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

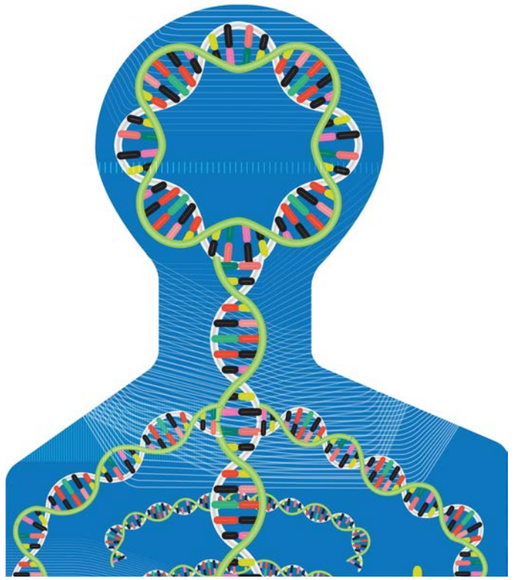
Victor Velculescu, co-director of the Cancer Genetics and Epigenetics program and a leading cancer biology researcher, developed methods for global gene expression analyses and coined the word "transcriptome" to describe the patterns in cancer and other cells. More recently, his group has developed non-invasive 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 anticancer 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


STEARNS


CONNOLLY


TORRES


YEGNASUBRAMANIAN

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.

"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

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.

"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."

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 DISCOVERY

1982: Genetic changes in the 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 br

east 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.

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.


WHARAM


CIVIN

CURT 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."


SMALL

DONALD 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.

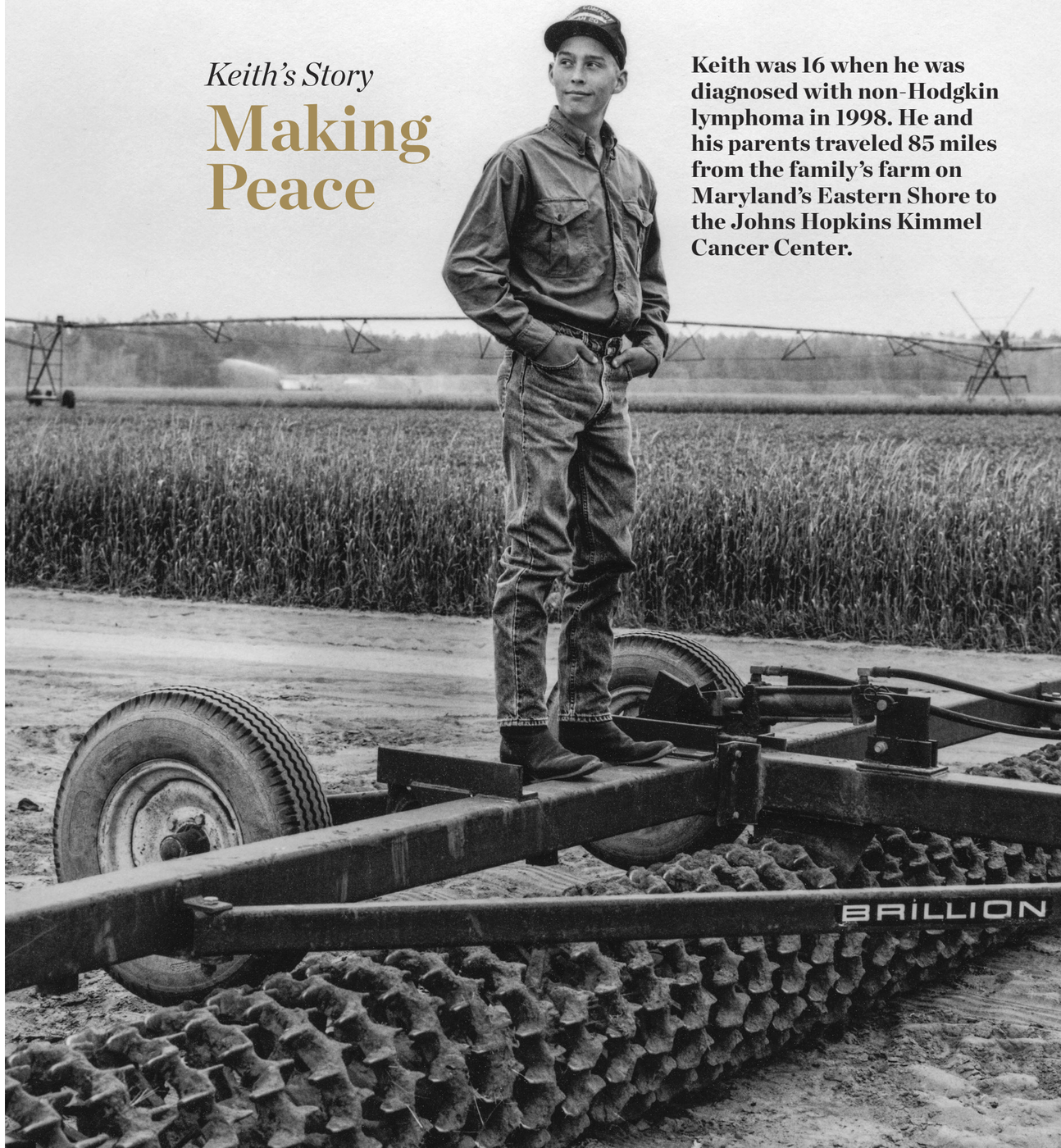
Phyllis, on the other hand, sees Heather as the hero in this story, but she is quick to mention a few other heroes.

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

KEITH ON HIS FARM

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.

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.

"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 grantmaking 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.

ELI, WITH HIS WIFE JAYNE AND DAUGHTER NORA

"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