THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS

FOUR DECADES of DISCOVERY
1973 – 2013

40 YEARS OF TURNING RESEARCH INTO RESULTS
OUR DECADE

IT IS HARD TO BELIEVE that 40 years have passed since we opened our cancer center. In 1973, the field of oncology was brand new, and scientists understood very little about what caused cancer and how it could be controlled. Our Center’s first director Dr. Albert H. Owens, Jr., had a unique vision for an interconnected program of laboratory research and patient care. Laboratory scientists worked side by side with clinicians to gain traction against the most feared disease of the time and bring cutting edge therapies to patients. Under the leadership of Dr. Martin Abeloff, we built upon these early successes, expanded our laboratories and clinics, and added to the talented group of clinicians and scientists. We began transforming cancer from a disease that almost always killed to one that today most patients survive.

Over the past four decades, these bench-to-bedside collaborations have allowed us to unravel the complex and intricate mystery that is cancer. Kimmel Cancer Center scientists have revealed the molecular schematic of alterations that cause it to begin, grow, and spread, identified treatment targets and developed the drugs that work with them, figured out why the immune system is tolerant to this relentless invader and retrained it to recognize cancer, and developed the technologies and tests that can detect and track cancer DNA from a few drops of blood.

As a physician-scientist who trained and worked at Johns Hopkins, I participated in this evolution and witnessed these advances firsthand. I became an oncology fellow under Dr. Owens and was recruited to the faculty in 1992 by Dr. Abeloff. Since 2008, I have been charged with ensuring our unparalleled success continues. I understand, for the patients and families affected by cancer, progress can never come fast enough. There are still many types of cancer that remain relentless, but even here we are making incredible strides. Progress we could only imagine 40, 30, or even 20 years ago is becoming a reality. We have entered the era of personalized cancer medicine where we will begin to use all of the information we have amassed on the cancer cell to track and disarm precancerous cells and to take down existing, potentially even advanced cancers, with therapies individualized to the unique characteristics of each patient’s cancer. This is our decade.

William G. Nelson, M.D., Ph.D.
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Imagine a time before there were fax machines, desktop and laptop computers, iPods or iPhones—i-anything, for that matter. That was the scene in the mid-1980s when, without the benefit of today’s automated gene sequencing technology, Drs. Bert Vogelstein and Kenneth Kinzler first cracked open the Pandora’s box that is cancer, revealing a series of genetic mistakes responsible for cancer. This work ushered in the age of molecular cancer biology. Dr. Vogelstein, the Clayton Professor of Oncology and a Howard Hughes Medical Institute investigator, and his collaborator Dr. Kinzler, co-director of the Ludwig Center at Johns Hopkins, developed a model for colon cancer initiation and progression that became the paradigm for much of modern cancer research. They developed the knowledge and the tools to find the rare errors in cell DNA that cause cancer. Far beyond the frequently touted needle in the haystack, Dr. Donald Coffey, former Deputy Director of the Cancer Center, likened their discoveries to finding a few critical typographical errors within 20 volumes of Encyclopedia Britannica and then figuring out how they got there.

Their studies through the 80’s and 90’s revealed how a tumor starts and how it progressively becomes more and more dangerous. Their work focused on oncogenes, that when altered accelerate cell growth, and cancer-controlling genes known as tumor suppressor genes. They identified the genes responsible for the major forms of inherited colorectal cancer, and these discoveries radically changed how patients with hereditary colorectal cancer and their families are managed in the clinic. In addition, they uncovered the genes that initiate the more common non-inherited forms of the disease as well as the genes responsible for tumor progression.

Still, experts wondered if there were other genes, besides those discovered by Drs. Vogelstein and Kinzler, that played a role in the cancer process. The investigators solved this mystery as well in 2007, when they and their team, including Drs. Victor Velculescu and Nicholas Papadopolous, developed a way to sequence every gene in a human cell. They used this technology to analyze colorectal, breast, pancreas, and brain cancers. This work represented the first time that any cancer had been analyzed in this way, and revolutionized the field. In a few years, every patient at Johns Hopkins and other major cancer centers throughout the U.S. will have their tumors sequenced routinely because of the door opened by the Vogelstein-Kinzler team.

At the same time that Dr. Vogelstein and team were deciphering the cancer genome, in another lab-
Drs. Velculescu, Papadopoulos, and Luis Diaz are considered the world leaders in finding cancer genes and interpreting their usefulness. Their discoveries have led to tests that can find cancer DNA in a small sample of blood or bodily fluids and have been used to detect cancer, personalize therapies to combat the unique genetic alterations contained within a tumor, and to monitor cancers’ response to treatment. Their goal is to develop tests that will prevent cancer by detecting the earliest genetic changes that precede the development of advanced stages of cancer.

Drs. Baylin, Herman, Malcolm Brock, Steve Gore and team led clinical trials of the first demethylating agent, a drug that blocks the excessive amount of methylation known to silence tumor suppressor genes. Promising results from these trials in leukemia and another pre-leukemic condition resulted in FDA approval of the drug. Now, the researchers are working with other clinicians and scientists, including Drs. Charles Rudin and Cynthia Zahnow, to study epigenetic-targeted treatments in lung, breast, and other cancers. A combined therapy, that uses a demethylating agent coupled with another drug that loosens the chromatin structure, is finding unparalleled success in a subset of patients with advanced, treatment-resistant cancers. These results earned them Stand Up to Cancer funding and “dream team” status. The team has gone back to the laboratory to personalize the treatment and determine the molecular fingerprint that will tell them exactly which patients will benefit.
IT IS NOT SURPRISING that the first nationally concerted effort in 1971 to fight cancer was called “the War on Cancer.” Some of the first drugs used to fight cancer were toxic gases used in World Wars I and II. Dr. Michael Colvin, a pharmacologist and one of our Cancer Center’s first investigators, was studying one of these gases, nitrogen mustard, because of observations that troops and civilians exposed to the gas experienced slowed bone marrow cell and lymph cell growth. Trials in lymphoma patients had promising results and sparked the search for other agents that might fight tumors. Nitrogen mustard was a predecessor to the commonly used and very successful cancer drug cyclophosphamide.

Dr. Colvin was an expert on cyclophosphamide and deciphered this important cancer drug’s mechanism of action. At this time, drug treatment was based more on observation than science. Experts describe early scenarios “of throwing drugs at the disease.” If it worked, they stuck with it, but they had no idea why it worked. Dr. Colvin changed that, and before the term “targeted therapy” had ever been uttered, began laying the groundwork for the science to decipher and understand what drugs did to the cancer cell and how to make them work even better. Our cancer center led the world in testing the toxicity of new anticancer drugs and for deciphering their mechanism of action and became a front runner in administering aggressive, high dose chemotherapy and in managing the treatment-limiting side effects of such intensive therapy.

Dr. Colvin’s work revealed that cyclophosphamide was not harmful to stem cells and helped spawn current stem cell therapies. This research, conducted in collaboration with Cancer Center colleagues Drs. Rick Jones, Saul Sharkis, and John Hilton, also led to the development of a stem cell isolation probe that is now a commonly used marker for identifying stem cells. With Dr. Colvin’s pioneering research, our Cancer Center became the site of the nation’s first cancer pharmacology program. Our experts began developing and testing novel new drugs and quickly earned an NCI grant to begin Phase I clinical trials of the drugs.

Investigators at the Kimmel Cancer Center were not just focused on finding new drugs that combatted cancer, but also on how they could make existing drugs work better. In the 1980s, research on the drug paclitaxel had been all but abandoned. Despite its promise in animal models, it was too toxic for humans. Dr. Ross Donehower developed medications that could be given before treatment to make it safe. As a result of his work, the drug that was about to be pulled from the market was proclaimed as the most promising new anticancer drug. From there, Dr. Donehower and team went on to demonstrate the benefits of a class of drugs known as topoisomerase inhibitors, which killed cancer cells by causing
fatal breaks in the cells’ DNA.

When our center opened, combined modalities did not exist. Today they are a staple of treatment. Not only do we combine drug treatment with radiation treatment and surgery, but our scientists and clinicians have invented drugs that make radiation treatment work more effectively, cancer vaccines that mop up cancer cells left behind after treatment, ultra tiny science-fiction like structures called nanoparticles and quantum dots that carry microscopic cargoes of cancer fighting drugs and deliver and dispatch them directly to the cancer cell, and chemical tags that make potent drugs smart bombs that zero in on and kill only cancer cells.

Drug discovery scientists are developing drugs that kill cancer directly as well as drugs and compounds that remove the cellular barriers to cancer cell death. These agents block and silence the cellular signals that promote cell growth or dampen an immune response to cancer. Agents, such as PD-1 and PD-L1, developed by Drs. Drew Pardoll, Suzanne Topalian and Julie Brahmer, make cancers vulnerable to an immune attack and are finding broad success in several tumor types.

Moreover, many of these new drug studies shift the paradigm away from the highest tolerable dose, to non-toxic, low-dose target-ed treatments that reprogram cancer cells and destroy tumors with little or no side effects for patients. Dr. Charles Rudin is directing clinical studies of a new targeted drug combination that reverts deadly lung cancer cells back to a normal state but also makes the tumors more responsive to standard drug treatments. In addition, natural compounds, such as sulforaphane, derived from broccoli sprouts, and extracts from the pomegranate fruit and muscadine grapes are being studied for their ability to prevent cancers.

Today, cancer drug discovery expert and Chemical Therapeutics Program leader Dr. Michael Carducci is working with Drs. Michelle Rudek, Nilofer Azad, and David Cosgrove to align the center’s Phase I clinical trials program with personalized cancer medicine. Unlike 40 years ago when drug studies were organized by cancer type, more and more they are being designed around the specific molecular characteristics of tumors and have patient mixes with many different tumor types. “Now, we can get genomic information on every patient’s cancer, we need to study drugs in the populations they are likely to help—those with the genetic alterations targeted by a drug,” says Kimmel Cancer Center Director Dr. William Nelson. This new model is providing greater access to new drugs for all patients, and particularly for patients with advanced cancers unlikely to respond to standard therapies.

THE TIME IS NOW – CONNECT WITH US
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BONE MARROW TRANSPLANT

THE KIMMEL CANCER CENTER has a rich history in developing and improving bone marrow transplantation. Dr. George Santos was one of the first physician-scientists at the Cancer Center. Many of the transformative advances made in bone marrow transplantation as therapy for cancer and other diseases can be traced to his early research.

Dr. Santos was working in the armed services research laboratories using animal models to study harmful effects of radioactivity and found that some mice exposed to lethal doses of radiation could be saved if they received transplanted bone marrow from a healthy mouse. This observation provided the background for studying if destroying the bone marrow and replacing it with new marrow from a healthy donor could cure patients with diseased bone marrow. In one of the first examples of bench to bedside cancer research, Dr. Santos performed one of the world’s first human bone marrow transplants on a young man with leukemia in 1968 before our Cancer Center had even officially opened its doors.

In these early days, bone marrow transplantation was fraught with serious immune complications, the most serious of which was graft vs. host disease (GVHD). In this life threatening complication, the donor marrow, which contains the donor’s immune cells, recognizes its new host, the patient, as a foreign invader and launches a potentially lethal attack against vital tissues and organs. Experts attempted to limit immune complications by using donors who were a near perfect match to patients. For decades, bone marrow transplantation could only be safely performed between siblings who both inherited the same two sets of genes from their parents. It occurred more rarely, but a large, national registry, united some patients with unrelated donors, who were, by chance, near complete matches. Only about half of patients who needed transplants had matches, and patients of certain ethnicities, such as African-Americans, could rarely find matches in unrelated registries. Moreover, even in these so-called “matched” transplants, the clever immune system recognized the switch and GVHD still frequently occurred.

Dr. Richard Jones, a student of Dr. Santos’ and his successor as director of Bone Marrow Transplantation, worked with other Kimmel Cancer Center scientists to further refine bone marrow transplantation and made the potentially curative therapy safer for patients. Pioneering discoveries led by Johns Hopkins investigators involved developing technologies to remove the culprit of GVHD, immune cells called T cells. It proved to be a delicate balance as these T cells, while at the crux of the dangerous side effects, also attacked tumor cells. The challenge was to remove the precise number of T cells to stave off GVHD but leave enough behind to maintain the anticancer effect they provided.

Drs. Ephraim Fuchs and Leo Luznik built upon the earlier work of Dr. Santos and the Cancer Center’s first director Dr. Albert Owens and found that high doses of cyclophosphamide, a drug commonly used to treat patients prior to transplant, could limit GVHD without hampering antitumor activity. This discovery prompted the use of the drug after transplant and led Kimmel Cancer Center researchers to pioneer a new type of bone marrow transplant, known as haploidentical or half-identical transplants. In this new type of transplant, almost all parents, siblings, and children of patients, and sometimes even aunts and uncles, nieces and nephews, half-siblings, and grandparents or grandchildren can safely serve as donors. It is considered one of the formative innovations in the field, making it possible for almost every patient who needs a bone marrow transplant to have one. Since pioneering the therapy, our experts have performed more than 500 half-matched transplants for adult and pediatric patients with blood cancers.

Our bone marrow transplant researchers continue to master the science and make refinements so that what was formerly one of the
most toxic and intensive forms of cancer therapy can now be delivered on a largely outpatient basis. 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 non-cancerous diseases, such as sickle cell anemia. More recently, a revolutionary study uses half-matched transplants to improve the effectiveness and safety of solid organ transplants with living donors. 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. This important work has already conquered the transplantation barrier — rejection — and what they learn could be applied to all solid organ transplants. Further, it facilitates the research being done in regenerative medicine where work to grow transplantable tissue and organs would ultimately be of no clinical use without the means to successfully and safely transplant them into humans.
PERSONALIZED CANCER MEDICINE

The understanding that cancer is a genetic disease caused by a series of alterations to DNA is considered one of the most significant advances in cancer research, and it was revealed, in large part, by pioneering discoveries amassed over the last four decades at the Johns Hopkins Kimmel Cancer Center. These findings are driving personalized cancer medicine forward, providing the critical information needed to develop targeted therapies directed at the unique cellular characteristics of each patient’s cancer.

Within the next few years, all cancer patients at the Kimmel Cancer Center will have their tumors analyzed to reveal the unique combination of molecular and cellular alterations driving their cancers. Because we can now quickly obtain genomic information on every patient’s cancer, our scientists can begin to redefine how clinical trials are conducted, testing drugs on the populations they are likely to help—those with the genetic and epigenetic alterations targeted by the drug—while sparing patients we can now determine will not benefit from a drug, the risk and adverse affects of treatments that will not work. Already in development are personalized cancer vaccines, targeted drug therapies, individualized cell therapies and drug delivery methods, and individualized gene-based tests that not only detect cancer but monitor, in real time, the effectiveness of treatments. Using our pioneering scientific discoveries to determine which treatments and screening interventions will work best for each patient is already beginning to improve treatment outcomes, and in the not too distant future will be used to thwart cancers before they develop and slash the cost of drug discovery.

Central to these monumental advances is a clinical sequencing laboratory, directed by Dr. Vasan Yegnasubramanian. The laboratory is focused on translating genetic and epigenetic research and findings into clinical tests that will guide cancer diagnosis, risk classifications, and therapy. The Kimmel Cancer Center’s strength in translational medicine has uniquely positioned it to bridge the research laboratory and the clinic so that these advances can make their way more quickly to patients. There are few places that have the human assets of the Kimmel Cancer Center with clinical experts, laboratory medicine experts, and genomics experts all working together to figure out how to move this science and technology forward to ensure, through personalized cancer medicine, that the right treatments get to the right patients at the right time.

Our strength in laboratory and clinical science placed our Cancer Center on the cutting edge of cancer discovery 40 years ago. This excellence continues today through the promise of personalized cancer medicine and the most transformative progress in the history of cancer medicine.
THE DEPARTMENT of Radiation Oncology and Molecular Radiation Sciences received individual departmental status with Dr. Theodore DeWeese selected as director in 2003. However, laboratory and clinical research programs in radiation oncology have been, from the onset, an integral part of the center’s cancer programs. From futuristic radiolabeled “magic bullets,” and knifeless stereotactic surgery in the 1980s, and radioactive seeds in the 1990s, to proton beam therapy and computerized data mining systems in the 2000s, it has been, and continues to be, on the cutting edge of cancer research and treatment.

Radiation oncology is a unique and complex field that depends upon and artfully unites physics, engineering, and medicine. State-of-art technology and advanced machines are used to plan and deliver care that is based on the intricate biologic underpinnings of cancer.

Among the trailblazing research and treatment innovations is a data-mining system called “Oncospace” that stores data on all previous patients and uses advanced computer technology to cull this information and apply it to improve the treatment of new patients. It represents one of the first demonstrations of how large data warehouses of patient information collected from previously treated patients can be used to make individualized treatment decisions for new patients.

Scientists also have pioneered new research methods. They have constructed downsized versions of the equipment used to treat patients and are performing never before done animal models to study the best ways to target radiation-based treatments so they destroy tumors but prevent damage to normal cells.

The newest form of targeted radiation therapy is Proton therapy. With its precision and safety, it has become the standard of care for pediatric tumors, tumors of the brain, spine and eye, lung, head and neck, and bone (sarcoma) cancers. With approval for a proton beam facility at the Kimmel Cancer Center Washington, D.C. campus, investigators are set to perform some of the first evidence-based research on proton therapy, potentially becoming the global leaders in the study of cellular response to proton therapy.

Other firsts include a new technology that makes it possible to effectively kill cancer cells without causing harm to surrounding healthy tissue and organs. Radiation sensitizers targets and kills cancer by preventing cancer cells, and only cancer cells, from repairing radiation damage. Moreover, this platform technology can be adapted to any cancer type.

Radiation Oncology scientists also are leading studies of a combined imaging/treatment approach at the molecular level that allows researchers and clinicians to see inside cancer cells and view them as they are being treated. They are using ultra-tiny structures, called nanoparticles, filled with an anticancer drug that also sensitizes cancer cells to radiation and a cell-imaging agent. The nanoparticle is targeted specifically to cancer cells so that it zeroes in on and delivers its anticancer payload only to tumors and also allows investigators to track and monitor the drugs journey and affect against its cancer target.

Radiation Oncology and Molecular Radiation Science experts are leading the way, inventing new systems and technologies that are revolutionizing the nature and delivery of radiation treatment. This pursuit of excellence has resulted in new discoveries that are transforming cancer care and advancing the safety and effectiveness of radiation delivery.

FOUR DECADES OF DISCOVERY
JIMMY BERENTS can tell the history of some of the research advances made at the Kimmel Cancer Center through his personal experience with cancer. He believes he is alive today because of this progress.

Jimmy was just three-years-old, in 1996 when he was first diagnosed with a rare form of lymphoma, known as anaplastic large cell lymphoma. Under the care of young pediatric cancer researcher and clinician Dr. Donald Small, Jimmy received a yearlong regimen of chemotherapy. Unfortunately, the cancer returned, and this time Dr. Small recommended a stem cell transplant. It was a Kimmel Cancer Center invention that made stem cell transplants possible, and this advance in treatment kept Jimmy’s cancer in check for many years.

Then, in August 2012, two days before he was to leave for college, Jimmy learned that his cancer had returned. He and his parents made the familiar trip to the Johns Hopkins Kimmel Center. Dr. Small, now the Director of Pediatric Oncology, greeted them with a hug and words of optimism. He told Jimmy and his parents about progress that had been made against the cancer since he was last treated. The improved therapy included a shorter regimen with standard anticancer drugs, but in addition, new-targeted drugs that shut down the cellular alterations they now knew from years of research contributed to the development and growth of lymphoma.

Jimmy is currently receiving this new, improved treatment. When asked if he was bitter about his lifelong battle with cancer, he answered with an emphatic, “No,” adding, “I consider myself very fortunate. I am so grateful for Dr. Small and Johns Hopkins. They saved my life three times.”