Cancer Center's first director of pediatric oncology, joining the Kimmel Cancer faculty in 1976. She launched the pediatric oncology inpatient and outpatient clinics. She was a pioneer in the prevention of treatment-related toxicities, working with pediatric radiation oncologist Moody Wharam, to scale back treatment for Hodgkin's lymphoma to prevent side effects, including second cancers later in life. In 1984, she helped found the Pediatric Oncology Group, which focused on collaborative research of pediatric cancers. A founding member and president of the Women in Cancer Research Council of the American Association for Cancer Research, she was honored with the Federal Women's Award in 1974 and the Outstanding Career Woman of the National Council of Women in 1979. She died in 1994.

"THESE WOMEN WERE SIGNIFICANTLY PRODUCTIVE IN THEIR OWN CAREERS, AND THEY HELPED SHAPE OUR CANCER CENTER, CREATING AN ENVIRONMENT THAT MADE IT BETTER FOR THE WOMEN WHO CAME AFTER THEM. THEY HELPED US SUCCEED."


PITHA-ROWE

**Paula Pitha-Rowe** was the Cancer Center's first basic science researcher and among the school of medicine's first female professors. She was an internationally recognized researcher who helped define the biology of interferon, proteins produced as part of the body's response to inflammation. She started her laboratory at the Cancer Center in 1971, leading to a major breakthrough with the development of a mechanism to detect interferon-encoding RNA, allowing for the cloning of interferon and paving the way for its clinical use. She also identified viruses that engaged the interferon systems, and started the Cancer Center's viral oncology program, considered among the best in the world. She was interested in how viruses stimulated the immune system, and her research and guidance helped advance the technologies in cell engineering that allowed our researchers to develop the first therapeutic cancer vaccines. Pitha-Rowe also oversaw the Cancer Center's training grant, creating the educational environment for basic research and shaping the collaborative, intellectual discourse that remains foundational to our Cancer Center. She died in 2015.


HAYWARD

**S. Diane Hayward** joined the Cancer Center faculty in 1976 and focused her research on virus-associated cancers. She twice received Merit awards from the National Cancer Institute for her research on Epstein-Barr virus and was recognized by the International Association for Research on Epstein-Barr Virus and Associated Diseases. Her laboratory studied the ability of Epstein-Barr virus and Kaposi's sarcoma-associated herpesvirus to manipulate cell signaling pathways. She was the co-director of the Cancer Center's Viral Oncology Program.


MANN

**Risa Mann** came to Johns Hopkins in 1977 as a cancer researcher and pathologist after a fellowship at the National Cancer Institute. She was a member of the National Pathology Panel for Lymphoma clinical studies involved in the classification of lymphomas for the National Cancer Institute. She also researched the association of the Epstein-Barr virus (EBV) with lymphoma and helped develop methods to detect EBV in clinical samples. She was a member of the Education Committee of the United States and Canadian Academy of Pathology. She died in 2015.


FORASTIERE

**Arlene Forastiere** is an internationally recognized expert in esophageal cancer and in head and neck cancer management. She made major contributions to the development of combined modality therapy, and establishing standards of care for the management of these upper aerodigestive cancers. In 2003, Forastiere reported on a combined treatment she developed that allowed many patients with laryngeal cancers to keep their voices. In an eight-year trial of more than 500 patients, Forastiere showed that by giving chemotherapy and radiation therapy at the same time, many patients were able to retain their larynxes and preserve their voices. Although some of the study participants required laryngectomies, 85% of patients remained disease-free after receiving the combined drug/radiation therapy. She served as chair of the National Comprehensive Cancer Network's Head and Neck Cancer Guidelines Panel.


VOGELSANG

**Georgia Vogelsang** focused on managing graft-versus-host disease, a major complication of bone marrow transplantation, including harnessing its antitumor potential. Her major contributions have been in mentoring and teaching, with dozens of trainees now in universities around the world.


DAVIDSON

**Nancy Davidson** is a former director of the Kimmel Cancer Center's breast cancer program and breast cancer research chair in oncology. She helped decipher the role of the estrogen receptor gene in driving breast cancer and in characterizing pathways by which cancer cells die, with the aim of developing new therapies to target the pathways. She oversaw the development of preclinical studies, including the role of DNA methylation in estrogen and progesterone receptor genes, and was lead investigator on many practice-changing breast cancer clinical trials. She was chair of the Breast Committee of the Eastern Cooperative Oncology Group and co-founder of the Translational Breast Cancer Research Consortium. She served as president of both the American Society of Clinical Oncology and the American Association for Cancer Research. Davidson was director of the University of Pittsburgh Cancer Institute, and is currently director of clinical oncology at the Fred Hutchinson Cancer Center.


GRIEDER

**Carol Grieder,** the Daniel Nathans Professor and Director of the Department of Molecular Biology and Genetics, and colleague **Elizabeth Blackburn** discovered the enzyme telomerase. In 2009, they were awarded the Nobel Prize in Physiology and Medicine for the discovery. Grieder's pioneering research of telomeres, the protective end caps on chromosomes, showed that telomerase restores telomeres and protects them from damage. The connections of telomeres and telomerase to cancer development and progression is a major area of research.


BHUJWALLA

**Zaver Bhujwalla** is dedicated to the applications of molecular imaging to understand and target cancer and the tumor microenvironment. She is a fellow of the International Society of Magnetic Resonance in Medicine, the American Institute of Biomedical Engineers and the World Molecular Imaging Society. She is director of the Cancer Molecular and Functional Imaging Program. She is also chair of the Career Development of Advisory Committee for the Department of Radiology and Radiological Science.


SEARS

**Cynthia Sears** is the Bloomberg~Kimmel Professor of Cancer Immunotherapy and leads the Microbiome Program at the Kimmel Cancer Center's Bloomberg~Kimmel Institute for Cancer Immunotherapy. She is an expert on the gut microbiome — the community of microorganisms that aid with digestion, metabolism and immunity, and how certain bacteria can cause inflammation that leads to cancer. Among Sears' discoveries are colon biofilms made up of bacteria that are able to invade the mucus that protects the cells lining the colon. She is the first to systematically study the potential role of biofilms in the development of colon cancer.


SUKUMAR

**Saraswati Sukumar** is the Barbara Rubenstein Professor of Oncology and former director of the Kimmel Cancer Center's Breast Cancer Program. Her research has led to a test called the Liquid Biopsy for Breast Cancer Methylation (LBx-BCM). In 4½ hours, it can detect methylation, a type of chemical tag, in one or more of nine genes altered in breast cancers, and may be particularly useful in improving survival in poorer countries. Sukumar has also delivered a method that uses a tiny catheter to deliver anticancer drugs directly into breast ducts, where cancer most often originates.


JAFFEE

**Elizabeth Jaffee** is the Dana and Albert "Cubby" Broccoli Professor of Oncology. She is deputy director of the Johns Hopkins Kimmel Cancer Center, co-director of the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care, associate director of the Bloomberg~Kimmel Institute for Cancer Immunotherapy, and director of the Convergence Institute. Jaffee is a cancer immunology pioneer, developing immune therapies for pancreatic cancer and identifying immune cell signals that play a role in pancreatic cancer development and progression. She developed the science and technology for therapeutic cancer vaccines to treat pancreatic cancer, including a GMP facility to manufacture the vaccines. She holds six patents for the vaccines, and she and young investigators she is training continue to develop better versions. Jaffee is past president of the American Association for Cancer Research, a member of the National Cancer Advisory Board, chair of President Biden's Cancer Panel and a co-chair of the Biden Moonshot Blue Ribbon Panel. She was the 2023 recipient of the Distinguished Mentoring Award and the 2024 recipient of the Society for Immunotherapy of Cancer Richard V. Smalley Memorial Award.


KARP

**Judy Karp** came to the Cancer Center in 1973 as a one of the first three fellows; David Ettinger, and Skip Trump, were the other two. She is one of the world's leading experts on leukemia and complications related to infections resulting from leukemia and developed clinical trials aimed at preventing infections. Karp and colleague Phillip Burke directed the Center's leukemia program. They developed timed sequential therapy for leukemia, employing short courses of high-dose anticancer drugs specifically timed to be given when cancer cells were reproducing and more sensitive to drug therapy. Their treatment resulted in long-term remissions of 70% in patients treated.


TOPALIAN

**Suzanne Topalian** is associate director of the Bloomberg ~Kimmel Institute for Cancer Immunotherapy and a Bloomberg ~Kimmel Professor of Cancer Immunotherapy. She joined the Kimmel Cancer faculty in 2006 as director of the melanoma program. Her studies of anti-tumor immunity have provided a foundation for the translational development of cancer vaccines, adoptive T cell transfer and immune modulating monoclonal antibodies. Her current research focuses on manipulating immune checkpoints, such as PD-1, which she helped reveal cancer cells use to shut down the immune response to tumors. The discoveries have cemented immunotherapy as a mode of cancer treatment and transformed the care and survival of people with melanoma skin cancer and lung cancer. She is focused on identifying biomarkers that can predict clinical outcomes. She was named one of Nature's 10 in 2014, and received the Karnofsky Award from the American Society of Clinical Oncology in 2015.


LAIHO

**Marikki Laiho** is the Willard and Lillian Hackerman Professor of Radiation Oncology, director of molecular radiation sciences, and co-director of the Kimmel Cancer Center's Cancer Chemical and Structural Biology Program. Laiho's research is aimed at better understanding the mechanisms cancer cells use to survive radiation therapies and developing ways to prevent them from sensing and repairing the damage. She studies a cellular machinery, called POL1, that cancer needs to survive. In her laboratory studies using human cells, new drugs, called small molecule inhibitors, break down this critical activity. She plans to study them in clinical trials.


GRIFFIN

**Constance Griffin** directed the Kimmel Cancer Center's Cancer Risk Assessment Program. Her research was focused on gene alterations in solid tumors and hematologic cancers. Her research of the ALK gene and its role in inflammatory responses helped provide proof that the inflammatory process was linked to cancer initiation. She was particularly interested in better understanding the inherited basis of cancer among families. She died in 2012.


ZEIGER

**Martha Zeiger** gained international prominence at Johns Hopkins as a leader in endocrine surgery and thyroid cancer research, where she led a molecular biology laboratory for two decades. She served as president of the American Association of Endocrine Surgeons. Currently, she is professor and chair of the Department of Surgery at the University of Virginia. Zeiger also served six years in the United States Navy as a general medical officer, commander and surgeon.


WEBER

**Kristy Weber** joined the Kimmel Cancer Center in 2003 as chief of the Division of Orthopaedic Oncology and director of the sarcoma program. She built a clinical practice and basic science program in sarcoma, studying the molecular mechanisms associated with cancers of the bone. She and her colleagues developed human bone metastasis-derived cell lines and novel targeted therapy strategies for cancers that spread to the bone. In 2006, she received the Kappa Delta National Orthapaedic Research Award for this work. She left the Kimmel Cancer Center to become director of the sarcoma program at the Abramson Cancer Center at Penn Medicine. She was the first woman president of the American Academy of Orthopaedic Surgeons. She also served as president of the Musculoskeletal Tumor Society and was the inaugural founder and first president of the International Orthopaedic Diversity Alliance, which champions diversity, equity and inclusion in orthopaedics worldwide.


CANTO

**Marcia Canto** came to Johns Hopkins in 1996 as the first woman director of therapeutic endoscopy and endoscopic ultrasonography, quickly achieving international recognition as an academic endoscopist in a male-dominated subspecialty. She is the international authority on Barrett's esophagus, a risk factor for esophageal cancer, and early detection of pancreatic cancer in high-risk individuals.


ELISSEEFF

**Jennifer Elisseeff** is a biomedical engineer and director of the immunoengineering program at the Bloomberg-Kimmel Institute for Cancer Immunotherapy. She develops smart materials for the repair and regeneration of tissues. She is investigating her biomaterials in research models as a way to slow the growth of cancer cells. Laboratory studies suggest that these biomaterials may also be able to find and kill cancer cells that have spread from the primary tumor to other parts of the body. Elisseeff is a member of the National Academy of Inventors.


IACOBUZIO-DONAHUE

**Christine Iacobuzio-Donahue** joined the Kimmel Cancer Center in 2003, where she developed a mathematical model that, for the first time, allowed clinicians to quantify the development of pancreatic cancer — the time it takes for a precancerous cell to develop into a cancer. The model revealed an 11- to 18-year window from precancerous lesion to advanced cancer, providing an opportunity to intervene early and potentially cure these cancers with surgery. Her discovery led to the development of technology that rapidly picks out proteins and other biomarkers to help predict and detect pancreatic cancer.


STEARNS

**Vered Stearns** joined the Kimmel Cancer Center in 2002 and was named co-director of the breast cancer program in 2010 and awarded the breast cancer research chair in oncology. She was instrumental in building the multidisciplinary translational team that supported innovative clinical trials. She worked with the Consortium on Breast Cancer Pharmacogenomics, evaluating the predictive role genetic variants play in the safety and efficacy of endocrine therapies. She also advanced research of liquid biopsy — the detection of circulating cancer cell DNA in blood — to help detect breast cancer and guide treatment. In 2023, she was recruited to Cornell University as its director of transitional breast cancer and associate director for clinical affairs at the Meyer Cancer Center, but she remains an adjunct professor at the Kimmel Cancer Center.


SLUSHER

**Barbara Slusher** is director of Johns Hopkins Drug Discovery and a member of the Bloomberg-Kimmel Institute for Cancer Immunotherapy. She leads the largest integrated drug discovery program at Johns Hopkins, translating basic science discoveries into novel therapies. She co-developed a cancer drug called DON, with Jonathan Powell, that targets cancer cell metabolism, cutting it off from the nutrients it needs to survive, diverting the nutrients instead to immune cells, which can attack cancer cells. She led the first-ever international consortium of over 130 Academic Drug Discovery Centers to coordinate and enhance university-led drug discovery efforts.


ARMSTRONG

**Deborah Armstrong** is director of the Breast and Ovarian Surveillance Center. She joined the Kimmel Cancer Center in 1993, where she developed a large clinical practice exploring new therapies for breast, ovarian and other gynecologic cancers. She is a national leader in investigational cancer therapeutics, including the revival of a half-century-old method for delivering chemotherapy directly into the abdomen. Her research resulted in renewed interest in the abandoned method, called intraperitoneal chemotherapy. She chaired the Oncology Drugs Advisory Committee for the FDA, received the Ladies Home Journal Breakthrough Achievement Award, the Rosalind Franklin Award for Excellence in Ovarian Cancer Research, the Kimmel Cancer Center's Director's Teaching Award in Clinical Science and was two-time recipient of the Johns Hopkins Osler Housestaff Teaching Award.


SOKOLL

**Lori Sokoll** a faculty member since 1997, studies ways to improve the clinical use of PSA (prostate specific antigen) tests. She is focused on the measurement, evaluation and clinical applications of cancer biomarkers, with a specific emphasis on tumor markers for prostate cancer.


AHUJA

**Nita Ahuja** came to the Cancer Center in 2003 as the Jacob C. Handelsman Professor of Abdominal Surgery. She discovered that abnormal methylation occurred early in colorectal cancers, and led multiple national clinical trials using epigenetic therapies for solid tumors. In 2018, she was recruited to Yale University as the chair of the Department of Surgery.


TRIMBLE

**Connie Trimble** is director of the Center for Cervical Dysplasia and built a clinical and basic research program in immune therapies for HPV, with the goal of eradicating disease and preventing cervical cancer without the need for surgery. She established a Cervix Center for women with abnormal Pap tests, and treats more than 1,000 women annually.


SMITH-RESAR

**Linda Smith-Resar** trained in hematology/oncology, where she became fascinated by the molecular underpinnings of cancer. She was recruited to Johns Hopkins and the Kimmel Cancer Center faculty, and established a basic science laboratory for her pioneering studies on High Mobility Group A1 (HMGA1) proteins in cancer. Her laboratory engineered the first animal model demonstrating that the abnormal expression of HMGA1 causes leukemia. She received Research Scholar Awards from the American Cancer Society and Leukemia & Lymphoma Society, and was awarded the David M. Levine Excellence in Mentoring Award in 2015.


WANG

**Tian-Li Wang** is director of the Molecular Genetics Laboratory of Female Reproductive Cancer and a member of the Kimmel Cancer Center's Breast Cancer and Women's Malignancies Program.


COX

**Andrea Cox** is an internationally recognized leader in the studies of immune responses to chronic viral infections, including HIV, hepatitis B and hepatitis C. She was principal investigator on the first prophylactic HCV vaccine trial in high-risk individuals. HCV is a risk factor of liver cancer. Cox is also a faculty adviser for the Association of Women Student M.D.-Ph.Ds.


GOURIN

**Christine Gourin** treats patients with thyroid cancer and other head and neck cancers. Her research interests focus on quality of life, functional outcomes and survival following treatment for head and neck cancer.


SHOCKNEY

**Lillie Shockney,** University Distinguished Professor of Breast Cancer, has worked at Johns Hopkins since 1983. She is certified as a breast imaging and breast cancer patient navigator. In 2011, she accepted the inaugural role as director of the Kimmel Cancer Center's survivorship programs. In 2012, she was named program director of the Academy of Oncology Nurse Navigators. Shockney, a cancer survivor, joined forces in 2012 with Kimmel Cancer Center Chief Administrative Officer Terry Langbaum, also a cancer survivor, to launch Work Stride to help people in the workplace diagnosed with cancer. Today, the program reaches more than 300,000 employees and their families across the country. Langbaum died in 2019.


KLEIN

**Allison Klein** directs the National Familial Pancreas Tumor Registry and created a tool, called PancPRO, that computes an individual's lifetime risk of developing pancreatic cancer. She joined the pancreatic cancer research team in 2004. In collaboration with Scott Kern, Michael Goggins and Ralph Hruban, she is deciphering the genetic determinants of pancreatic cancer. Klein is also leading a study of 2,000 African Americans, who are 20% more likely to develop pancreatic cancer, to look for genetic differences among 1,000 patients with pancreatic cancer and 1,000 healthy participants to help decipher this cancer disparity.


SNYDER

**Claire Snyder** is focused on quality of cancer care with an emphasis on quality of life for people with cancer and coordination of cancer care between cancer specialists and primary care providers. Among her interventions are patient questionnaires that help clinicians identify and address quality of life issues. She developed the PatientViewpoint webtool to link questionnaire responses with patients' electronic medical records. Snyder has conducted multiple studies using large databases to examine quality of care for cancer survivors, including preventive and primary care, underlying health conditions and cancer follow-up.


ARMANIOS

**Mary Armanios** studies telomere dysfunction and is director of the Telomere Center, which is at the forefront of individualized care for patients and families affected by telomere disorders. Telomeres are protective endcaps on chromosomes. Armanios defines approaches to surveillance, diagnosis and treatment of telomere-related diseases, including cancer, bone marrow failure/aplastic anemia, idiopathic pulmonary fibrosis and liver cirrhosis. Armanios is also associate director of cancer research career enhancement.


BRAHMER

**Julie Brahmer** is co-director of the Cancer Immunology Program and director of the Thoracic Oncology Program. She led clinical trials of gene-targeted drug therapies and immunotherapy for lung cancer and mesothelioma, including practice-changing trials of anti-PD-1 therapies. Brahmer is co-principal investigator on the Johns Hopkins Clinical Trials Network. She is one of the founding board members for the National Lung Cancer Partnership and is on the medical advisory board of the Lung Cancer Research Fund and the Mesothelioma Applied Research Foundation.


VISWANATHAN

**Akila Viswanathan** is director of the Department of Radiation Oncology and Molecular Radiation Sciences. She is a leading expert in the use of image-guided brachytherapy for gynecologic cancers, and was the first in the U.S. to use real-time magnetic resonance-guided interstitial brachytherapy for the treatment of gynecologic cancers.


BLAKELY

**Jaishiri Blakely** is the Marjorie Bloomberg Tiven Professor of Neurofibromatosis in Neurology, Oncology and Neurosurgery. Her clinical research is focused on the development of clinical trials for nervous system tumors.


SHARMA

**Dipali Sharma** focuses her research on the molecular links between obesity and breast cancer. She discovered a molecule produced by fat cells, called leptin, that canceled out the drug tamoxifen's ability to prevent breast cancer in laboratory studies. She is also studying a natural compound derived from magnolia trees, called honokiol, known to have cancer-protective properties. Sharma was named the 2023 Fetting Fund for Breast Cancer Prevention Scholar.


LOTAN

**Tamara Lotan** is a genitourinary cancer expert. Her research described a novel mechanism of tumor formation in kidney cancers driven by over-expression of one gene, the mechanistic target of rapamycin complex 1 (mTORC1) signaling pathway, and loss of expression of another gene, the tuberous sclerosis complex (TSC) tumor suppressor gene. The findings point to potential therapeutic targets for some of the most aggressive renal cell cancers. She is also a researcher on the RESPOND study, the first large-scale, multi-institutional study of African American men with prostate cancer to better understand why they are at higher risk for developing more aggressive forms of the disease and are more likely to die from it. The study will be the first in any racial group to fully integrate genetic alterations with gene expression data, social determinants of health and markers of tumor aggression.


WEERARANTNA

**Ashani Weeraratna** is a Bloomberg Distinguished Professor and the E.V. McCollum Professor and Chair of Biochemistry and Molecular Biology at the Bloomberg School of Public Health. She is also co-director of the Kimmel Cancer Center Cancer Invasion and Metastasis Program. She is among the first to study and uncover age-related differences in how people respond to cancer therapy. The research earned her recognition by the National Cancer Institute during its commemoration of the National Cancer Act 50th anniversary. Weeraratna researches melanoma skin cancer, and has led public health initiatives to install sunblock dispensers in public spaces and to educate children about the dangers of sun exposure. She is also an advocate for the contributions of immigrant scientists and is a mentor for junior faculty members, women and people of color in science. In 2021, she was among seven scientists appointed to the National Cancer Advisory Board.


TAUBE

**Janis Taube** is director of the Division of Dermatopathology, co-director of the Tumor Microenvironment Laboratory at the Bloomberg-Kimmel Institute for Cancer Immunotherapy, and co-director of the Mark Foundation for Advanced Genomics and Imaging. Her research is focused on identifying biomarkers that predict response to immunotherapy. She and collaborator Alexander Szalay developed AstroPath, a comprehensive platform for imaging and mapping microscopic sections of tumors to guide precision immunotherapies for cancer.


LENNON

**Anne Marie Lennon** is director of the Multidisciplinary Pancreatic Cyst Clinic. She specializes in the management of patients with pancreatic cysts and precancerous lesions. Collaborating with the Kimmel Cancer Center Ludwig Center laboratory, directed by Bert Vogelstein and Kenneth Kinzler, she helped develop a test called CompCyst, a laboratory test that uses artificial intelligence tools and has the potential to more accurately sort out which people with pancreatic cysts will go on to develop pancreatic cancers. Only a small fraction of cysts progress to cancer. The ability to distinguish benign cysts from cancerous cysts would allow clinicians to identify patients who will not require follow-up and those who will need long-term follow-up or immediate surgical resection.


RUDEK

**Michelle Rudek** directed the Kimmel Cancer Center's Analytical Pharmacology Shared Resource, leading a team that conducts tests to see how promising new drugs travel through the body, are absorbed, distributed and metabolized, and what effect they have on cancer cells. Collaborating with Michael Carducci, they test drugs being used in the National Cancer Institute (NCI) Experimental Clinical Trials Network and support the NCI's Adult Brain Tumor Consortium and AIDS Malignancy Consortium. Rudek also researched and managed drug interactions among people with cancer who have underlying health conditions, such as liver or other organ dysfunction, to ensure they can safely receive anticancer drugs. She was the first nonphysician recipient of the NCI's Michaele Christian Oncology Development and Lectureship Award. She passed away in 2023.


FAKHRY

**Carole Fakhry** is the Charles W. Cummings, M.D., Professor of Otolaryngology and Director of the Head and Neck Cancer Center. She was recently appointed the associate dean for clinical affairs. She will work collaboratively to help develop and implement strategies for the Clinical Practice Association to help ensure patient-centered, safe and efficient care delivery. Fakhry is an internationally recognized expert in head and neck cancer, and her research has been pivotal to advancing the understanding of these cancers and helped define a distinct type of head and neck cancer, with the human papillomavirus (HPV) as a biomarker, in the National Comprehensive Cancer Network guidelines. She also oversaw the development, implementation and growth of the clinical trials infrastructure and portfolio in collaboration with the Bloomberg-Kimmel Institute for Cancer Immunotherapy.


AZAD

**Nilofer Azad** is director of the Cancer Genetics and Epigenetics Program and the Colorectal Cancer Research Center of Excellence. Her research is aimed at developing new drug combinations for patients with advanced cancer. She leads clinical trials to explore how epigenetic therapies target chemical alterations to genes that promote cancer development and growth. She is the principal investigator for Johns Hopkins on the Stand Up to Cancer Colorectal Cancer Dream Team and a member of the Epigenetics Dream Team, leading the GI cancer initiatives. She is a member of the National Cancer Institute Colon Cancer Task Force and its Molecular Analysis for Therapy Choice (MATCH) Agents and Genes Working Group, the largest trial of precision, or individualized, medicine in the country. Recently, she was appointed to the National Cancer Advisory Board.


GROCHOW

**Louise Grochow** was a graduate of the Johns Hopkins University School of Medicine and one of the Cancer Center's first medical oncologists. She helped launch its drug discovery program and pioneered advances against solid tumors, particularly colorectal cancer.


LE

**Dung Le** is the Bloomberg~Kimmel Professor of Cancer Immunotherapy. She led the clinical trials that established a genetic defect called mismatch repair deficiency/microsatellite instability as a predictor of response to immunotherapy with drugs that block the PD-1 immune checkpoint. The findings led to a historic 2017 FDA approval of the immunotherapy drug pembrolizumab across all cancer types for any cancer that contains the mismatch repair deficiency/microsatellite instability genetic defect. Le, who is a gastrointestinal cancer expert, also developed a low-dose, five-drug combination that has proven effective against pancreatic cancer.


PLATZ

**Elizabeth Platz** is co-director of the Cancer Prevention and Control Program and is the Martin D. Abeloff Scholar in Cancer Prevention. A major focus of her research is the use of molecular and genetic epidemiology approaches to understand the mechanisms underlying prostate incidence and progression. She conducts her work with an eye toward translation of findings into prevention and treatment strategies. She is at the forefront of population research on the role of inflammation, a target for prevention, in the development of prostate cancer, and on telomere length as a prognostic marker for poor outcomes after treatment for prostate cancer. She is a fellow of the American Association for the Advancement of Science, was appointed to the Maryland State Council on Cancer Control and is a steering committee member and former chair of the Maryland Cancer Collaborative.


SCHWARTZ

**Cindy Schwartz** was a Kimmel Cancer Center pediatric oncologist with a particular interest in survivorship. She contacted nearly 1,000 former pediatric patients successfully treated at the Kimmel Cancer to learn about their experiences with side effects of cancer therapy, such as infertility and organ damage. The information she accumulated was used to create a large statistical database to help predict and manage late effects of cancer therapy. Currently, she is medical director of hematology/oncology at the Medical College of Wisconsin.

**Nancy Shaper** researched glycoconjugates, a major class of molecules located on the cell surface, and how they interacted with proteins. Her work was foundational to the basic understanding of molecular genetics and the quest for gene alterations associated with cancer development.


SYMONS

**Heather Symons** is clinical director of the Pediatric Oncology Blood and Marrow Transplant Program. With Kimmel Cancer Center-pioneered science that made haploidentical, or half-matched, bone marrow transplants safe and effective, Symons began performing about 50 per year in pediatric patients. The procedure became so safe, about one-third of the transplants were in pediatric patients with noncancer immune and genetic disorders. Symons is also pairing donor lymphocytes (white blood cells that activate the body's immune system) with chemotherapy to determine if this combination will "awaken" patients' immune systems to the danger of existing cancer cells and, in turn, elicit an immune response.


VISVANATHAN

**Kala Visvanathan** is director of the Clinical Cancer Genetics and Prevention Service and is the inaugural Fetting Fund for Breast Cancer Prevention Scholar. She is an expert in breast cancer prevention in diverse populations. Her research includes predicting the risk of invasive cancer among women with atypical hyperplasia, evaluation of screening in high-risk women, and studying benefits of tamoxifen in individuals who are overweight or obese. There is a panel of genes experts look for in breast cancer to tailor early detection and preventive care, and Visvanathan is developing short, patient-driven, culturally sensitive videos to help patients and families understand the importance of genetic testing.


ZINREICH

**Eva Zinreich** was one of the Kimmel Cancer Center's first radiation oncologists and helped build the program.

# Kimmel in the Community

*The Cancer Center's outreach to the community has always existed, but it has changed and expanded over its 50-year history.*


ETTINGER

COMMUNITY OUTREACH was initiated in 1978 to make sure advances against cancer made at Johns Hopkins were available to patients throughout Maryland, across the U.S. and around the world.

**David Ettinger**, one of the Cancer Center's first fellows and faculty members, spearheaded the initial efforts to engage cancer experts in the community. It began informally.

It was not unusual for Ettinger to field multiple calls in a day to help physicians in Maryland and other states who were treating patients with cancer. There was a constant barrage of faxes and phone calls, such as a physician in New Jersey treating a patient with lung cancer calling to discuss the latest treatment options. Another from Western Maryland wanted to know the best possible use of a cancer-fighting drug. Someone else had a question concerning the current guidelines of the National Comprehensive Cancer Network for small cell lung cancer. Ettinger made time for all of them.

Telephone and face-to-face communication were the only tools for outreach.

"When I joined the oncology team in 1975, there were no fax machines and no computers," says Ettinger.

He began hosting monthly meetings open to all cancer specialists in the community to come to Johns Hopkins and hear about research advances and to discuss challenging cases.

Today, in the era of computers and smartphones, most are familiar with the term virtual medicine, but decades before these technologies were available, Ettinger and others had already begun to envision them.

In 1989, collaborative radiation oncology services were established among the Cancer Center and St. Agnes Hospital in Baltimore and Chambersburg Hospital in Pennsylvania. In the late 1990s, with the advent of computers, Ettinger and other experts began to use sophisticated computer connections to review patient X-rays and CAT scans from as far away as Singapore. Ettinger called it telemedicine.

At the same time, we began to see that working with community physicians was not enough. There were many people, particularly those who did not have health insurance, those living in poverty and racial minorities, who were suffering in silence. They were not seeking help for health issues.


WILSON

We began in our own neighborhood. Reverend **Doug Wilson**, director of community outreach, worked with local clergy to bring cancer screening and detection programs to the communities of East Baltimore.

In 1999, Cancer Center social worker **James Zabora** took over as director of community outreach.


ZABORA

"I looked out of my office window directly into the neighborhoods with possibly the highest cancer rates in the nation. I realized, as a comprehensive cancer center, we had an obligation to apply our knowledge to help these communities," said Zabora.

In the late 1980s, an analysis of health disparities based on ZIP codes confirmed what Zabora already suspected. The life expectancy for a resident of low-income neighborhoods along Madison/East End was 64, compared with 84 for residents of the higher-income neighborhood of Roland Park, even though the communities were only 5 miles apart.

He began working with churches, community centers and local organizations to provide education about cancer screening.

In 2002, with the establishment of the Maryland Cigarette Restitution Fund (CRF, see page 106), Zabora's efforts were aided by a $1.5 million public health grant to expand outreach, with a particular focus on Maryland's most common cancers.

Zabora and team took on Baltimore City's prostate cancer death rates — the highest in the nation— providing physical exams and PSA (prostate specific antigen) tests to 2,500 African American men. The grant meant that, if a cancer was detected, treatment at the Kimmel Cancer Center could be provided at no cost.

Building upon Reverend Wilson's earlier outreach, Zabora continued partnering with ministers and community activists. Cancer screening sites opened at the Bea Gaddy Center, Garden of Prayer Baptist Church, Morgan State University and the Korean Resource Center, and thousands were being reached.


FORD

**Jean Ford** joined the Kimmel Cancer Center in 2006 as director of community programs and cancer health disparities research. He was focused on understanding the barriers to care and increasing participation in cancer prevention and treatment trials.

Under his leadership, the East Baltimore Medical Center was set up as the headquarters for the program. "We wanted our staff to be located right in the community," said Ford.

**Connie Ziegfeld**, former assistant director of nursing for the Kimmel Cancer Center, was now worked with Ford as a clinical nurse specialist and case manager for the CRF-supported prostate cancer screening program.

Ziegfeld quipped that she didn't know whether to say she was a public health nurse, patient advocate, travel agent, counselor or health educator. Community members said she was all that and more.

Years of working as an oncology and ambulatory care nurse allowed her to efficiently navigate the potentially restrictive factors that can block patients' participation in their own health care.

"I'm doing something for a population that is frequently overlooked in our society," she said. "It touches me positively every day."

In 2010, the Kimmel Cancer Center established the Johns Hopkins Center to Reduce Cancer Disparities with the goal of providing all Maryland communities equal access to cancer prevention and treatment services.


SCOTT

One project, led by **Theron Scott**, assistant director of community education, focused on smoking cessation. Scott, an African American and former two-pack-a-day smoker, took a smoking cessation program to Latrobe Homes, an East Baltimore public housing development near Johns Hopkins. The program was so successful, it quickly expanded to other low-income neighborhoods

There was success. All of the efforts were making an impact. Overall, cancer death rates declined in our state, and the gap in cancer death disparities between African American and white Marylanders narrowed by more than 60% since 2001, far exceeding national progress. Like **Albert Owens** and **Martin Abeloff** before him, Kimmel Cancer Center Director **William Nelson** was committed to eliminating the gap.


LANSEY

Enter **Dina Lansey**, Nelson's choice to direct efforts to increase minority participation in clinical trials. Lansey, a seasoned expert in addressing racial disparities in cancer, developed ways to better measure and understand why many African Americans, women, elderly people with low income, and Baltimore City residents often chose not to participate in clinical trials.

Lansey began gathering data and identified cost and convenience of transportation as one barrier, launching a pilot project to provide free parking or taxi transportation to Baltimore City residents.

She also launched a clinical trials awareness campaign, including in-depth videos that explained clinical trials and offered patient testimonials, to help patients and families better understand the purpose of clinical trials and the value of considering them when making treatment decisions. She also instituted mandatory training for all clinical faculty and staff.

Under her leadership, Johns Hopkins became the first institution to use its electronic medical records to support conversations about clinical trials. Lansey matched minority and low-income patients to available clinical trials, and used a database to track reasons patients declined to participate. She used the information to help guide the development of ways to remove fixable barriers that kept patients from treatments that could help them. The system also documented that clinical trials were discussed with patients, and communicated names of interested patients to study teams.

Her action plan included collaborating with investigators as studies were designed to identify barriers to participation from the onset and develop targeted interventions aimed at those most in need.

Lansey's efforts had promising results. As the number of patients from Maryland treated at the Kimmel Cancer Center increased, the disparities gap continued to narrow.


BRAWLEY

In 2019, the program again expanded with the recruitment of **Otis Brawley**, a nationally renowned authority on cancer screening and prevention, as director of community outreach and engagement. Brawley, a Bloomberg Distinguished Professor, had been chief medical and scientific officer for the American Cancer Society and director of the Georgia Cancer Center at Grady Memorial Hospital in Atlanta.

Together, Lansey and Brawley have taken the program to a new level, establishing a Community Advisory Board and recruiting clinical health educators.

In 2022, they launched a community health education program, with the clinical health educators providing live webinars and in-person sessions to educate communities about healthy living, ways to reduce cancer risk and cancer screenings. The program was launched with a series of sessions offered to the more than 900,000 Johns Hopkins Community Physicians patients through its network of community practices throughout Maryland and Washington, D.C.

Between March 2022 and January 2023, they hosted 10 events and reached more than 1,600 citizens with presentations on colorectal and breast cancer awareness, cancer risk reduction, HPV awareness, cancer and nutrition, and the dangers of vaping. Upcoming sessions on nutrition and exercise are planned.

They seek answers to some very important questions: How do race, income and ZIP code influence life and death? Brawley notes that ZIP code may be more important than genetic code in predicting health outcomes.

Our experts continue to identify pockets of cancer health disparities and work to develop effective interventions. In addition to Baltimore City, some of Maryland's rural areas are highest in cancer deaths and new cases, which we are addressing. With the Kimmel Cancer Center's expansion to the National Capital Region at Johns Hopkins' Sibley Memorial Hospital, additional outreach to Wards 5, 7 and 8 in Washington, D.C., which has some of the highest cancer rates in the country, has started.

Building upon efforts that began in 2003 to establish a collaboration between the Kimmel Cancer Center and Howard University Cancer Center in Washington, D.C., to address cancer burden in minority populations, new efforts have begun to ensure that the diversity of care providers reflects the diversity of people with cancer.

**Fabian Johnston** and **Mary Armanios**, co-directors of the Center's Diversity, Equity and Inclusion in Education and Training, organized efforts, including social justice dialogue, programs and outreach to historically Black colleges and universities in Maryland, to enhance recruitment, mentorship and retention of underrepresented trainees and faculty members at Johns Hopkins.


JOHNSTON


ARMANIOS

Today, Community Outreach and Engagement has grown to embrace a full scope of outreach, from our community and patients to future scientists and clinicians, and it has become interconnected with every research program and clinical activity at the Kimmel Cancer Center.

# DIVERSITY AND DISPARITIES | ADVANCES

### NATIONAL REPORT ON CANCER DISPARITIES

In 2022, the American Association for Cancer Research released its inaugural Cancer Disparities Progress Report, described as a collective effort of a number of the world's foremost thought leaders in cancer health disparities research. **William Nelson**, director of the Kimmel Cancer Center, contributed to this first-of-its-kind report as a member of the steering committee, and faculty member **Jelani Zarif**, the Robert E. Meyerhoff Professor, also contributed. The report was presented to the U.S. Congress in a virtual ceremony. ***"Many cancer disparity gaps have persisted for decades. We hope this report will serve as a guide for how research questions can help address and close these gaps,"*** said Zarif.

### HELPING MARYLANDERS QUIT SMOKING

Tobacco use is the leading cause of preventable death, and it disproportionately affects marginalized and underserved communities, so Johns Hopkins Tobacco Treatment Clinic Director **Panagis Galiatsatos** took his clinics on the road to public housing communities throughout Baltimore. He combines medicine and counseling to help people quit smoking and offers lung cancer screening, when indicated. School-based tobacco education curriculums, which also cover e-cigarettes, were launched in Baltimore City and Baltimore, St. Mary's and Calvert counties.

A link between mental health and smoking was also presented to the Maryland Cancer Collaborative's Tobacco Committee. Current smokers were almost twice as likely as nonsmokers to report depression and 63% more likely to report two or more weeks of poor mental health in a month. Galiatsatos reports that people often smoke to alleviate anxiety, depression and isolation, and that relapse among those who have quit occurs when personal struggles arise. To address this, our tobacco treatment clinics provide mental health support and help with coping mechanisms.

### PROGRAM ADDRESSES HEALTH INEQUITY AS A DRIVER OF PROSTATE CANCER DISPARITIES

A $5 million commitment from the Fredrick D. and Karen G. Schaufeld Family Foundation, launched in 2021, the Schaufeld Program for Prostate Cancer in Black Men aimed at reducing the impact of the disease among African American men, particularly in the Baltimore and Washington, D.C., areas.

***"We fashioned and imagined a program that would be community-facing and serving, scientifically based, and focused on promoting education, all integrated around the clinical work we do in Baltimore City and in the National Capital Region,"*** says **Mohamad Allaf**, director of the Schaufeld Program. "It's a targeted approach to partner with the community to close a gap in outcomes in a disease that afflicts 1 in 8 Americans."

Prostate cancer is about twice as common among Black men as other populations, and 2.5 times more lethal. Access to care plays a major role in the heightened mortality rate, the program's chief adviser, **Otis Brawley**, says. "If they are treated at a major American facility, once we look at stage, race doesn't matter. Yes, Black men are more likely to get the disease," he explains, "but in the United States as a whole, Black men who are stage 2 have an increased risk of dying from prostate cancer when compared with white men who are stage 2."

Potential biological differences may also play a role in the disparity, says **Tamara Lotan**, the program's co-director. Her lab studies molecular biomarkers – genetic changes that happen in the prostate tumor. "We're trying to better understand the contribution of both of those components."

The Schaufeld Program will also partner with departments across Johns Hopkins to bolster the next generation of physicians and scientists.

The program's community partnership will give providers the opportunity to determine how to best deliver complex information.

***"Our goal is that – regardless of race, socioeconomic status or geography or where they live – all men have the information they need so they feel empowered to make an informed decision about their own care,"*** says **Dina Lansey**, the program's senior adviser, "whether that is prostate screening or choosing the best cancer treatment option for them."

### UNITY, MORE THAN A CLINIC

A unique collaboration with Unity Health Care to bring cancer screenings, evaluation and navigation to underserved communities in Washington, D.C., got much-needed support from Judy and Peter Kovler, longtime philanthropists to Johns Hopkins. This new clinical program supplements Johns Hopkins' supported programming underway for the communities of Wards 5, 7 and 8 in Washington, D.C., which has some of the highest cancer rates in the country.

Based at Unity Parkside Health Center in Ward 7, a nurse practitioner and navigation professionals from Sibley have been working in Wards 7 and 8 to evaluate patients for cancer. Patients and families who need to access the Kimmel Cancer Center at Sibley Memorial Hospital may receive novel precision navigation funded through the Kovlers' unique investment. Additionally, the Alexander and Margaret Stewart Trust have provided funding to build onto this programming to include a new dimension of peer support.

The Kovlers were inspired to get involved to ensure that everyone has equal access to excellent health care. As active members of the Sibley Memorial Hospital Foundation Board of Trustees and the Kimmel Cancer Center National Advisory Board, the Kovlers joined with Cancer Center leadership to make outreach to underserved communities a priority.

They noted the recruitment by Kimmel Cancer Center Director **William Nelson** of **Otis Brawley** to lead community outreach and engagement for the Kimmel Cancer Center, and **Ashwani Rajput** to direct the Kimmel Cancer Center in the National Capital Region.

***"We were impressed with Dr. Nelson's leadership in bringing Dr. Brawley, the world's most distinguished figure in medicine, particularly in understanding the needs of minority communities, and Dr. Rajput's ideas for elevating care throughout the city. It was the perfect team at the perfect time – a great combination of good ideas and talented people,"*** said Peter Kovler.

### CULTURALLY INFORMED PATIENT NAVIGATION

**Fabian Johnston**, assistant director for diversity, equity and inclusion in education and training at the Kimmel Cancer Center, developed a culturally tailored navigation program for African American patients with advanced solid tumors aimed at advancing care planning, pain management and hospice referral.

### CONTROLLING COLON CANCER

African Americans die disproportionately from colon cancer, and **Norma Kanarek**, identified a higher death rate among African American men living along the I-95 corridor from Prince Georges County to Baltimore. Collaborating with Kimmel Cancer Center Community Outreach and Engagement Director **Otis Brawley**, Bloomberg Distinguished Professor, the Maryland Department of Health Center for Cancer Prevention and Control, and Radio One, they initiated the DontDelay.Today campaign for colon cancer prevention and early detection among African Americans. The initiative, promoted by Radio One, directly addresses a problem identified in the community and provides information on the importance of colon cancer screening. It connects people to no-cost screening and information on healthy diet, habits and exercise.

### DIALOGUE ON RACE IN MEDICINE

The Johns Hopkins Kimmel Cancer Center presented a three-part virtual series addressing access to cancer care, social determinants of health and ethnic composition of cancer physicians. Kimmel Cancer Center Director **William Nelson**, **Akila Viswanathan**, director of radiation oncology and molecular radiation sciences; **Otis Brawley**, director of community outreach and engagement; and **Ashwani Rajput**, medical director of the Kimmel Cancer Center for the National Capital Region, led discussions and an interactive exchange on urgent issues of race in medicine.

### DIVERSITY IN RADIATION ONCOLOGY

**Curtiland Deville**, Proton Therapy Center medical director and clinical director of radiation oncology at the Kimmel Cancer Center at Sibley Memorial Hospital, is working to increase racial diversity among radiation oncologists, serving as a mentor and speaking at universities and before student organizations. He also studies how racism and social injustice manifests into health inequities. He is excited about partnering with other doctors in the community and other local institutions, such as United Medical Center, Howard University and Children's National Hospital.

***"These clinical collaborations enhance our impact on patients in the broader National Capital Region and beyond, providing convenient access to unique care and world-class treatments, such as the most advanced radiation therapies and clinical innovations,"*** says Deville.

### CURE FOR CANCER

At an early age, **Jelani Zarif** had an interest in science. He participated in his annual school science fair and wondered how and why many things around us worked. His interest in cancer and cancer research was sparked in high school, when he began working as a certified nursing assistant at a nursing and rehabilitation center in Chicago.

***"Some patients recovered from therapies without relapse of disease, and some, unfortunately, did not,"*** he recalls. ***"These experiences inspired me to want to understand cancer and how we can treat cancer better."***

He is now a CURE K22-funded researcher working within the Cancer Immunology Program to identify ways to circumvent cancer immune evasion and to activate anti-tumor immune responses in advanced cancers.

As a CURE (Continuing Umbrella of Research Experiences) scholar, Zarif is among an elite group of scientists who are from the populations who suffer from cancer disproportionately – the same populations that are traditionally underrepresented in science careers – and are working to produce research that can successfully reduce that burden.

### A DAY AT THE MARKET

In 2007, **Barbara Bates-Hopkins**, senior community engagement coordinator, started the Day at the Market program under the auspices of the Center for Urban and Environmental Health. It is held twice a month at Northeast Market in East Baltimore, and brings to the market Johns Hopkins nurses and doctors, other professional staff and students to offer tips on cancer prevention, screening, detection, treatment and healthy living.

The program, which is supported by the Kimmel Cancer Center, the departments of epidemiology and environmental health and engineering, Johns Hopkins Government Affairs, and the Johns Hopkins Institute for Clinical and Translational Research, has been recognized by the Maryland Department of Health and Mental Hygiene and the Maryland Cancer Collaborative, the group that implements the Maryland Cancer Control Plan.

# "Clinical Trials Saved My Life —*Twice.*"

**COL. GARY STEELE**
WITH HIS WIFE, MONA

COL. GARY STEELE had faced adversity before. The 77-year-old retired Army colonel is a graduate of the U.S. Military Academy at West Point. As a cadet in 1966, he broke the color barrier, becoming the first African American to play varsity football at West Point.

In 2011, he faced a different battle — prostate cancer. Since his diagnosis, he has made it a mission to inform other African American men about their increased risk of prostate cancer and the importance of screening.

"I didn't know I was at higher risk, but now I do, and I want to make as many people as possible aware."

Col. Steele's two sons are among those he told. They have been screened and are now helping to spread the word.

Despite early diagnosis, robotic surgery to remove his prostate, and radiation therapy, Steele's prostate cancer returned, and even worse, it had spread. The doctors who had been treating him had no other options to offer. That's when Col. Steele turned to the Johns Hopkins Kimmel Cancer Center and prostate cancer expert **Michael Carducci.** It was the first time anyone discussed clinical trials — research studies of promising new treatments.

Since coming to the Kimmel Cancer Center, Steele has participated in two trials. The first therapy didn't help his prostate cancer, so in 2015, he began the second clinical trial — one that compares standard hormonal therapy to increased doses of hormonal therapy.

Col. Steele says he feels very emotionally connected to his Kimmel Cancer Center team.

"I believe in the people I have met at Johns Hopkins. I trust them, and have faith that they care about me and are trying to do the best for me. They are not doing something that is just about research," says Steele.

The second treatment worked, and Col. Steele's prostate-specific antigen level (PSA) steadily declined until it became undetectable, an indicator that the treatment he received during the second clinical trial was working. There has been no sign of prostate cancer since 2014.

"If they learn something from this study that could one day help someone else, that would be wonderful," he adds.

This ability to think beyond himself in service to others was instilled in him by his parents.

Col. Steele's father, Frank Steele, enlisted in the U.S. Army in the 1940s, and his first duty station was at West Point, where he served in a regiment composed of Black soldiers, known as the Buffalo Soldiers.

Decades later, Col. Steele and his brother attended West Point as cadets. Col. Steele gained a great appreciation for the value of teamwork on the football field.

"I was just one person. I was the only Black guy on the team, but we were a team," he said. "It takes more than one to win."

Col. Steele has since been inducted into the Army Sports Hall of Fame. Military and football taught him about discipline and hope in the face of adversity. It had helped him many times in his life, including during his battle against prostate cancer, and in 2017 he would need to call upon it again, when he learned the cause of the severe back pain he was experiencing was multiple myeloma.

Multiple myeloma is rare cancer of the blood plasma cells that can cause bony lesions that lead to pain and even fractures. It disproportionately affects African Americans.

Despite its rarity, Col. Steele was not unfamiliar with the cancer. A long-time family friend and wife of a fellow West Point cadet had died from multiple myeloma. During her treatment, she participated in a clinical trial that led to a new therapy that is now a standard treatment for the cancer and is helping thousands of patients. Steele is one of them.

It hit home for him as another deeply personal reminder of the value of clinical trials.

He does not know what researchers learned from the prostate clinical trial and how it may be used to help patients. He has two sons. He thinks about the possibility of what the researchers learned one day helping them, and he offers some advice.

"Educate yourself, take care of yourself, think of your family and pay it forward," he says. "At the end of the day, there is that one saying on your tombstone. There is the date you were born. And there is the date you die, but there is also a dash in between. So, the question is really about what you do with that dash."

*The Convergence Institute*

# Unraveling Cancer Chaos

THE EXPERTISE and information to solve almost any cancer problem — even the most difficult ones, like pancreas cancer — exist at Johns Hopkins.


JAFFEE


LAHERU


FERTIG

**Elizabeth Jaffee**, the Dana and Albert "Cubby" Broccoli Professor of Oncology and one of the world's foremost pancreas cancer experts, is leading research and patient care in a new direction.

Jaffee created a Convergence Institute, where doctors, nurses, astronomers, engineers, computer scientists, physicists, bioethicists, biologists, materials scientists, mathematicians and other experts from a variety of fields will work side by side to amass and apply their knowledge to cancer.

Beginning with pancreas cancer, they will solve complicated and vexing problems, build new technologies and consider out-of-the-box, creative new approaches that can only be found through this type of directed collaboration. Together, they will plan and chart new cancer prevention, detection and treatment strategies that intricately apply every bit of knowledge available.

It represents a new tactic, different from the assembly line approach that, although useful, applies consecutive contribution of expertise, implementing one thing at a time and offering separate and distinct components of the whole. Instead, it brings a convergence of expertise — people coming together in synergy to merge their ideas and knowledge into a new whole.

Imagine, for example, Madame Curie, Katherine Johnson, Albert Einstein, Frederick Douglass, Steve Jobs, Leonardo da Vinci, Aristotle, Stephen Hawking and Sally Ride working together, combining their ideas and expertise to solve a problem. This is what Jaffee envisions for cancer.

## AMASSING TALENT

Jaffee recognized the immense talent amassed at Johns Hopkins and had the vision to bring it all together to combat cancer, which is among the most complex diseases. While each new discovery advanced the understanding and treatment of the disease, it tended to also reveal new ways the cancer cell corrupted and disarmed natural biological processes that threaten its ability to survive, grow and spread.

"Cancer is a complicated problem, and to solve this problem, we need more than cancer biologists and cancer doctors," she says.

The answers, she says, lie in the data we are accumulating, but it requires physicists, engineers, computer scientists and others to turn it into meaningful information that can be used against cancer. Real progress will be measured by who is best able to interpret and use these massive amounts of data to help patients.

"Convergence is the only way to assemble the expertise to make use of all of the tools available and to tailor them to cancer discovery and medicine," Jaffee says. "It will allow us to convert data chaos into data order."

## ALL HANDS ON DECK

**Daniel Laheru**, co-director of the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care, says the Convergence Institute has an all-hands-on-deck philosophy. It is physically located on the seventh floor of the Skip Viragh Outpatient Cancer Building, but in practice, it extends to every specialty — 34 departments from five Johns Hopkins University Schools — and includes experts who do not typically have a seat at the table in the world of medicine.

"Engineers, physicists and other scientists we don't typically work with, come at a problem from a different perspective. They find clues we don't see," says Laheru. For cancer clinicians and scientists who pioneered the multispecialty approach of bringing together all the medical specialists involved in treating pancreas cancer to develop a treatment plan, expanding this approach to include experts from other scientific areas makes sense.

They begin with development workshops. A cancer doctor like Laheru explains the problem to this expansive and diverse group of experts who make up the Convergence Institute. After, there is a thorough, often hours-long discussion of the problems.

"We speak a different technical language in medicine than an engineer or physicist, so we have to make sure we have a common understanding of the problem," says Jaffee. "Then, working together, we bring our different tools to the problem." Teams form to develop and study different ideas and approaches and determine which one or ones work best and merit further investigation.

Jaffee wants to make sure they share information rapidly. She says their colleagues from other fields don't wait a year for a publication to get the word out on their research, as is often the case in medicine. Instead, they put it out on websites right away so they can share their computation methods and get insights from other experts.

Convergence Institute experts have already begun designing their first studies.

"We're really the only ones doing it clinically," says Laheru. "We're ahead of the curve."

## FROM MATH TO MEDICINE

"Every problem — even cancer — can be informed by math," says **Elana Fertig**, mathematician and computational biologist and co-director of the Convergence Institute. The Convergence Institute is helping her make the math-to-medicine connection.

Fertig, who began her career as a weather forecaster, made the career change to cancer researcher because of cancer's complexity. In predicting weather, Fertig says the challenges were taking different sources of data and integrating them with computer models to improve forecasts.

Now, she is applying the same strategy to cancer, gathering data, developing computer models to analyze it to predict how a cancer will behave and how it will respond to different types of treatments.

Fertig developed artificial intelligence methods that decipher the complex circuitry and interconnectivity of gene activity that controls cell growth, death and other behaviors in tissue and organ development, and relates this gene activity to what occurs in other tissues and across different species.

"We are bridging experimental models and divides by building a community of people who are cross-disciplinary to engage with the Cancer Center," says Fertig. "We're getting at things we haven't gotten at before and looking at them in a new way, taking principles from other fields to figure out how to overcome failures in treatment."

Most laboratories start with a pipette to do an experiment. Fertig and collaborators start with data. "We go in the reverse direction. We start with the data that has already been generated, and then we go to the lab to see what we can learn about them," she says. "Cancer is a puzzle, and we piece it together using different technologies and different areas of expertise that will get us the answers."

Jaffee believes the Convergence Institute brings the people together and provides the tools needed to fully understand every cancer. As a pancreatic cancer expert, she believes it represents a new era of cancer research.

"I've been researching pancreas cancer for 25 years, and I am very optimistic that we are on the verge of turning this very deadly disease into at least a chronic disease patients can live with," says Jaffee. "It gives me goose bumps knowing that the work we're doing in the Convergence Institute and all that we've learned will save lives."

### ALWAYS FORWARD THINKING

In 1982, **Ray Lenhard**, **Hayden Braine**, and **Rein Saral**, collaborated with the Department of Biomedical Engineering and Applied Physics Laboratory to establish the Oncology Clinical Information System (OCIS), the original data system to support the clinical, educational and patient care goals of the Oncology Center. In 1983, **John Enterline** became Director of Information Systems at the Cancer Center and took over management of OCIS. Lenhard became Vice President for Information Systems for the Johns Hopkins Hospital. Our biostatics and quantitative sciences visionaries, including **Steven Piantadosi**, **Steven Goodman**, **Gary Rosner**, **Giovanni Parmigiani**, and **Hao Wang** continued this bioinformatics support of clinical research.

### COMMONWEALTH FOUNDATION AND TRANSFORMATIONAL CANCER RESEARCH

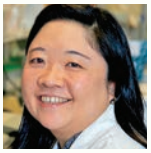
Commonwealth Foundation for Cancer Research continues to provide transformational philanthropy to support research in the Center for Personalized Cancer Medicine, including: "theranositics." radiopharmeceuticals that treat and track cancer; research that revealed circulating tumor DNA as a biomarker of response to immune therapy; innovative therapies using testosterone as drug therapy for prostate cancer; the identification of the FLT3 gene-positive as a subtype of treatment resistant leukemia as well as drugs to target the mutation; the potential of epigenetic therapies to prime cancers to respond to immune therapies; and the development of post bone marrow transplant cyclophosphamide as a new standard of care to prevent severe cases of a common complication known as graft vs host disease.

## THE TOOLS OF CONVERGENCE

**THE GOOGLE MAPS OF CANCER:** New computational approaches are providing a never before seen view – at the single cell level – of the tumor and all of the cells in and around it that contribute to its survival. Similar to Google Maps, the fine details these new technologies provide offer a detailed view of how and where the tumor exists in the body and how it interacts with surrounding tissues. It's possible to zoom in on spatial features and also pull back to get a fuller view. Pathologist **Bob Anders**, can do the same thing at the cellular level to provide a "Google Map" of an organ and surrounding tissue and organs. Provided with any list of proteins, Anders can quantify their abundance, where they are in the tumor and how they are affecting the growth and spread of a cancer.


TAUBE


SZALAY


KAGOHARA

**FROM ASTRONOMY TO CANCER:** The images of the night sky that astronomer and computational scientist **Alexander Szalay**'s datasets created are remarkably similar to the terrain of the cancer cell and its environment. Szalay and his Kimmel Cancer Center collaborator **Janis Taube**, developed AstroPath, a comprehensive platform for high-quality imaging and mapping of microscopic sections of tumors. Taube and Szalay are co-directors of the Mark Foundation Center for Advanced Genomics and Imaging.

These deep-learning algorithms, derived from artificial intelligence, provide sophisticated models that help predict what treatment is the best option for a patient. Jaffee and other cancer experts can use their technologies to determine how likely a cancer is to respond to different types of immunotherapy or other treatments.

**SINGLE CELL SEQUENCING:** **Luciane Kagohara** uses a specialized technology called single cell sequencing, which offers a detailed view of the tumor composition and enables scientists to measure all cell types in the tumor and examine their function. With the rapid advances in the field, it's now possible to zoom in on spatial features and identify how those same cells interact with one another without dismantling the tumor samples. This approach can help scientists and clinicians discriminate between treatment resistance built into the tumor and resistance that is acquired during treatment.

**ORGANOIDS:** Small, natural replicas of human tissue, called organoids, are another example of a new technology used in the Convergence Institute. **Richard Burkhart** and pathologist **Laura Wood** are using pancreas organoids, ultra-tiny replicas of a patient's pancreas, grown from their own cells, to better understand the mechanisms of how a cancer originates and grows, and as a unique way to test responses to treatments. Wood and Burkhart think the organoids reflect the tendencies of the actual patient tumor. For example, if an organoid grows more quickly, it could be a warning sign that the tumor may be more aggressive and dangerous.

# The Johns Hopkins Proton Therapy Center Opens

THE JOHNS HOPKINS Proton Therapy Center opened Oct. 1, 2020, giving adult and pediatric patients access to a highly targeted cancer treatment that spares nearby healthy tissues and organs and reduces potential side effects, including the risk of recurrence.

In addition, as an academic proton therapy center, research is performed in a dedicated gantry.

DEVILLE

"I am excited to be part of an academic center at the forefront of solving issues and questions about proton therapy," says **Curtiland Deville**, medical director of the Johns Hopkins Proton Therapy Center. "What are the best indications for proton? Where can we increase benefit, and where can we reduce toxicity? Where are we not getting such benefit and can let go? This is an area that is lacking, and our center will be solving these unknowns and leading future progress."

Proton therapy is an effective way of killing cancer while minimizing harm to healthy, surrounding tissue. The proton beam releases its energy entering the tumor, and stops at the tumor. There is no exit dose, so the risk of harm to healthy surrounding tissue is reduced.

LADRA

Unlike traditional radiation, which uses X-rays to destroy cancer cells, proton therapy uses subatomic particles with about 2,000 times more mass, explains **Matthew Ladra**, assistant professor of radiation oncology and molecular radiation sciences and director of pediatric radiation oncology for the Kimmel Cancer Center at Sibley Memorial Hospital.

The new 80,000-square-foot Proton Therapy Center — one of the largest and most advanced in the world — houses state-of-the-art proton therapy equipment, including four treatment gantries equipped with the most advanced technologies. The center's experts are using this advanced technology, supported by the latest research, to deliver individualized care.

"These advanced imaging facilities give our expert, disease-focused physicians exceptional ability to use very precise anatomy to plan proton therapy," says **Akila Viswanathan**, director of the Department of Radiation Oncology and Molecular Radiation Sciences.

A large mechanical arm called a gantry can move the beam 360 degrees around the patient, treating the tumor from several angles, layer by layer, killing cancer cells with the most advanced pencil beam delivery. Our highly trained radiation oncologists and physicists direct the proton beam to the tumor with pinpoint accuracy, and treatment is conformed to the size and shape of the tumor.

It is the only proton center with CT imaging integrated with treatment to ensure accurate and precise treatment planning and treatment delivery. Respiratory gaiting technology tracks the proton beam to movement of the tumor and stops the beam if the tumor moves. Our experts helped invent and develop both technologies.

The proton therapy center is one of the few in the world — and the only one in the Washington, D.C., region — with a dedicated pediatric team that specializes in caring for young oncology patients.

Viswanathan and **Marikki Laiho**, director of molecular radiation science, are excited about what Kimmel Cancer Center experts can offer to advance the understanding and use of proton therapy.

"Although it has been around for a long time, it is very much in its infancy in terms of exploration and potential," says Viswanathan. "There are many aspects we are still learning about and many research opportunities," adds Laiho. "That's something unique we bring to the table."

# Facing a Pandemic

THE COVID-19 PANDEMIC shook the world, but cancer doctors and researchers — no strangers to difficult challenges — were among the Johns Hopkins experts who led efforts to understand and contain this novel, history-making virus.

Cancer treatments often deplete immune cells, weakening the immune system, so the COVID-19 pandemic placed cancer patients among the most vulnerable to infection. Given the dangers the virus presented to patients, our doctors and nurses sprang into action to keep our patients safe.

It was all hands on deck, and administrative staff members also stepped up, helping to screen patients and visitors for signs of the infection.

Not unlike the early days of our Cancer Center, when doctors, scientists and nurses worked together to develop novel strategies to make progress against a disease that was poorly understood, ideas for how to treat the virus and ways to protect our patients were almost immediate.

Working together, our clinicians created guidelines for treatment to help prevent cancer patients from contracting COVID-19 and to help those infected with the virus safely continue cancer therapy. These guidelines were shared and adapted by other cancer care providers across the nation and the world.

A trained team made tens of thousands of COVID-19 testing kits in a Kimmel Cancer Center lab uniquely outfitted to meet special quality control standards required for manufacturing pharmaceutical products. Research laboratories throughout the Cancer Center donated supplies needed to complete the kits.

Within days of the outbreak, **Gina Szymanski**, incident commander, and **MiKaela Olsen**, clinical nurse specialist and operations chief of the Kimmel Cancer Center's COVID-19 Command Center, opened the Curbside Shot Clinic — a drive-up treatment delivery system — for outpatients and a special urgent care bio clinic for patients with cancer who were infected with the coronavirus.

Patients were able to drive up to the front of the Skip Viragh Outpatient Cancer Building, where they were met by nurses to have their blood drawn and checked and to receive single injections of therapy drugs, cancer vaccines, or growth factors that stimulate production of blood cells diminished by cancer treatments — every kind of treatment except chemotherapy IV infusions — without ever leaving their cars.

To provide care to patients with cancer who had COVID-19-like symptoms or who were already diagnosed with the virus, the nursing team quickly converted space in the Weinberg Building into an urgent care biocontainment clinic. The clinic — which is available to patients at all of our Kimmel Cancer Center locations — was uniquely set up to care for patients with infectious diseases, keeping them safe and cared for while preventing the spread of the infection to other patients.

Radiation Oncology established special simulation and treatment rooms for adult and pediatric patients at all five of our Kimmel Cancer Center radiation oncology sites. Like the biocontainment clinic, these rooms were set up with unique air flow and filtering to care for patients with infectious diseases.

As a result of this quick action, just 26 Cancer Center patients became infected with the coronavirus — unrelated to their visits to Johns Hopkins — and most importantly, they all recovered.

In addition to caring for our own patients, our doctors and nurses cared for patients transferred from other hospitals and clinics throughout the state that were not set up to care for patients with COVID-19. We worked collaboratively with Maryland elected officials and our colleagues at the University of Maryland to construct a field hospital to address the additional strain the virus placed on Maryland.

On the research side, our researchers proposed an innovative therapy to prevent an inflammatory process called cytokine storm syndrome, which is associated with COVID-19 severity and death. A test of white blood cells was developed to identify individuals in need of early intervention to prevent the acceleration of their COVID-19 disease. Kimmel Cancer Center Director **William Nelson** was appointed to head the Johns Hopkins committee charged with reviewing proposed research and activating the most promising projects.

"History is important, and it taught us that we can treat very sick patients as outpatients," said Szymanski. "We don't wing it, and we don't place artificial limits on ourselves." She reminds us that what the Kimmel Cancer Center team did to help our patients during COVID-19 is a continuation of what we've always done: work on the cutting edge of science and blaze new trails to make rapid progress against threats to health.

"The progress made against cancer is nothing short of amazing. Today's advances save lives at a far faster pace than before. When it comes to cancer, we live longer, we diagnose sooner, we prevent better and advocate more strenuously. Still, there are a half million plus deaths a year, so we know our work is not done. This is a time of great research opportunity, and we must test the unknown to continue to make progress. Imagination is a beautiful thing. Can you imagine a world without cancer?"

—Sidney Kimmel

SIDNEY AND CAROLINE KIMMEL

## FULL PROFESSORS WITH A PRIMARY APPOINTMENT IN ONCOLOGY

**Ambinder, Richard**
Hematologic Malignancies

**Armanios, Mary**
Education

**Armstrong, Deborah**
Women's Malignancies

**Azad, Nilofer**
Cancer Immunology/GI Clinical

**Baylin, Stephen**
Cancer Biology

**Brahmer, Julie**
Upper Aerodigestive Cancer

**Brawley, Otis**
Oncology Community Programs

**Carducci, Michael**
Urologic Oncology

**Casero, Robert**
Cancer Biology

**Cohen, Kenneth**
Pediatric Oncology

**Cooke, Kenneth**
Pediatric Oncology

**Dang, Chi**
Cancer Biology

**Denmeade, Samuel**
Urologic Oncology

**DeZern, Amy**
Hematologic Malignancies

**Donehower, Ross**
Medical Oncology

**Eisenberger, Mario**
Urologic Oncology

**Ettinger, David**
Upper Aerodigestive Cancer

**Fertig, Elana**
Biostatistics

**Fetting, John**
Greenspring

**Forastiere, Arlene**
Upper Aerodigestive Cancer

**Friedman, Alan**
Pediatric Oncology

**Fuchs, Ephraim**
Hematologic Malignancies

**Gojo, Ivana**
Hematologic Malignancies

**Grossman, Stuart**
Brain Cancer

**Hahn, Noah**
Onc Urologic Oncology

**Hayward, Gary**
Viral Oncology

**Jaffee, Elizabeth**
Cancer Immunology/GI Clinical

**Jones, Richard**
Hematologic Malignancies

**Kern, Scott**
Cancer Immunology/GI Clinical

**Kinzler, Kenneth**
Cancer Biology

**Klein, Alison**
Cancer Immunology/GI Clinical

**Laheru, Daniel**
Cancer Immunology/GI Clinical

**Le, Dung**
Cancer Immunology/GI Clinical

**Levis, Mark**
Hematologic Malignancies

**Luznik, Leo**
Hematologic Malignancies

**Meade, Javier Bolaños**
Hematologic Malignancies

**Nelson, William**
Oncology Chair

**Nicholas, John**
Viral Oncology

**Papadopoulos, Nickolas**
Cancer Biology

**Pardoll, Drew**
Immunology Lab Research

**Pearce, Erika**
Cancer Immunology Lab Research

**Pearce, Edward**
Cancer Immunology Lab Research

**Sharma, Dipali**
Women's Malignancies

**Sidransky, David**
Cancer Biology

**Small, Donald**
Pediatric Oncology

**Smith, B. Douglas**
Hematologic Malignancies

**Smith, Thomas**
Women's Malignancies

**Stearns, Vered**
Women's Malignancies

**Sukumar, Saraswati**
Women's Malignancies

**Swinnen, Lode**
Hematologic Malignancies

**Varadhan, Ravi**
Onc Biostatistics

**Velculescu, Victor**
Cancer Biology

**Wagner-Johnston, Nina**
Hematologic Malignancies

**Wolff, Antonio**
Women's Malignancies

**Yegnasubramanian, Srinivasan**
Urologic Oncology

**Zambidis, Elias**
Pediatric Oncology

**Zheng, Lei**
Cancer Immunology/GI Clinical

## ASSOCIATE PROFESSORS IN THE DEPARTMENT OF ONCOLOGY

**Anagnostou, Valsamo**
Upper Aerodigestive Cancer

**Brennen, William**
Urologic Oncology

**Chen, Allen**
Clinical Quality/Analytics

**Cope, Leslie**
Bioinformatics

**De Jesus-Acosta, Ana**
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**Desai, Prashant**
Viral Oncology

**Easwaran, Hariharan**
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**Feliciano, Josephine**
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**Forde, Patrick**
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**Gaillard, Stephanie**
Women's Malignancies

**Ghiaur, Gabriel**
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**Gondek, Lukasz**
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**Huang, Peng**
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**Levy, Benjamin**
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**Llosa, Nicolas**
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**Markowski, Mark**
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**Pishvaian, Michael**
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**Raabe, Eric**
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**Ruble, Kathy**
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**Sahebjam, Solmaz**
Brain Cancer

**Scharpf, Robert**
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**Sharfman, William**
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**Wang, Zheyu**
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**Zhou, Shibin**
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**Ali, Syed Abbas**
Hematologic Malignancies

**Ambinder, Alex**
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**Baretti, Marina**
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**Bever, Katherine**
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**Bonifant, Challice**
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**Botsis, Taxiarchis**
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**Brait, Mariana**
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**Canzoniero, Jenna**
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**Choi, Young Bong**
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**Christenson, Eric**
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**Cooper, Stacy**
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**Dalton, William**
Hematologic Malignancies

**Deshpande, Atul**
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**Douville, Christopher**
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**Gocke, Christian**
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**Ho, Won Jin**
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**Imus, Philip**
Hematologic Malignancies

**Jain, Tania**
Hematologic Malignancies

**Johnson, Burles**
Urologic Oncology

**Kammers, Kai**
Biostatistics

**Kamson, David**
Brain Cancer

**Karantanos, Theodoros**
Hematologic Malignancies

**Koldobskiy, Michael**
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**Krumm, Sharon**
Oncology Community Programs

**Ladle, Brian**
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**Lam, Vincent**
Upper Aerodigestive Cancer

**Lansey, Dina**
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**Lee, Valerie**
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**Lemberg, Kathryn**
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**Leone, Robert**
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**Lim Seiwert, Tanguy**
Upper Aerodigestive Cancer

**Marrone, Kristen**
Upper Aerodigestive Cancer

**Marshall, Catherine Handy**
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**Misale, Sandra**
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**Pabani, Aliyah**
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**Paul, Suman**
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**Phallen, Jillian**
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**Ravi, Rajani**
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**Santa-Maria, Cesar**
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**Schratz, Kristen**
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**Scott, Susan**
Upper Aerodigestive Cancer

**Sena, Laura**
Urologic Oncology

**Shaikh, Fyza**
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**Shenderov, Eugene**
Urologic Oncology

**Sheng, Jennifer**
Women's Malignancies

**Tao, Jessica**
Women's Malignancies

**Toska, Eneda**
Women's Malignancies

**Tsukamoto Kagohara, Luciane**
Cancer Immunology/GI Clinical

**Wang, Yuxuan**
Cancer Biology

**Webster, Jonathan**
Hematologic Malignancies

**Zabransky, Daniel**
Cancer Immunology/GI Clinical

**Zaidi, Neeha**
Cancer Immunology/GI Clinical

**Zarif, Jelani**
Urologic Oncology

**Zimmerman, Jacquelyn**
Cancer Immunology/GI Clinical

## *Remembering*

**Benjamin Baker**
**R. Robinson "Bricks" Baker**
**Hayden "Bud" Braine**
**Richard Humphries**
**Hugh Jewett**
**Edward Lewison**
**Fray Marshall**
**Michelle Rudek**
**Saul Sharkis**
**Philip Waalkes**

JOHNS HOPKINS

MEDICINE

THE SIDNEY KIMMEL
COMPREHENSIVE CANCER
CENTER