Giants of Cancer Care™

INAUGURAL CLASS ALBUM

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FOREWORD

The concept for an annual recognition program for oncologists has been germinating in my mind for a long time. My roots in medical publishing stem from a rich family history in the publishing industry that has created in me an innate passion for professional education. My father built a successful career in medical publishing that spanned several decades, exposing me at an early age to the life and career struggles of the practicing physician and their ever-changing need for clinical information, and instilling in me a long-standing respect for all medical professionals.

During a 30-year career spent developing a diverse platform of print and digital publications, live accredited meetings, and market research within the healthcare marketplace, I have been fortunate to have worked with some of the best physicians and nurses in the field. Many are world-renowned physicians who have been celebrated as heroes for their contributions to general medicine, such as cardiology, surgery, or primary care medicine. However, I have long felt that oncologists—especially those who are enrolling patients into clinical trials and treating patients in the community—are often overlooked for their tireless efforts to eradicate cancer, perhaps due to the stigma and fear associated with the disease.

It is for this reason that we have created a new international awards program, "Giants of Cancer Care," to honor the oncology specialists whose work has helped save, prolong, or improve the lives of the millions of patients who have received a diagnosis of cancer. Our goal is to recognize and celebrate the individuals who have achieved landmark successes in the field of oncology, while also helping to support the efforts of promising young scientists and clinicians who are just beginning their careers.

An advisory panel of eminent oncologists selected 12 honorees from different oncology specialties to represent the inaugural class of Giants. This commemorative album profiles the 12 recipients of the 2013 Giants of Cancer Care award. The honorees fall into two broad categories: "Pioneers," who have made their mark through a large body of work, and "Innovators," who have made significant contributions within the past 10 years.

Please join us in honoring these leaders and in celebrating their remarkable achievements in the oncology community that have transformed cancer from a deadly disease into a story of hope, survivorship, and ultimately cure.

Mike Hennessy
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Pioneer in our understanding of the biology and treatment of breast cancer

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2013

Bernard Fisher, MD

BREAST CANCER

Bernard Fisher, MD

University of Pittsburgh

When Bernard Fisher, MD, first became involved in breast cancer research, the only treatment option available to patients was the radical mastectomy, a horribly disfiguring surgery that had been the undisputed standard of care since the late 1800s. In 1894, William Halsted developed the procedure for the radical mastectomy, which involved removing the entire breast, the underlying chest wall muscles, and all of the underarm lymph nodes. At that time, cancer was widely thought to be a local disease that spread in a predictable way, and so it was believed that extensive surgery could theoretically remove all of the cancer cells and cure the patient. Despite a lack of reproducible data to prove this theory or the success of the radical mastectomy, Halsted's procedure remained the unequivocal treatment for breast cancer for nearly 100 years. The only thing physicians disagreed about was whether or not the surgery was sufficiently radical.

In the 1960s, Fisher and his brother, Edwin Fisher, MD, a world-renowned breast cancer pathologist, conducted laboratory experiments that questioned the Halstedian view of metastasis. Through these experiments, which were conducted on animals, they discovered that tumor cells spread via the lymph nodes and the bloodstream, indicating that breast cancer is a systemic disease, not a local one as had always been theorized.

Over the next several decades, Fisher conducted laboratory investigations and prospective clinical trials that systematically advanced the understanding of tumor biology, resulting in an improvement in the standard of care for women with breast cancer. Fisher's research proved that radical mastectomy is no more effective than the less extensive total (simple) mastectomy, which limits the surgical procedure to removal of the breast only.

Fisher's subsequent investigations showed that lumpectomy followed by breast irradiation is as effective as modified radical mastectomy (total mastectomy plus the removal of the underarm lymph nodes). Then, in the early 1970s, his research revealed that adjuvant chemotherapy administered after surgery can improve the survival of women with early-stage breast cancer. In another study, he demonstrated that the oral hormonal therapy tamoxifen could reduce the risk of breast cancer recurrence and improve survival, and also that tamoxifen could reduce the incidence of breast cancer by nearly 50% when given to healthy women at high risk for developing the disease.

Step by step, Fisher's research launched the breast cancer community into the modern era of new, promising treatment strategies that improved patient outcomes. The most important aspect to remember, though, is that each of these advancements was supported by laboratory research and clinical evidence.

In Data We Trust

Something that may not be readily understandable to the modern reader is that clinical trials as we know them today have not always been the answer to clinical questions. The first randomized clinical trial, conducted by Austin Bradford Hill on the use of streptomycin for tuberculosis, took place more recently than one might think, in 1948. Before then, anecdotes were the main source of information informing treatment strategies. According to Norman Wolmark, MD, current chairman of the National Surgical Adjuvant Breast and Bowel Project (NSABP), who was a protégé of Fisher's for decades, "Clinical trials were not yet in the mainstream, so Bernie was certainly a pioneer."

Early on in his medical career, Fisher's interest in research was initiated by his work in the late 1940s with Julius M. Rogoff, MD, who was professor of Endocrine Research at the University of Pittsburgh, Pennsylvania, and then from 1950 to 1952, when he was under the tutelage of Isidor S. Ravdin, MD, chairman of the Department of Surgery and director of the Harrison Department of Surgical Research at the University of Pennsylvania. When the first clinical trial was being conducted, Fisher was studying liver regeneration, hypothermia, transplantation biology, and biology of metastasis in the laboratory setting. He was invited in 1957 to discuss the creation of the organization that would become the NSABP. As a result of his laboratory experience, Fisher was familiar with the scientific method, and he consequently viewed clinical trials with proper controls, statistics, and other elements as the appropriate venue for evaluating alternative hypotheses such as the worth of radical mastectomy, and then the worth of lumpectomy.

According to Daniel A. Osman, MD, who just recently retired from his 30-year tenure as the director of the Miami Breast Cancer Conference—a conference organized in large part due to Fisher's groundbreaking data—Fisher had a credo, "In God we trust; all others require data," which was a radically new viewpoint then.

Driven by Truth

Not only was Fisher challenging the status quo, but he was also admitting that surgeons did not have all the answers for treating breast cancer. Another of his colleagues, Jay R. Harris, MD, chair of the Department of Radiation Oncology at the Dana-Farber Cancer Institute, said that "One of his [Fisher's] fundamental contributions globally was [that] he was an American surgeon who got up at meetings and said, 'We don't know the answer to this question. We need to do a clinical trial to answer it.' Even to this day, surgeons are not prone to saying, 'We don't know the answer.' And in the 1960s, it was unheard of."

As one can imagine, this practice did not make him particularly popular among his colleagues. Harris said, "He was practically vilified by his specialty initially." Osman also recalled, "When he started with lumpectomies, the surgeons of the United States hated him for it." Luckily for the breast cancer community, Fisher was not to be dissuaded by the negative feedback. According to Wolmark, Fisher "was driven by applying the scientific method to clinical problem solving. He was driven by the truth. He was driven by the value of the data rather than by the value of opinion."

It was his devotion to discovering the scientific truth that made it possible to persevere with cutting-edge research, which takes a special kind of personality. "There's no doubt he has a big personality, and that's what was required. He made such fundamental changes in the thinking of American physicians in getting them to do clinical trials. The ego strength that he had to have to face all that pushback and rejection, to keep on going…I could see somebody calling him brash, but that's not the part of it that I think is key to the man. He had a vision for advancing care for breast cancer patients, and he was relentless in pursuing it," recalled Wolmark.

In addition to a drive for truth, a facet of Fisher's personality that has enabled him to succeed as a clinical scientist is the ability to reformulate his own hypotheses when needed. Wolmark reflected that "No matter how enamored he was of a hypothesis, the minute the data indicated that the hypothesis was not supported, it was abandoned, which is absolutely remarkable. No matter how much time and effort and intellectual commitment there was, if the data showed that the hypothesis was not supported, Fisher abandoned the resarch." Anyone who has devoted hours and energy to a difficult cause knows how hard it is to let go of a theory when it is proved to be incorrect, and it is rare indeed to find someone who has the strength to relinquish that intellectual attachment and move on.

Setting the Stage for Change

Fisher also challenged his colleagues to be objective. According to Wolmark, "His standard

admonition to the membership of the NSABP was, 'When you cross the threshold into this room, you cease to be a medical oncologist or a surgeon or a radiotherapist. You become a clinical investigator, and you leave your biases outside." It may have been a difficult expectation to live up to, but Fisher gave this NSABP membership all of the tools they needed for success. "Bernie provided a unique environment. Aside from the clinical trials, we had a very active bench research lab, and there was a seamless interface between the lab and the clinical trial process, where hypotheses developed in the lab could be tested globally in a clinical trial. We weren't certain where this was leading, but we knew that, wherever it was going, that the treatment of breast cancer would be inexorably and irreversibly changed," continued Wolmark.

Decorated for Service

Fisher's tenure at the NSABP spanned 47 years, as a founding member in 1958 and as chairman from 1967 to 1994.

He is currently a Distinguished Service Professor of Surgery at the University of Pittsburgh. He lectures occasionally and is writing a historical account of his 50+ years of laboratory and clinical research related to cancer. Throughout his medical career to date, his contributions have been recognized by countless awards, chairs, and appointments, including appointments by Presidents Carter and Reagan, and he has participated in both national and international committees and panels devoted to furthering the science and treatment of breast cancer.

The breast cancer community is very fortunate to have such a living legend as a champion of its cause, and perhaps owes a thank you to his wife, three children, and five grandchildren for their willingness to share him with this cause. His clinical trials have provided the evidence to transform the way breast cancer is viewed, treated, and how it can be prevented, and Fisher has provided a legacy whereby alternative hypotheses can be formed and rigorously tested. As Dr. Wolmark asked, "How many of us can say that we left the state of the art in far better shape than we found it?" Fisher may be one of the few.

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Pioneer who discovered the molecular basis of colorectal cancer

Bert Vogelstein, MD

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GASTROINTESTINAL CANCER

Bert Vogelstein, MD

Johns Hopkins Medicine

Bert Vogelstein had no idea that a young girl would start him on a journey that would forever change humanity's understanding of cancer. He was an intern fresh out of medical school when the girl's parents brought their daughter to Johns Hopkins to find out why she'd grown so pale and started bruising so easily. The tests revealed cancer. When Vogelstein delivered the news to the stunned parents, they asked how and why a preteen could develop cancer.

Decades later, Vogelstein can still remember how terrible it was to be unable to provide an answer. "I just threw up my hands and said, 'I don't know. Nobody knows. It's just this total black box, this thing that just strikes people randomly, when they shouldn't be struck.' And, right then and there, it became clear to me that if I wanted to spend my life on a puzzle, on a problem that I could apply my skills toward, that was going to be a good one," he recalled.

Vogelstein's epiphany launched a lifelong hunt for the root causes of cancer, a hunt that unveiled in 1989 the most important cancer suppressor gene, and went on to unearth much of what we know about the mutations found in many tumor types.

Vogelstein has published more than 450 papers since 1976, and those papers have been cited more than 200,000 times—a tally that illustrates their incredible impact. Vogelstein's work not only launched a wave of genetic research around the globe, but also laid the groundwork for today's era of targeted assays and therapeutics.

Choosing a Path

Vogelstein was born on June 2, 1949, in Baltimore, Maryland, and raised in the city, which then as now saw much of its scholarly life dominated by the various arms of Johns Hopkins University.

He came from a long line of rabbis, starting with his grandfather and going back 13 generations. His father, however, was a lawyer, as were many other men in his family, and, law—not medicine—was what appealed to Vogelstein in grade school. It wasn't until high school that he developed a love of science and mathematics that determined the course of his life.

He left Baltimore after high school for the University of Pennsylvania in Philadelphia, majoring in math and graduating summa cum laude. (He also, perhaps to appease his rabbinical ancestors, won the school's Rosenbaum Award for undergraduate work in Semitic languages and literature.)

After briefly pursuing graduate studies in mathematics, Vogelstein felt called upon to pursue a career path that would help others more directly. Vogelstein returned to Baltimore to study

medicine at Johns Hopkins, receiving his medical degree in 1974 and remaining at Johns Hopkins for his internship and pediatrics residency. He was serving that residency, wondering what he wanted to do with his professional life, when he diagnosed that little girl's cancer and struggled to explain it to her parents.

He soon undertook a post doctoral fellowship at NCI, where he learned the basic principles of molecular biology, and then returned to Johns Hopkins, where he has remained ever since.

"I still had to decide whether I should continue to see patients and practice medicine, or devote all of my energies to research, so I tried doing both," he said. "I found myself during the days seeing patients and during the nights going to the lab and trying to do a little bit of research. And I found at night I was really happy. I felt stimulated. I couldn't wait to get to the lab at night so I could start experiments."

Embarking on a Research Road

Vogelstein's is one of the great careers in all of medical research—and it nearly ended before it began. The first two grant proposals he ever submitted to the National Institutes of Health (NIH) were rejected.

"I was getting really worried, because there's only a limited time you can go in science without getting funded, or else you're going to be driving a cab or something," he said.

The Tumor Suppressor Gene Theory

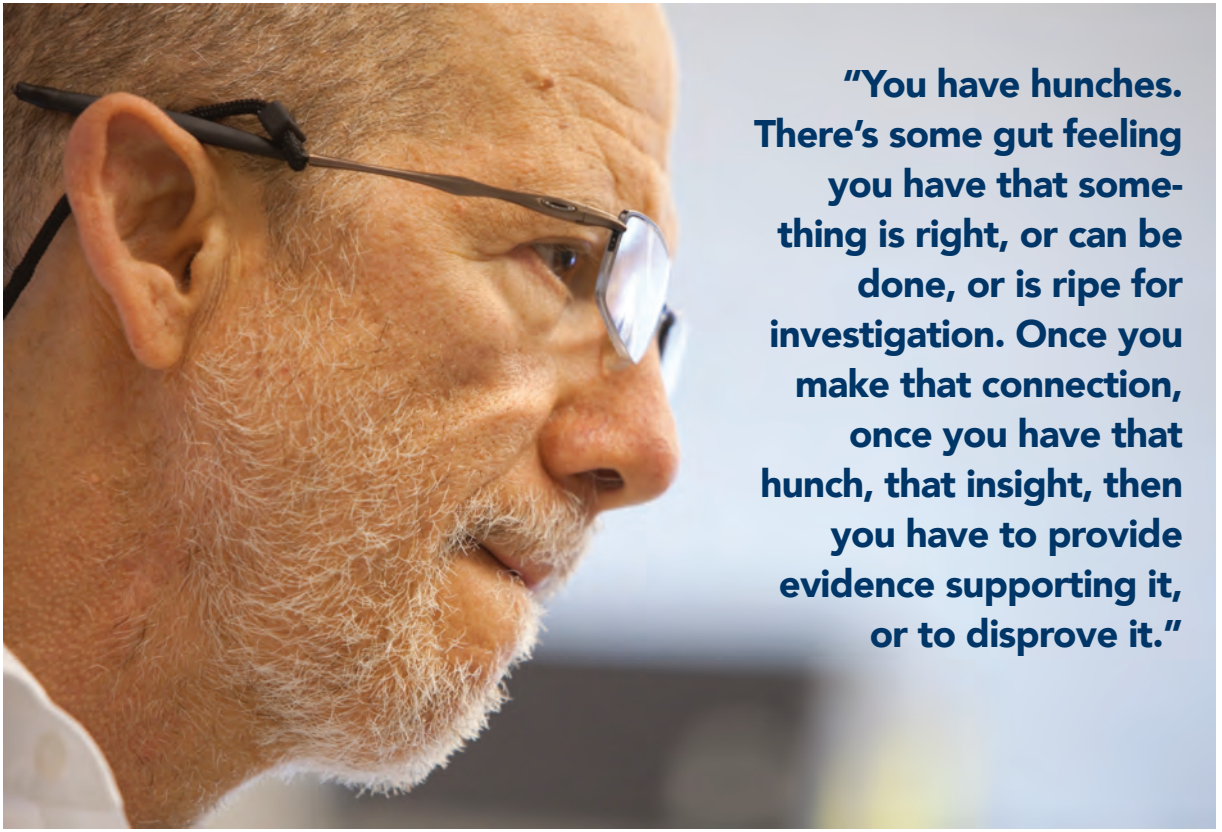
But once money began flowing into his lab, Vogelstein focused his attention on colon cancer. He amassed a large collection of tissue samples at each step in the progression from fully healthy to malignant carcinoma, and found that colon cancer, rather than developing uniquely in each patient, went through similar genetic steps in many patients.

In a 1988 article published in *The New England Journal of Medicine (NEJM)*, Vogelstein posited that the progression required two different types of genetic mutations: (1) the activation of oncogenes (such as the *Ras* gene that had already been identified); and (2) the inactivation of tumor suppressors.

The existence of tumor suppressors—genes that prevent cells from multiplying too quickly—had always struck Vogelstein as logical, particularly in light of the observation that tumor cells were almost always missing specific chunks of DNA that were present in normal cells.

The tumor suppressor theory also explained why cancer is relatively rare in the general public despite the frequency of cell mutations: most people have two copies of each tumor suppressor (one inherited from each parent), and thus would need both copies incapacitated before developing serious problems.

The theory made sense, but it suffered from one big problem. Neither Vogelstein nor anyone else had ever identified a tumor suppressor gene. Given technology at the time, there was no way scientists could scour the entire human genome for tumor suppressors, but Vogelstein realized he didn't need to cast such a broad net. He looked instead at the far smaller chunks of DNA that tumors often lacked, reasoning that some of the



relatively small number of genes therein must be tumor suppressors.

Zeroing in on *TP53*

Vogelstein found his quarry almost immediately and, just a year after his *NEJM* article, he published evidence that *TP53*—a gene long thought to stimulate rather than inhibit cell growth—was a tumor-suppressing gene. Indeed, Vogelstein's paper noted that both copies of *TP53* were always missing or mutated in colon cancer cells.

Further research by Vogelstein and his team revealed that *TP53* and its mutations play a similar role in many human cancers. In fact, subsequent research has shown that tumor growth does not hinge upon one particular

mutation of *TP53*. A mass of analyses that was initiated by Vogelstein's paper has found more than 20,000 possible different mutations, many of which reduce or eliminate its tumor-suppressing qualities. *TP53* is now recognized as the most commonly mutated gene in human cancers, virtually operating as their common denominator.

All of these discoveries conformed to what Vogelstein had hypothesized before the first tumor suppressor had been found, a fact that Vogelstein believes to illustrate how science really works. "You have hunches. There's some gut feeling you have that something is right, or can be done, or is ripe for investigation. That's not methodical at all, or analytical. The analytical part only comes later," he said. "Once you make that connection, once you have that hunch, that insight, then you have to provide evidence supporting it, or to disprove it. That's an execution process, rather than a discovery process per se."

Finding More Genes in Colon Cancer

After documenting the function of *TP53*, Vogelstein joined forces with Kenneth W. Kinzler, PhD, a onetime grad student in Vogelstein's lab who is now a fellow professor at Johns Hopkins. Working together, the researchers identified additional genes involved in colon cancers, genes such as *APC*. Vogelstein and Kinzler showed that mutations of *APC* occurring in single colorectal epithelial cells start the entire sequence of changes that lead from healthy tissues to adenomas, the benign tumors.

The pair also identified genes such as *PIK3CA*, which, when mutated, are responsible for the next step in the process, creating malignant tumor cells from the adenoma cells.

"I still had to decide whether I should continue to see patients and practice medicine, or devote all of my energies to research, so I tried doing both."

All told, Vogelstein and his protégé have documented much of the genetic activity surrounding a host of cell mutations in the colorectal tract, including how patients with inherited *APC* mutations develop a disease called *familial adenomatous polyposis* and grow hundreds or thousands of benign tumors in their colons and rectums.

Improving Early Diagnosis and Forging Ahead in Cancer Genetics

Much of Vogelstein's recent research has focused on making early diagnosis tools less invasive. For example, his lab has developed sensitive blood tests that are now used in the clinic to identify patients with inherited mutations in genes known to be involved in colorectal cancer.

Vogelstein has also worked to create therapies that exploit the knowledge of cancer genetics that researchers like him have recently uncovered. He and his team have used an oxygen-hating, soil-dwelling bacterium to kill tumor cells—which often develop faster than their blood supply, and are thus low in oxygen—in animal cancers. (This last concept also draws heavily on the work of the

cancer pioneer Judah Folkman, MD, who uncovered much of what we know about how tumors recruit blood vessels to spur growth.)

Vogelstein has also used new tools to speed up his exploration of cancer genes. Beginning in 2004, Vogelstein and Kinzler, working with Victor Velculescu, MD, PhD, and Nickolas Papadopoulos, PhD, and others in their group, began to perform large-scale experiments to identify mutations throughout the human genome. They were the first to perform exomic sequencing, the determination of the sequence of every protein-encoding gene in the human genome. The first analyzed tumors included colon, breast, pancreas, and brain. In the process of analyzing protein-encoding genes within cancers, Vogelstein and his colleagues discovered several novel genes that play a pivotal role in cancer, such as *IDH1, IDH2, ARID1A, ARID2, ATRX, DAXX, MLL2, MLL3, CIC,* and *RNF43*.

That work has enabled Vogelstein and his team to create and publish genomic maps of cancer for breast, colon, and many other cancers. "Cancer is, in essence, a genetic disease," he said. "Mutations are just clocks. Every time a cell divides it mutates at a low rate, and those changes are recorded in the cancer genome."

Vogelstein still has much to discover before he will be able to give a fully satisfactory answer to questions such as those asked by the parents of that little girl all those years ago, but he has gotten far closer.

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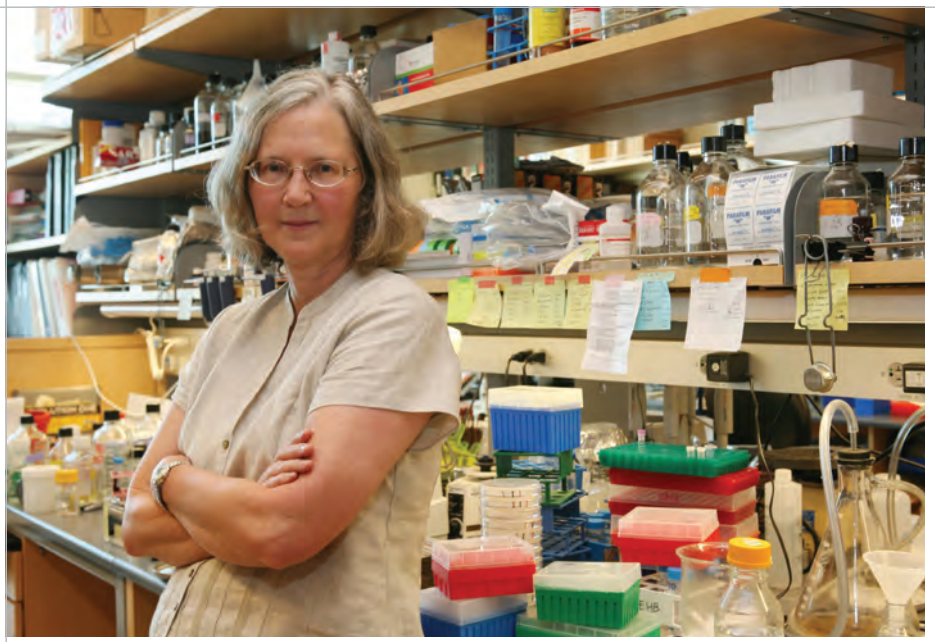
Innovator in the genetic composition and function of telomeres



Elizabeth H. Blackburn, PhD

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GENETICS

Elizabeth H. Blackburn, PhD

University of California, San Francisco

Nobel laureate Elizabeth H. Blackburn, PhD, who received the Nobel Prize in Physiology or Medicine in 2009 for the discovery of how telomeres (the eukaryotic ends of chromosomes) are protected by the enzyme telomerase, has undoubtedly contributed an immense amount to the understanding of cancer biology, and in particular, telomere biology.

An Early Passion for Science

Science and medicine are certainly in Blackburn's blood. Her parents were family physicians, and her maternal grandfather and great-grandfather were both geologists. Regarding her parents, Blackburn writes in her Nobel biography, "From them I imbibed a sense of the importance of serving people kindly and as well as one can. I continue to believe that bioethics, done well and underpinned by the best available scientific evidence, can be an important part of our consideration, as a society, of the impact on people of scientific research in the biological sciences and medicine."

Born in 1948 in Tasmania, Australia, Blackburn spent her early years developing her love for biology. She recalls, "Perhaps arising from a fascination with animals, biology seemed the most interesting of sciences to me as a child. I was captivated by both the visual impact of science through science books written for young people, and an idea of the romance and nobility of the scientific quest…By the time I was in my late teens, it was clear to me that I wanted to do science."

Blackburn attended a girls' school for much of her childhood, where several schoolteachers had a profound impact on her interest in science. She recalls, "Growing up, three of my schoolteachers in particular encouraged my interest in biology and chemistry and mathematics, not least by letting me know that they believed in my abilities to succeed in these areas—Nan Hughes, Jenny Phipps, and Len Stuttard."

Blackburn then attended the University of Melbourne, Australia, from which she graduated in 1970 with an honors degree in biochemistry. She then completed her master's degree in 1972, studying the metabolism of glutamine in the rat liver before beginning her coursework and research for her PhD from the Laboratory of Molecular Biology at the University of Cambridge, England, under Frederick Sanger, PhD. While at Cambridge, Blackburn carried out sequencing of regions of bacteriophage phiX 174, a small single-stranded DNA bacteriophage, and graduated with her PhD in 1975.

Balancing Family and Work

After receiving her doctoral degree, Blackburn traveled across the ocean to the United States, where she completed a postdoctoral fellowship at Yale University under Joseph G. Gall, PhD, attempting to sequence DNA found at the terminal regions of "minichromosomes" in the ciliated protozoan *Tetrahymena thermophila*.

After finishing her postdoctoral research in 1977, Blackburn and her husband John Sedat, PhD, moved to San Francisco, California, where she accepted a research track position in the Department of Biochemistry at University of California, San Francisco (UCSF), during which she studied *Tetrahymena* telomeres. In 1978, only months after starting at UCSF, Blackburn was offered and accepted an assistant professor position at University of California (UC), Berkeley, where she readily moved her still-new research laboratory.

In 1986, Blackburn was promoted to full professor at UC Berkeley, the same year that her son Benjamin was born. In order to balance her family and work time, Blackburn made the difficult decision in 1993 to move her laboratory back to UCSF and become part of the Department of Microbiology and Immunology. It is there that Blackburn has remained ever since.

Today, Blackburn still credits her family with helping her achieve success and delve deeper into her scientific inquiry. "My husband, himself an accomplished scientist, has always urged me to dig deeper into myself and find the reserves of strength I might not have tapped — his encouragement in this way has helped me through years of doing science. Our son Ben inspired me to try to find ways of combining family and science, something that I have tried to convey to young scientists making their careers," Blackburn writes.

Path to the Nobel Prize

While in Joe Gall's lab at Yale University, Blackburn first chose to work with *Tetrahymena* due to the presence of abundant short linear chromosomes; this represented a system in which she could readily address her question of what protects the ends of chromosomes. By 1976, Blackburn was able to deduce the (TTGGGG)n sequence that is tandemly arrayed on the termini of *Tetrahymena* chromosomes, and in the late 1970s and early 1980s she worked on extrapolating these data to other species, including ciliated protozoans and yeast linear plasmids.

Once she established her own laboratory at UCSF and then at UC Berkeley, Blackburn began her work to identify telomere-associated proteins, after becoming curious about how the TTGGGG repeats that she had previously identified were placed on the ends of the chromosome. By 1980, Blackburn showed that *Tetrahymena* telomeres were encapsulated in protective proteins that did not include histones or nucleosomes, which package the majority of DNA in a cell. Throughout the early 1980s, Blackburn was able to accumulate evidence that an enzyme, now known as telomerase, could extend the telomeres on the ends of chromosomes.

Throughout the 1990s, the function of telomerase, in which the enzyme provides a template

from which DNA repeats are added to the ends of the chromosomes, was deduced. Through her research, Blackburn was able to find that without telomerase, V cells, which can normally divide indefinitely, become mortal and can divide only a finite number of times before their telomeres were depleted. This finding, therefore, helped Blackburn define the function of telomerase.

In 2009, Blackburn, along with Carol W. Greider, PhD, and Jack W. Szostak, PhD, was awarded the Nobel Prize in Physiology or Medicine for the discovery of how telomeres are protected by telomerase. In her Nobel lecture, Blackburn described telomerase as "this beautiful creature, prancing and dancing around the DNA...It's very elaborate, it's very dynamic, it's very beautiful, all the molecular mechanisms that go on."

Pioneering Clinical Trials

Currently, Blackburn is researching how telomerase functions in cancer cells. Malignant human cancer cells generally have high levels of telomerase, enabling the cells to divide indefinitely while maintaining telomere length. By mutating the repeats that are added to the ends of chromosomes by telomerase, Blackburn's lab has been able to arrest malignant cell growth in model systems. In her Nobel lecture, Blackburn described this by saying, "We are turning the high telomerase activity of tumor cells back onto the cells to cause cell death."

Through her methodical and careful research, Blackburn has contributed a wealth of information to the fields of molecular and cell biology. By extrapolating her findings on telomeres in model systems, Blackburn has been able to extend telomere biology to pioneer clinical trials in a variety of cancers, though results are yet to be reported. Additionally, Blackburn and her colleagues are investigating how telomerase impacts age-related diseases.

Throughout her career, Blackburn has been honored with numerous awards, including the Albert Lasker Award for Basic Medical Research (2006), *TIME* Magazine's 100 Most Influential People in the World (2007), and the Nobel Prize in Physiology or Medicine (2009).

Blackburn also serves on multiple editorial boards and is active in several professional associations, including *Cancer Discovery*, *Cell*, *Aging*, Biomed Central Biology Image Library Editorial Board, and *Molecular and Cellular Biology*. She currently serves as a member of the California Legislature Senate Rules Committee Stem Cell Research Advisory Panel.

Blackburn is likely to continue her quest to unlock the secrets of telomere biology, which she sums up as "basic biological research on the molecular nature of telomeres and their maintenance mechanisms, from human life stories and their effects on telomere maintenance, to the impact of telomeres on health and disease."

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Pioneered a lifesaving treatment for testicular cancer

Lawrence H. Einhorn, MD

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GENITOURINARY CANCER

Lawrence H. Einhorn, MD

Indiana University

It was a once-in-a-career achievement, the medical equivalent of a walk on the moon.

By adding a single agent to a fledgling treatment regimen, Lawrence H. Einhorn, MD, transformed testicular cancer from a methodical killer of young men into a highly curable condition for many patients, including famed cyclist Lance Armstrong, whom Einhorn treated.

The medical oncologist had been on the faculty at Indiana University (IU) for only a year when he read about a promising early trial of cisplatin for the treatment of testicular cancer. He thought it would make sense to add the metal to a regimen that had also demonstrated some success in treating the disease: bleomycin and vinblastine.

"We did a phase II study in 1974, when the cure rate for metastatic testicular cancer in patients in their 20s and 30s was 5% to 10%," recalled Einhorn, now 71. "In my youthful exuberance, I was hoping the cure rate would go to 15% or 20%, but over 70% of study participants achieved complete remissions, all but 10% of them lasting. It's not often that the FDA will approve a drug based on a non-randomized, single-institution study. In this case, the results were so profound that it was hard not to be solidly convinced."

In the 40 years since, Einhorn, now a distinguished professor and Livestrong Foundation Professor of Oncology at the IU School of Medicine, has driven other major advances in the treatment of testicular cancer, coming up with a more effective and less toxic standard regimen and revealing important principles that are being applied to the treatment of other cancer types. At the same time, he has helped develop new treatment strategies for small cell lung cancer.

A Life-Changing Discovery

Einhorn's goal upon arriving at IU was to study cancers that were already somewhat responsive to chemotherapy, so that small changes in treatment might lead to big improvements in outcome.

In addition to small cell lung cancer, he focused on testicular cancer, initially using the regimen of doxorubicin, bleomycin, and vinblastine that had been developed for other applications at The University of Texas MD Anderson Cancer Center in Houston, where he had recently completed a fellowship.

Although the combination was useful, Einhorn was looking for something still more effective when, in 1974, he learned of a phase I trial of single-agent cisplatin that had sparked brief remissions in patients with testicular cancer who had previously been treated with chemotherapy. He thought the drug would work well with bleomycin and vinblastine, a pairing that was also developed at MD Anderson, in this case specifically for patients with testicular cancer.

"In 1974 or 2013, the principles of putting drugs together are the same," Einhorn said. "The drugs in the recipe all should have single-agent activity against cancer, different mechanisms, and different types of side effects. You need evidence of a synergistic effect that can be demonstrated in the lab, as was the case with vinblastine and bleomycin, and later with platinum and other drugs."

At the time, cisplatin was being used in cancers with no standard therapies, after patients had failed other regimens; however, it caused nausea, vomiting, numbness and tingling in the legs, kidney problems, and ringing in the ears before it could do much to fight disease.

Einhorn "figured out how to get around that" by hydrating patients with IV fluids before and during treatment, preventing accumulation of platinum in the kidneys. He also collaborated with pharmaceutical companies to study drugs that could work as antiemetics, including the first-in-class 5HT3 receptor antagonist ondansetron.

Those work-arounds, and cisplatin's success in treating testicular cancer, saved the heavy metal from extinction as a medical treatment, Einhorn said.

"Here we are 40 years later, and platinum is used in first-line chemotherapy for 10 different diseases," he said. "It's used more widely in more diseases than any single cancer drug, yet it almost never made it out of the gate."

Einhorn's trifecta with the regimen is a reminder, he said, that other landmark treatments may be waiting in the wings as investigators research new drugs, such as molecular targeted agents, to treat cancer.

"I wish that we had a drug like platinum in the other diseases I treat," he said, "but at least it shows you what is possible, and underscores the urgency of doing clinical trials, because if we're not looking at new drugs and new studies in other cancers, we're always going to be at the status quo."

Chipping Away at Testicular Cancer

Once the "Einhorn regimen" was standard, Einhorn trained translational researchers to help him refine therapy for testicular cancer. He also founded the Hoosier Oncology Group, a consortium of Midwestern oncologists committed to collaborating on studies.

With a strong team behind him, Einhorn led trials of treatments for testicular cancer.

In a phase III study from 1976 to 1978, Einhorn and colleagues demonstrated that the dosage of vinblastine routinely given to patients with testicular cancer could be lowered to reduce the incidence of low white blood cell count and neuropathy, with no reduction in the regimen's cure rate.

From 1978 to 1981, the group "challenged a basic dogma of oncology, that we had to give a long duration of therapy," Einhorn said. "Earlier studies gave vinblastine for two years of chemotherapy, even though patients progressed way before the two years were up. We did a phase III randomized trial in which patients in the control arm got two years of chemotherapy versus stopping vinblastine after 12 weeks in the experimental arm, and there was no difference in the cure rate."

But what about patients who were resistant to, or who recurred on, the Einhorn regimen? Einhorn and his colleagues tested a salvage therapy that combined just platinum and etoposide, and 25% of the patients studied were cured. "It was the first

time an adult tumor had been cured with a second-line therapy," Einhorn said.

From 1981 to 1984, the team followed up with a study substituting etoposide for vinblastine in the standard treatment regimen. The study made the Einhorn regimen "a historical footnote," he recalled, "because we showed we had fewer side effects with etoposide and a higher cure rate."

Then, an investigation considered shortening the duration of the new standard therapy. "We gave patients three courses of bleomycin plus etoposide plus platinum over 9 weeks versus four courses over 12 weeks, with the same cure rate," Einhorn said. "Platinum has cumulative side effects, so this was eliminating the most toxic course, the fourth one. Now, the majority of patients can be cured with just nine weeks of chemotherapy."

For patients who relapsed on the new standard regimen, Einhorn found that ifosfamide was effective; in fact, substituting ifosfamide for bleomycin in second-line chemotherapy reduced lung toxicity. Einhorn's work with the drug helped to move it toward FDA approval.

Finally, his team discovered a strategy for patients whose testicular cancer could not be cured with standard chemotherapy: high-dose chemotherapy with peripheral blood stem-cell transplant.

Continuing the Quest

These days, Einhorn, the married father of an adult son and daughter, remains immersed in the work that has captivated him for the last four decades. He spends two and a half days each week seeing patients who have testicular cancer, lung cancer, and "a smattering of rare diseases that don't fit into any organ type, like cancer primary site unknown."

He splits his remaining time between lecturing and attending conferences; designing and running clinical trials; and teaching interns, residents, and fellows. Einhorn reminds the students to interact with their patients, despite the distractions of modern technology.

"Doctors are turning their backs to patients and clicking away on their computer screens, typing while they are talking," he said. "That needs to be done, but I don't want us to lose the ability to communicate with patients and show our real concern for the struggle they are facing."

Einhorn's recent work in the fight against testicular cancer is focused on the long-term effects of therapy for the disease.

"Our pediatric colleagues have done a great job, with leukemias and sarcomas, of curing patients and then looking at what the late consequences of therapy are, what their prevalence is, how to predict them, and whether there are preventive strategies," Einhorn said, "and that's what we're focusing on now."

In addition, Einhorn and his colleagues continue to investigate new drugs for the treatment of testicular cancers that cannot be cured with existing therapies.

At the same time, they are continuing to study psychosocial aspects of testicular cancer. "This is a unique patient population we deal with," he said, "so we have a lot of collaborators who look at a variety of different aspects, including romantic relationships and fertility issues."

Becoming a Giant

Einhorn's interest in becoming a doctor sprouted during high school in Dayton, Ohio, when he

accompanied his father, a community physician, on hospital rounds. "He was a good role model," Einhorn said. "He treated patients with respect, and the respect he got, he earned."

After earning a BS from IU, Einhorn attended medical school at the University of Iowa. Then, it was back to IU for an internship, residency, and fellowship, with time away from that path from 1969 to 1971, when he was drafted during the Vietnam War to treat patients at an Air Force base in Wichita, Kansas.

His service completed, Einhorn returned to IU and his mentor, Robert J. Rohn, MD, who had inspired him to treat cancer patients. Rohn suggested that Einhorn pursue the research and treatment of solid tumors, possibly as a fellow at MD Anderson, and the young doctor did just that, studying with Emil J. Freireich, MD, and developing an interest in experimental therapeutics.

He returned to IU Medical Center in 1973 as an assistant professor, and began working his way up the ladder at the institution. Along the way came unforgettable experiences, particularly treating John Cleland, the first patient in the world to receive the Einhorn regimen.

"John had failed to be cured with several other forms of chemotherapy and came to me with the idea that we were going to give him platinum," Einhorn recalled. "We had no idea what it would do, but knew it would come with terrible side effects. To have the courage to go through therapy that makes you that sick without knowing if it will make you live longer, and to do it again and again through four courses, is very altruistic and courageous. Thirty-nine years later, we still keep in touch socially; he's a friend."

Countless other patients received the Einhorn regimen, including cyclist Lance Armstrong, whom Einhorn treated and who has since become the most well-recognized spokesperson for testicular cancer.

"He did a great deal of good when he was first diagnosed in increasing public awareness of the disease," Einhorn said. "Most 25-year-old men had no idea there was such a disease. The Livestrong Foundation, which he set up by himself with his own funds, blood, sweat, and tears, has done a remarkable job of helping the cancer community."

In all his years at IU, Einhorn has never been tempted to leave.

"We have a cohort of investigators here that I couldn't find at any other place in the world," he said, "and I don't think there's another institution in the country that could have allowed me access to the patient population I've worked with, because this is a rare disease."

Although Einhorn describes his work as a "cruel mistress" that doesn't leave him much time for hobbies like reading crime novels, playing tennis, and attending sporting events, he enjoys what he does, especially in light of a simple lesson it has taught him.

"In oncology, you learn to appreciate the fact that, as long as you're healthy, nothing else matters," he said.

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Everett E. Vokes, MD

HEAD & NECK CANCERS

Everett E. Vokes, MD

University of Chicago

In 2007, when Everett Vokes, MD, first saw Grant Achatz, the 33-year-old patient already had stage 4 squamous cell carcinoma of the tongue, and the assurance of two eminent doctors that amputation was his only hope to survive more than a few months.

That surgery would hinder speech and nearly eliminate all sense of taste—a hardship for anyone but a nightmare for this particular patient, who happened to be one of the world's most celebrated chefs. Even if he was one of the "lucky" 31% of patients who was alive 3 years after the surgery, he'd have a life he couldn't imagine wanting to live.

Luckily for Achatz—and the foodies who have circumnavigated the globe to visit his Chicago restaurant, Alinea—Vokes was then running a clinical trial, one based on previous work that had boosted survival rates to the 70% range and minimized the need for surgery with a combination of three drugs, and then two months later, chemoradiation.

Vokes was able to save both the patient and his tongue. It was another victory for the various combinations of chemotherapy and radiation that Vokes has helped to develop, test, and implement as standards of care for locally advanced head and neck cancer (HNC).

Discovering Medical Oncology

Vokes was born in New York City to parents who were both studying at The Juilliard School. His parents divorced when he was 4, and his mother took him to live in West Germany.

Vokes, though an American citizen, grew up entirely in West Germany and attended medical school in Bonn, which Vokes describes as a "small and fairly sedate city," despite being the nation's capital during his time there. One thing that Vokes did not encounter at medical school in Bonn was medical oncology. It was not common in Germany, even in the 1970s, and so Vokes had no experience with it until a three-month exchange rotation in Sydney, Australia.

"After graduating from medical school I 'returned' to the United States without knowing whether I'd stay," Vokes said. "I started my postgraduate education at Ravenswood Hospital in Chicago—which was a small community hospital at the time but no longer exists—and where I again encountered medical oncology and became fascinated by the concept of treating malignancies with systemic therapy as opposed to surgery or radiation therapy. I had a feeling that there was much work to do in cancer care."

Seeing the Need to Enhance Chemotherapy

"I was a first-year fellow the first time I saw chemotherapy used to treat a head and neck cancer tumor. It was part of a trial. The tumor shrank dramatically, but the study found no survival benefits," Vokes said. "None of the early individual studies did, indicating cross-resistance with radiotherapy."

Many doctors inferred that chemotherapy's lackluster performance in those early trials indicated its irrelevance to HNC treatment. As a result, many forgot all about the tumor shrinkage and continued the status quo: surgery followed by radiation in most cases, or, sometimes, just one or the other.

Vokes, on the other hand, remembered the dramatic shrinkage and wondered how to enhance chemotherapy's obvious effect, how to augment something that was already strong enough to kill *most* of the cancer to the point that it could kill *all* of the cancer. By the mid-1980s, when he was working his way up the ladder at the oncology-hematology section at the University of Chicago Medical Center, Vokes believed the answer might lie in giving patients chemotherapy and radiation simultaneously.

He secured both permission and funding, and then began testing concomitant chemoradiation, along with several other protocols that used different timetables to combine chemotherapy with radiation and surgery. Concomitant chemoradiation therapy was the runaway winner. It produced highly encouraging results from the start, curing patients with many of the late-stage tumors that almost always eluded existing standards of care and killed patients.

"The early trials were small and they lacked randomized control groups, but the results were dramatic," said Vokes, who, based on his institutional experience, thought that chemoradiation had proven its value by the early 1990s and hoped that other HNC specialists would also adopt it. "There were a number of factors that made people reluctant to begin the regular use of radiation and chemotherapy at the same time, including the very intensive nature of such a program," Vokes said.

Chemoradiation Becomes the New Standard of Care

Indeed, the chemoradiation programs that fared best in Vokes' studies were far harder on patients than existing standards of care. That said, the numbers showed that such harsh programs offered huge rewards—rewards that went beyond higher cure rates—to patients who endured the exhaustion, nausea, and other miseries.

"Chemoradiation attacks cancerous tissues, but it can be also toxic to the healthy tissues that neighbor the tumors. It shrinks them, causing

"There were a number of factors that made people reluctant to begin the regular use of radiation and chemotherapy at the same time..."

fibrosis, leads to mucosal ulcerations and pain on swallowing, and can lead to serious long-term functional deficiencies. But in the end, if the cancer is eliminated, many of the toxicities will improve," Vokes said. "Surgically removing cancerous tissue, on the other hand, is permanent, and reconstruction efforts can't compensate for the loss, especially following large surgical procedures."

In order to definitively prove all of the benefits suggested by Vokes's smaller studies, skeptics demanded national and international trials based on the gold standard of medical research: large, double-blind trials that compared chemoradiation to established treatments at multiple facilities. Vokes did not lead those trials—the dramatic results he had already achieved with chemoradiation made him deeply uncomfortable with the idea of assigning patients to the non-chemo arm of any trial—but the trials were conducted.

It took the better part of a decade for other researchers around the globe to conduct sufficiently large trials, follow patients for sufficiently long periods, and assemble the data in sufficiently compelling form to convince everyone, but the results of these trials did ultimately make chemoradiation the new standard of care for most advanced HNC. The breakthroughs discovered by Vokes and his colleagues have thus saved many lives. These discoveries also provided today's relatively large cohort of HNC survivors with a far higher quality of life than that experienced by the very small group that beat the disease in the recent past.

Current Research

Vokes' research today focuses on several different areas, including lung cancer. He has long carried out lung cancer work in parallel with his HNC studies and, to some degree, worked along the same lines: testing combinations of radiation and chemotherapy.

Lung cancer has turned out to be a much harder-to-treat malignancy, and the results have been less striking. Still, progress does continue, and new trials offer the opportunity for more.

"A very intensive form of radiation called stereotactic ablative radiation is increasingly producing exciting data," he said. "It's currently used to treat inoperable patients who have early

stages of disease. We are investigating a similar approach in stage III disease."

Among patients with HNC, where chemoradiation has already established itself as the standard of care, Vokes and his team continue to look for improved treatments that will increase survival rates, ease the pain of treatment, or both. The technique that first got Vokes interested in using medicine to combat HNC, induction chemotherapy, has begun to make a comeback after its original failure to increase survival times banished it from favor.

The introduction of new and improved chemotherapies such as paclitaxel in the 1990s has induced Vokes and his colleagues to revisit the idea and test it with a new twist: using combination chemotherapy to shrink tumors before further treating them with chemoradiation (rather than radiation alone), and reserving surgery for those patients who have remaining disease in the head and neck after completion of therapy. This type of trial began after observations that patients whose tumors involved several lymph nodes frequently had later recurrences outside of the head and neck area, an observation that indicated a possible need for more systemic therapy.

Vokes was running just such a trial of induction chemotherapy in 2007, when chef Achatz came to visit. That experimental induction chemotherapy consisted of paclitaxel, carboplatin, and the antibody cetuximab. A full course of chemoradiation followed several weeks later. (Achatz also had several lymph nodes removed.) It was an extremely intense regimen for patients with very serious disease. Although the survival data exceeded 70%, the results still did not specifically justify the added administration of induction chemotherapy. Nonetheless, testing of this approach for patients with extensive lymph node involvement continues to be of interest—as do far less intensive treatment options for different types of patients.

Hope for Less Aggressive Treatments

Indeed, despite spending some of his research time examining more aggressive treatments for the sickest patients, Vokes sees much reason to hope that many HNC patients will soon experience far milder treatments that work just as well as current standards. "It's not just that our tools and our skill at using them keep improving—though obviously they do—it's also that the patient population in HNC is undergoing a transformation that may well have a big impact on treatment."

The transformation in question stems from a huge increase in HNC caused by human papillomavirus (HPV) that is happening at the same time as a huge decrease in HNC caused by a sharp

drop in tobacco and alcohol use. Overall, HNC rates are rising despite the lower rates of tobacco use, but the tumors created by HPV seem far less aggressive and far less resilient than those created by cigarettes and snuff.

"Tobacco damages DNA over decades and thus creates tumors that are not only genetically complicated but also highly variable from one to the next. HPV, on the other hand, creates a simpler tumor in a very standardized way," Vokes said. "Yet despite all the differences between tobacco tumors and HPV tumors, we still treat everything with protocols developed to beat tobacco tumors. There's no guarantee we'll be able to treat tumors arising from HPV with less intensive treatment protocols, but it is certainly a plausible enough theory that it merits investigation and represents a major hope for patients."

Establishing a Work-Life Balance

Vokes' time at Ravenswood Hospital in Chicago introduced him to something even more fascinating than medical oncology: the woman who was to become his wife. Now the father of two adult daughters, Vokes enjoys vacations with the family, including recent biking trips to Provence, Tuscany, and Canada.

But he also delights in his work, particularly his work with patients. "I find taking care of patients to be one of the most rewarding activities, as it keeps me grounded in reality and focused on the need to advance the field through giving the best possible care today and improving treatment options for tomorrow."

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LEUKEMIA

Brian J. Druker, MD

Oregon Health & Science University

Take a prognosis of 3 years, multiply it by 10, and what do you get? A staggering improvement in the survival of patients with chronic myeloid leukemia (CML), and a crucial stepping stone on the road to the targeted treatment of cancer.

Brian J. Druker, MD, director of the Knight Cancer Institute at Oregon Health & Science University (OHSU) in Portland, was the driving force behind those accomplishments when, in May 2001, his research led to the FDA's approval of imatinib (Gleevec), an oral tyrosine kinase inhibitor (TKI) initially indicated for patients with CML that proved to be one of the earliest and most successful targeted therapies in the oncology armamentarium.

Today, patients with CML who take imatinib are projected to survive an average of 30 years, Druker said, a far cry from the 3- to 5-year prognosis that was standard when he began practicing medicine in the 1980s. And imatinib has been approved for the treatment of additional tumor types, including Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) and *KIT* (CD117)-positive gastrointestinal stromal tumors.

On a broader scope, the insights that led to the development of the drug have helped lay the groundwork for the creation by other labs of several approved treatments for imatinib-resistant CML, as well as targeted therapies for other cancers including the TKIs vemurafenib, erlotinib, gefitinib, and crizotinib.

Most recently, Druker helped to develop ponatinib (Iclusig), which was granted accelerated approval by the FDA in December 2012 to treat CML—or Ph+ ALL—that is resistant or intolerant to prior TKI therapy.

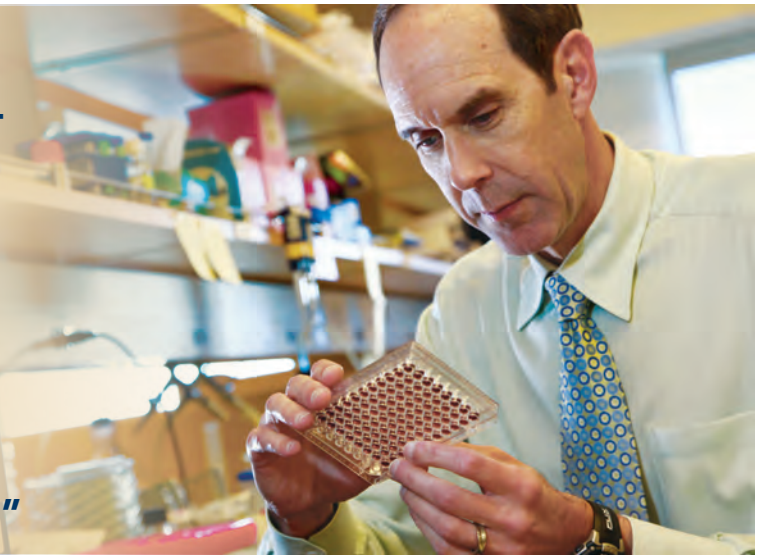
Developing Imatinib

Druker started testing imatinib in 1993, after joining OHSU as an associate professor, a member of the Department of Cell and Developmental Biology, and co-director of the Center for Hematologic Malignancies.

Previously, in a lab at Dana-Farber Cancer Center in Boston, Massachusetts, he'd worked with tyrosine kinases, developing an antibody that could detect the modification of tyrosine residues by the addition of a phosphate. The tool showed when certain enzymes were activated, and when an inhibitor had succeeded in shutting them off. Specifically, the measurement system zeroed in on an enzyme, Bcr-Abl tyrosine kinase, associated with CML.

"I thought about what human diseases were caused by this family of enzymes, and CML was one of them," Druker said. "It made sense to me to work on a disease where I had lab expertise, but also in which we someday may have been able to treat patients."

"I'd always come into this with the view that chemotherapy seemed barbaric, so I had no desire to continue to treat patients that way. I decided I was going to go into the lab and not come out until I had something better—that was my commitment."



He hoped to take the next step—applying the measurement tool in the development of a therapy for CML—when he began his work at OHSU. With that in mind, Druker headed to Portland determined to find a promising CML treatment that he could test for activity, and then bring to patients in the clinic.

To accomplish this, he needed to locate a company that had developed such a compound, one that inhibited CML cells without harming normal ones. Amazingly, Druker found what he needed with a single phone call to Nicholas B. Lydon, PhD, at the former Ciba-Geigy Corporation.

Lydon previously had called upon Druker and his colleagues at Dana-Farber for help in establishing a pipeline of TKIs. Now, Lydon "thought he had compounds worth my testing," Druker recalled. "It was really lucky, but if that hadn't worked, I didn't plan to stop. I would have continued to call people until I found a company with the right compounds."

Pushing Through Barriers

Druker used his antibody tool to test the compounds, and found that one, known as STI-571, looked especially promising. The compound moved through a battery of lab tests and was transformed from an intravenous to an oral formulation after a problem with blood clots in animal subjects. In 1997, Novartis—formed through the merger of Ciba-Geigy and Sandoz—was still testing the compound, but was concerned about liver and bladder toxicity in dogs and rats.

"As an oncologist who gives extremely toxic chemotherapy drugs to patients, I didn't think that should kill the development program," Druker recalled. "I asked if they had talked to the FDA, and they said that they weren't ready."

So Druker did it himself. He called someone at the FDA, described the data he'd compiled about STI-571, and asked whether the drug sounded ready to move into the clinic. Druker was told that he and Novartis had compiled more information than most companies with drugs already in clinical trials, and that the drug's toxicity profile didn't sound like a deal breaker.

"When I called Novartis back, they weren't happy I had circumvented them, but it forced them to rethink whether they might get the drug into the clinic," Druker said. The company gave the green light to the first trials Druker had ever led, and the phase I studies of imatinib amounted to a hole-in-one.

In one trial, Druker and colleagues found that imatinib restored normal blood counts in 53 out of 54 patients with interferon-resistant CML, a response rate rarely seen in cancer with a single agent (*N Engl J Med*. 2001;344[14]:1031-1037). Fifty-one of the patients were still doing well after a year on the medication, and most reported few side effects.

Imatinib was groundbreaking not just because of those results, but also because of how it generated them. While previously approved molecular-targeting drugs interfered with proteins associated with cancers, imatinib was the first to directly turn off the signal of a protein known to cause a cancer.

The doctor presented phase I results at the annual meeting of the American Society of Hematology on December 3, 1999, to a standing-room-only crowd. "You could have heard a pin drop during my presentation, and there was pretty thunderous applause at the end," Druker recalled. "That was unusual, because the typical reaction to a phase I trial is, 'That's interesting, but it's still pretty early—we'll need more studies to confirm it.' In this case, there was just this incredible validation and genuine enthusiasm."

Imatinib was approved while phase II trials were still in progress and after an FDA review of less than three months, an all-time speed record.

Gathering Resolve

As an undergraduate at the University of California, San Diego, Druker conducted research in molecular biology and gene cloning, and he moved on to immunology research—the stimulation of T cells and their suppression of immune response—during medical school at the same institution. However, during his residency at Barnes-Jewish Hospital at the Washington University in St. Louis, Missouri, Druker turned away from research to treat patients. He continued his training with a focus on oncology patients at Dana-Farber Cancer Institute at Harvard Medical School. And that's when his passion for finding new therapies began to grow.

"Taking care of cancer patients was pretty trying," Druker recalled. "As medical oncologists, we were treating patients with breast, lung, colorectal, and prostate cancers who had metastatic malignancies. We could help them live a little longer with chemotherapy, but that often made it worse, not better, and it cured very few. I'd always come into this with the view that chemotherapy seemed barbaric, so I had no desire to continue to treat patients that way. I decided I was going to go into the lab and not

come out until I had something better—that was my commitment."

After his fellowship, Druker stayed at Dana-Farber to join the lab of Thomas M. Roberts, PhD, whose focus was the study of oncogenes. "I was the least experienced person there," recalled Druker, who was hired as an instructor in medicine. "The last time I had worked in a lab was six years prior, or more, and lots of techniques had changed. Everybody had more training than I did."

Still, Druker persevered. At the same time, he was moonlighting one night a week as medical director of oncology at Nashoba Community Hospital in Ayer, Massachusetts, in order to keep his skills sharp when it came to treating patients. He kept up that schedule until 1993, when he asked to be promoted to the position of assistant professor at Dana-Farber—and was refused.

"I was told that they thought other people were more worthy of investment—basically, that I didn't have a future there," Druker recalled. "I could have stayed as an instructor forever, but I had bigger, better things to do."

Soon, he'd found the position at OHSU, where he dedicated himself almost exclusively to research, living a solitary life and working 16-hour days. His efforts paid off when the FDA approved imatinib.

CML Still a Focus

In the dozen years since, Druker's life has changed—and stayed the same. Druker still spends a fair amount of time conducting research in his 16-person lab at OHSU, where he remains focused on finding new and better treatments for CML and other leukemias. Of particular interest has been overcoming the resistance to imatinib that arises in about 15% of patients with CML within five years of beginning treatment.

Until recently, while there were already three TKIs on the market for refractory CML, "there was still one mutation that none of those drugs would shut down—*T315I*," Druker said. "We worked for close to six years testing drugs that Ariad Pharmaceuticals designed until we identified one that shut this down," Druker said. "The drug, ponatinib, works incredibly well against that mutation and also across the board in CML."

The bulk of Druker's remaining time is filled by his "main job" as the "face of the cancer center," which involves "setting the strategic vision, recruiting faculty, engaging in philanthropy, and forging relationships with our industry partners—biotechs, software and hardware vendors, equipment companies, anyone who helps us do the work." Druker also spends one day a week treating patients, teaches several classes a year, occasionally runs a clinical trial, and dedicates a day or two each month to lecturing around the world.

But despite all he does, and his commitment to it, Druker has established at least some of the balance he lacked when imatinib was at the center of his life. In 1996, he met his future wife, reporter Alexandra Hardy, when she came to interview him about imatinib. They met again when she returned to interview him in 2000 and, learning of his monastic lifestyle, chided him for being "pathet-

ic." It turned out that the two worked out at the same gym. They became friends, married in 2002, and are now the parents of three children. To make sure he has time for his family, Druker limits his travel and teaching activities and farms out many of the day-to-day tasks involved with running the center and his lab.

Druker's contributions have made an enormous difference to patients with CML, including one man who said that the doctor's work "put 'future' back in the vocabulary of patients like me." Druker remains just as amazed at what imatinib, and now ponatinib, can accomplish. "Patients in the clinic who were diagnosed 10 or 15 years ago are still doing great—living, thriving, and doing all the things they enjoy," he said. "I think, 'How is that possible?' To me, it's still remarkable to think about where things were a decade ago and where they are now."

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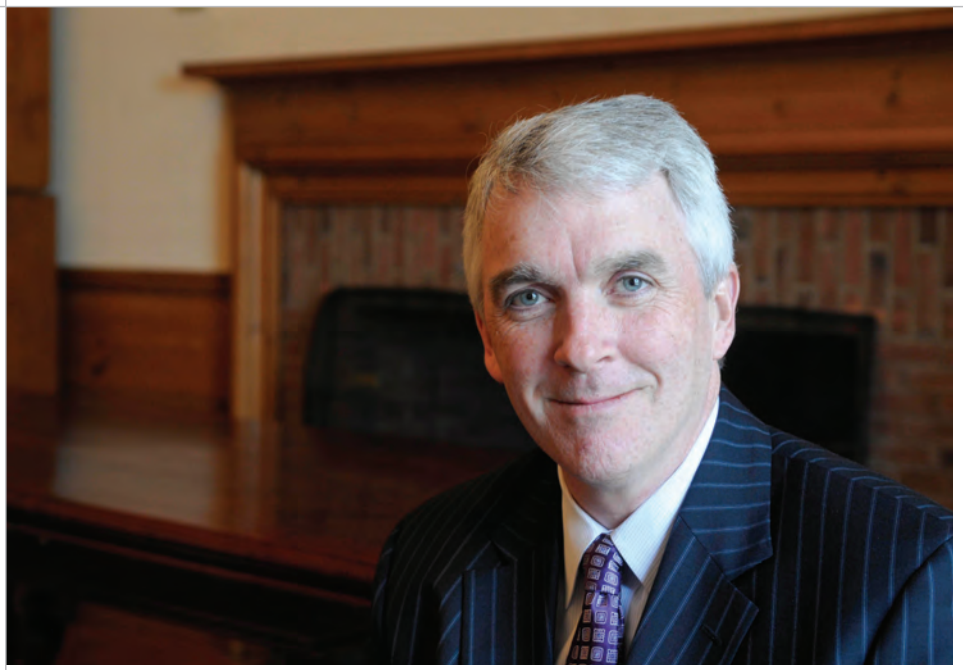


Thomas J. Lynch, Jr, MD

Giants of Cancer Care™ inaugural class 2013

LUNG CANCER

Thomas J. Lynch, Jr, MD

Yale Cancer Center

As director of the Yale Cancer Center and physician-in-chief of the Smilow Cancer Hospital at Yale-New Haven, Thomas J. Lynch, Jr, MD, wears many hats. And, having built a career united around two abiding goals of clinical discovery and personalized patient care, that's just the way he likes it.

"I am actually very lucky; I have two fantastic jobs," Lynch said. His responsibilities at Smilow, which opened in the fall of 2009, following his own appointment as physician-in-chief in April of that year, have given him the opportunity "to bring a spectacular facility online and deliver the very best care to patients with cancer."

The hospital consolidated Yale Comprehensive Cancer Center and Yale-New Haven Hospital's inpatient and outpatient cancer services into one facility. Treatment is organized around 12 cancer program teams, currently treating more patients with cancer than any other hospital in Connecticut.

"My role at Smilow has been very helpful in keeping me focused on patients and why we do what we do," Lynch continued. "I get to work very closely with patients, with their families, and with providers."

When Lynch is wearing his other hat at the helm of the Yale Cancer Center, he is involved in organizing and running a large, complex academic institution focused on cancer research, an arena in which he has distinguished himself for his pioneering work in lung cancer for more than three decades.

"What I find so complementary about these two positions is that they really go hand in hand. Without the clinic, the focus of cancer research is lost, and without cancer research, the opportunity to make progress is lost. I'm very fortunate to be able to work in both areas."

One of Lynch's many responsibilities at Yale includes developing the Cancer Biology Institute, established in 2010 as the research arm of the Yale Cancer Center. Under the leadership of founding director Joseph Schlessinger, PhD, MSc, chair of Yale University's Department of Pharmacology, this interdisciplinary institute is dedicated to finding the causes of and potential treatments for cancer through collaborative research. The research is conducted by senior and junior scientists whom Lynch helps to recruit, working in such fields as cell signaling, cancer immunotherapy, and the development of genetically precise treatments geared toward each patient's molecular profile.

Clinical Research–Front and Center

Research has been a central focus of Lynch's work since earning his undergraduate and medical degrees from Yale in the 1980s—and actually, even before that.

The Boston native grew up in a medical family, and he wanted to be a doctor all of his life, he recalled. "My father was one of the first hematologists in the country, so I knew about cancer as a kid. It's something that I saw as a real problem for patients and families, even when I was a small child."

"As I began my medical education and training," he continued, "I was really drawn to the idea that clinical research and the ability to take new drugs and new paradigms and bring them to patients was very exciting and stimulating."

Lynch carried this ethos with him to Massachusetts General Hospital (MGH), where he completed his internship and residency, joining the medical staff there in 1993 and embarking on a remarkable career dedicated to lung cancer care, research, and teaching.

Breakthrough Discovery of *EGFR* Mutations in NSCLC

Lynch has conducted dozens of studies focused on personalized cancer therapies and has published more than 100 original scientific papers. He worked with Daniel A. Haber, MD, PhD, director of the MGH Cancer Center, on one of the research teams that delineated the role of *EGFR* mutations in treatment response among patients with non–small-cell lung cancer (NSCLC).

Using the molecular profile of lung tumors, Lynch and his research team have developed methods to predict a tumor's response to targeted drugs based on confirmed mutations in the *EGFR* gene. The resulting information enables oncologists to create treatment plans that more effectively target each patient's specific tumor type. This kind of customized care and personalized medicine is a standard of practice at Yale Cancer Center and Smilow Cancer Hospital.

Lynch describes the discovery that "*EGFR* mutations were associated with this terrific response to gefitinib" as a major breakthrough in the search for more effective lung cancer treatments. Working with Haber's laboratory at MGH, along with laboratories at Memorial Sloan-Kettering Cancer Center and Dana-Farber Cancer Institute, he added, "We were able to show that *EGFR* mutations were clearly related to responses to tyrosine kinase inhibitors. When we got the results back from the laboratory and saw that eight of nine patients who we suspected might have the mutation actually did have the mutation—that was a really exciting moment." This discovery marked the first time in the treatment of lung cancer that a genetic event could be linked to the effectiveness of a drug.

Making Enormous Strides in Treating Cancer

"When I started in lung cancer, we were using step-chemotherapy—drugs which we still use today—platinum-based drugs which have been shown to make patients live longer, but they

didn't have the kind of revolutionary impact that the kinase inhibitors have had in patients who have oncogene-driven disease," explained Lynch.

"Over the course of my career, we have seen an extraordinary improvement in our understanding of the fundamental biology of lung cancer, appreciating the *EGFR* mutations and the *ALK-1* and *RAS-1* translocations. These are all important drivers of malignancy, and finding drugs that can improve outcomes for these patients is a great accomplishment."

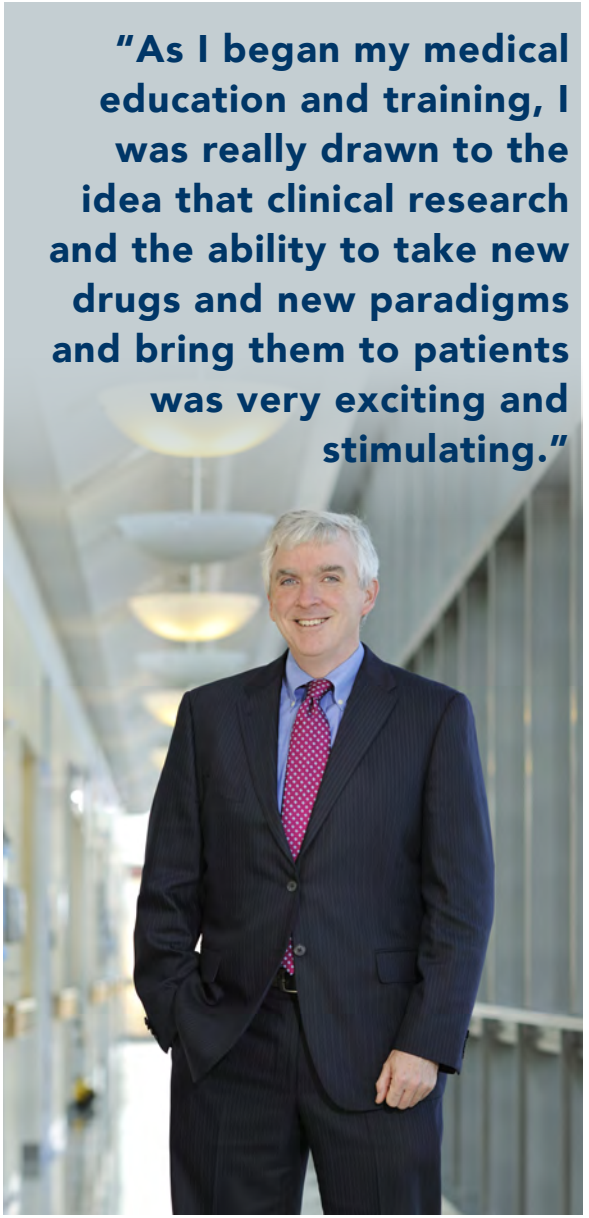
The Importance of Clinical Trials

The crucial role played by clinical trials in the quest for more effective therapies remains a top priority for Lynch, a focus that goes hand in hand with his desire to offer patients something "that is new, that has the hope of a better outcome than what we're currently doing," and is a prime motivator behind his work.

As a doctor, husband, and father, he said that he recognizes that the treatments currently available to treat cancer are not good enough and emphasized that better treatments depend upon more robust participation in clinical trials. Currently only 3% of cancer patients participate in clinical trials in the United States, a rate Lynch deemed "completely unacceptable."

"What I find is that the vast majority of patients want to participate in clinical trials, they want to advance medicine, so that the next person has a better option than they have. We need to be able to offer these options to every patient with cancer."

"As I began my medical education and training, I was really drawn to the idea that clinical research and the ability to take new drugs and new paradigms and bring them to patients was very exciting and stimulating."



"To miss that opportunity because we were shortsighted in our investment in research would be a tragedy," he said.

Connecting With Patients

This appreciation for improving patient care by connecting more patients to the right clinical trial stems from Lynch's overarching concern for enhancing the patient's experience throughout the course of the disease, a focus he honed early in his career. Lynch was part of the care team at MGH that treated Kenneth Schwartz, a Boston healthcare attorney and nonsmoker who was diagnosed with advanced lung cancer at the age of 40 years. After Schwartz's 10-month ordeal in battling and ultimately succumbing to the disease, a center in his name was established in 1995 whose primary mission is to optimize and maximize the interaction between patients and caregivers.

Lynch, a founding member and current chair of the Schwartz Center for Compassionate Healthcare's Board of Directors, said that Schwartz taught him a "tremendous amount about how important it is to remember that the patient is the focus of what we do. Ken taught us to focus on the patient's experience, on the small things we may sometimes forget about in our busy lives, which mean so much when you are on the other end of the doctor–patient relationship."

The Schwartz Center's reach extends well beyond Boston. Its signature program, the Schwartz Center Rounds, for example, has been adopted by hundreds of hospitals and healthcare institutions across the country, including Yale—bringing together caregivers from multiple disciplines to discuss the challenging emotional and social issues that arise in caring for patients.

"As we become more technologically savvy, as we embrace new technologies and new therapies," said Lynch, "we still need to come back to the fundamentals—that a patient has come to you scared, a patient has come to you with a problem, a patient has come to you needing help."

"Closer to Free" Through Team Science

Lynch is very optimistic about the future of lung cancer research and the availability of new therapies emanating from all of the players engaged in "team science," among them the researchers working in the laboratory, physicians in their clinics, and the National Cancer Institute's collaborative groups.

Currently standing out among these team-driven developments are "the initial responses to the anti-PD-1 therapy that we've seen here at Yale," said Lynch. "My colleague Scott N. Gettinger, MD, was involved with anti-PD-1 early in its development, and seeing these kinds of responses to immune checkpoint inhibition has been incredibly exciting. It tells me that the next 10 years will be a time of terrific advancement in lung cancer and the discovery of new approaches."

"There are many questions we can answer moving forward with the application of genetics and immunology to cancer and other diseases," Lynch continued. He forecasts that the next

decade in NSCLC research will continue to yield improved outcomes through therapeutic combinations involving chemotherapy, tyrosine kinase inhibitors, and immunotherapies.

"Some of the responses that we've seen with the immune-based checkpoint inhibitors have caused us to rethink the paradigms for how we treat lung cancer and when we should incorporate new drugs into the treatment of this disease. It's really very encouraging."

At Smilow, where these research accomplishments can translate into changing patients' lives, the goal of supporting much-needed research through its "Closer to Free" initiative stands as a guiding mantra and mobilizer for the patients, survivors, doctors, and other caregivers working tirelessly to combat the disease.

And that is a philosophy completely in step with that of the cancer hospital's physician-in-chief.

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LYMPHOMA

Vincent T. DeVita, Jr, MD

Yale Cancer Center

When Vincent T. DeVita, Jr, MD, began testing a cocktail of four chemotherapies against advanced Hodgkin disease back in 1964, the disease was uniformly fatal. Many patients were desperate enough to try anything, even a combination of cell-killing poisons that guaranteed them nothing except excruciating pain.

Their gamble paid off with an unimaginable breakthrough, one that DeVita and his colleagues first reported in 1967: The so-called "MOPP" combination (Mustargen, Oncovin, Procarbazine, and Prednisone) produced complete remissions in 80% of patients.

Had DeVita retired the day after he announced those results, he'd still rank among history's top oncologists, but the 32-year-old doctor was just getting started. Over the next five decades, he continued to distinguish himself as an innovator with his contributions to cancer research, including developing a treatment protocol that is still used in breast cancer, publishing more than 400 scientific papers, and running the National Cancer Institute (NCI) for nearly 10 years.

Starting on the Research Path

DeVita stumbled into cancer research by accident. "I actually thought I would ultimately go into [private clinical] practice. But then once you're involved in a major discovery, you're hooked! From that point on, I was never even tempted to go into practice," he said.

Born in the Bronx and raised largely in Yonkers, New York, DeVita stood out as a fast-talking Yankee at The College of William and Mary in Virginia, which was still a school with a very "southern" culture when he graduated in 1957 with a degree in chemistry. He married shortly thereafter and moved on to medical school at George Washington University in Washington, DC, in 1957.

DeVita conducted some cardiology research during his time there and managed to get several of his studies published. So, when he decided to continue his studies with a fellowship at the National Institutes of Health (NIH), he expected that any position he landed would be in cardiology. He ended up, instead, at the NCI in 1961, just as research into combination chemotherapy was taking off.

More than a decade had passed since Sidney Farber, MD, first demonstrated that a folic acid antagonist could induce remissions in childhood leukemia. Euphoria about chemotherapy's promise had been replaced with dire pessimism as each new chemical agent to emerge from the labs failed to produce anything more than temporary remissions.

By that point, DeVita said, "Nobody felt you could kill cancer with drugs"—nobody except DeVita's new colleagues at NCI, who believed that chemotherapies that failed as individual treatments just might cure cancer when used together.

MOPP's Difficult Beginnings–and Ultimate Success

It is difficult to imagine, now that combination therapy is a cornerstone of cancer treatment, just how controversial this idea was at the time. Nearly the entire medical establishment viewed the "fathers of combination therapy" not only as idiots, but also, thanks to the terrible side effects of their experiments, as sadists to boot. Even colleagues within NCI accused the most aggressive experimenters of running "a butcher's shop" that performed "cruel and insane" work that should be forbidden outright.

DeVita's experimental MOPP regimen produced side effects that were extreme even by those standards. Nausea struck patients with indescribable intensity, while the toxins eradicated their immune systems and made any malady a life-threatening condition.

Among those who survived, most of the men and some of the women were rendered permanently sterile. Some escaped Hodgkin disease only to succumb about a decade later to leukemia induced by their treatment.

Nevertheless, DeVita and his colleagues knew almost instantly that they had succeeded beyond anyone's wildest dreams. Thirty-six of their first 43 patients achieved complete remissions within 6 months of treatment.

"In research, it can't be done alone, it takes immensely talented researchers and a dedicated staff of professionals to make innovative scientific discoveries that can positively impact the lives of cancer patients."

The only problem was the name of the new regimen. DeVita called it "Combination 2" until his boss, Emil Frei, III, MD, suggested something catchier. "They'd put together VAMP and BIKE, and because these acronyms were quick, people could remember them," DeVita said, "But I called it 'Combination 2.' And so Frei said, 'Right. It's MOPP.' And it's been forever MOPP."

On the Fast Track at NCI

DeVita's early success at NCI led to rapid promotion. He was appointed head of NCI's Solid Tumor Service in 1968, chief of its Medicine Branch in 1971, and clinical director for the entire Institute in 1975. Each position brought more administrative responsibility, but DeVita managed to find time for prodigious amounts of research throughout those years.

Most important among that research was the work, conducted with George P. Canellos, MD,

that led to the development of the combination chemotherapy regimen CMF. A pair of programs were designed and tested at the NCI's Clinical Center. The first used L-phenylalanine mustard (L-PAM) alone. The second used the CMF program, a combination of cyclophosphamide, methotrexate, and 5-fluorouracil. Both programs demonstrated activity in patients with metastatic cancer, but the results with CMF were more impressive. Canellos and DeVita published results in 1974 that showed the overall response rate was over 50%, and about 20% of patients actually achieved complete remission.

As this research was under way, DeVita and his NCI colleagues were working to launch studies of L-PAM and CMF as an adjuvant treatment for earlier-stage breast cancer, but they struggled to find surgeons willing to subject patients with relatively good prospects to harsh chemotherapy. Eventually, they contacted Gianni Bonadonna, MD, of the Istituto Nazionale dei Tumori, in Milan, Italy. Bonadonna came to the NIH Clinical Center to review the results of the CMF protocol, which had not yet been published, and agreed to conduct a randomized, controlled trial of a slightly dose-reduced version of CMF versus no therapy.

The first, very positive results were published in *The New England Journal of Medicine* in 1976, and set off a flurry of research into the use of combination chemotherapy as a neoadjuvant treatment.

Personal Tragedy

These triumphs in the laboratory came at a time when DeVita and his family were suffering personal tragedy. "My son, in 1972, was diagnosed with aplastic anemia. I brought him in to see Dr. Ronald Yankee, and the diagnosis was made, and Yankee put him in a laminar air flow room, which he never left. He lived in the laminar air flow room for about eight years."

For all those years, DeVita spent several hours a day, nearly every day, talking to Ted, the son who soon became a counselor to the father. It was Ted who advised his dad to accept a presidential appointment from Jimmy Carter and take charge of the NCI, with its staff of 2000 people and its annual budget of $1 billion.

A few months later, in early 1980, Ted died of complications resulting from repeated blood transfusions. Vincent DeVita was 45.

Cancer Research Faces a Disillusioned Public

His nine-year tenure at the head of the NCI began at a time when the general public had grown disillusioned with cancer researchers. A decade had passed since Nixon had declared the "War on Cancer," and despite some real gains, cancer appeared in little danger of unconditional defeat.

Even DeVita appeared disillusioned with cancer research. In a 1981 interview with *People* magazine, he sympathized with critics who called the NCI too conservative and questioned whether the NCI he ran would be courageous enough to fund the MOPP experiments he'd conducted 15 years before.

Nevertheless, he managed to win wide support for his work as the organization's head. DeVita was one of very few Carter appointees in any

area of the federal government to keep his job when Ronald Reagan became president. He also proved adroit at getting a president who had promised domestic spending cuts to keep increasing funds for cancer research.

Eventually, DeVita grew weary of the political and bureaucratic demands of running the NCI, so he left for Memorial Sloan-Kettering Cancer Center in 1989. After another five years, he moved on to Yale University, where he has remained in various capacities ever since.

Continued Involvement

In recent years, DeVita's research has been focused on evaluating potential molecular mechanisms of physiologic drug resistance in cancer. How, he wants to know, can cancer cells potentially manipulate molecular pathways to circumvent drug resistance?

Another area of interest is identifying appropriate molecular targets for combination, targeted treatment. "For the true potential of a predictive marker to be realized, the underlying pharmacokinetic parameters of the drug need to be well defined," he said.

Outside of the lab, DeVita serves as both the volunteer president of the American Cancer Society and a member of its board of directors. He writes the blog *DeVita on Cancer*, posting his thoughts on current cancer news as well as on the history of the "War on Cancer."

He has, of course, won a large number of awards and accolades for his work over the past five decades, but says he owes much of his success to the very high quality of his colleagues.

"In research, it can't be done alone," DeVita said. "It takes immensely talented researchers and a dedicated staff of professionals to make innovative scientific discoveries that can positively impact the lives of cancer patients."

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Steven A. Rosenberg, MD, PhD

MELANOMA

Steven A. Rosenberg, MD, PhD

National Cancer Institute

Steven Rosenberg always knew that he wanted to become a physician scientist, and he quickly advanced to become the chief of surgery at the National Cancer Institute (NCI) at just 34 years of age. Throughout his years at the NCI, he has pioneered cell transfer therapies in patients with a variety of widespread metastatic cancers and saved countless lives in the process. Rosenberg credits his success in cancer therapies to the hard work and focus instilled in him at a very young age.

Rosenberg notes, "There are two properties that I think are associated with ability to succeed in science, and especially in the kind of translational science that I'm doing—trying to apply modern science to improve the care of cancer patients, which is what I've spent my entire career trying to do. You have to be passionate about what you do and you have to be highly focused in what you do." He is certainly both of these things.

Early Influences

Rosenberg was introduced to the importance of hard work early on. As a young boy, his father owned a string of luncheonettes. Rosenberg wrote in his biographical work *The Transformed Cell*, "My parents' influence on me was profound but subtle. No matter how early I got up in the morning, my father had already left for work. And my own experience in the luncheonette taught me an enormous amount about life, about how difficult it could be—not only my father's but those of his more Runyonesque customers—and about how hard one must work to accomplish anything."

From an early age, Rosenberg dreamed of becoming a doctor. He writes, "I recall my first ambition, aside from becoming a cowboy, was to become a doctor and a scientist. They were heroes to me. I often cut out newspaper articles about the exploits of a scientist or a doctor, kept them in a scrapbook, and daydreamed about them."

Rosenberg credits his older brother, who is a surgeon and scientist, with mentoring him when he was a young boy. "My brother…gave me books, usually about science. He was then studying medicine and was my role model. He believed that if he gave me enough stimulation, something would excite me, something would click. He was right," Rosenberg recalled.

A Scientific Goal

Rosenberg excelled in academics throughout his early years. While still in high school, he laid out his plan to become a physician scientist. Rosenberg attended a 6-year program from 1957 to

1964 at John Hopkins University, during which he earned both his bachelor's degree and his MD and completed a surgical internship at Peter Bent Brigham Hospital. However, he did not stop there. He still required training to become the scientist he dreamed about.

Rosenberg writes, "From my very first interest in medicine as a boy, I wanted to combine research and clinical work. I intended to master medicine and probe deeply into the nature of disease. The goal never varied." To achieve this goal, Rosenberg worked on his PhD in biophysics after his medical training, from 1964 to 1968 at Harvard University.

Following his graduate research at Harvard, Rosenberg returned to Peter Bent Brigham Hospital as a surgical resident from 1968 to 1969. However, he soon grew restless and took a leave of absence to return to Harvard to perform immunological research from 1969 to 1970.

Rise to Chief of Surgery

After a year at Harvard as a research fellow, Rosenberg left for his first position at the NCI as a clinical associate in the Immunology Branch. He recalls that this experience excited him about the NCI, being able to work with some of the most talented scientists in the country. However, he missed medicine and taking part in the clinical care of patients. To fulfill this desire, he completed a surgical residency at Peter Bent Brigham Hospital, during which he was able to continue performing his research.

After two years spent completing his surgical residency, Rosenberg turned down an offer for the chief of surgery position at the Dana-Farber Cancer Institute to return to the NCI. Rather, he decided to accept a position as the chief of surgery at the NCI in order to continue both his research and his patient care in a fast-paced, fostering environment. Rosenberg writes of his decision, "…NCI had a mixture of laboratory and clinical resources that could not be duplicated anywhere else in the world."

Thus, in 1974 at just 34 years of age, Rosenberg become the chief of surgery at the prestigious NCI, an impressive feat for anyone, but even more so for a young man who only recently had completed his medical training. Rosenberg has remained in this position for nearly 40 years, and still works from 7:00 AM to 7:00 PM every day, spending about half of his time guiding laboratory research, about 40% of his time in the clinical care of patients, and the remaining 10% of time performing his administrative responsibilities.

Cancer...a Natural Enemy

Rosenberg's research had always focused on cancer—from studying how cells differentiate self from non-self during his PhD research, to identifying tumor antigens during his first stint at the NCI. Rosenberg writes, "In the lab and in my residency, my focus was on cancer…It was my enemy, and I wanted to know my enemy and grow intimate
with it."

Rosenberg recalls what drove him to work so intricately with cancer. "To me, [cancer] resembles a holocaust. It is a disease you can hate. Other diseases, including heart disease, tend to attack older people, but cancer kills randomly, and it kills young."

"The possibilities of gene therapy are extraordinary. Manipulating genes creates an entirely new and almost unlimited way to deal with disease that could change the way medicine is practiced in the twenty-first century."

Rosenberg was intrigued after examining a patient who was cured of cancer without any treatment. After trying—and failing—to cure others with cancer using blood from the cured patient, Rosenberg was determined to use the innate ability of the body's own cells to destroy cancer cells. The experiments, observations, and successful (and some not so successful) treatments that followed resulted in him becoming a clear leader in the cancer immunotherapy field.

In 1985, Rosenberg showed for the first time that the administration of interleukin-2 (IL-2) to patients could aid in the regression of established invasive human cancers, which led to the FDA approval of this therapy in patients with metastatic renal carcinoma in 1992 and metastatic melanoma in 1998. Rosenberg also found that IL-2 can support the growth of cancer-fighting human lymphocytes in the laboratory, and this work led to the characterization of multiple human cancer antigens.

Adoptive cell therapy (ACT)—a technique pioneered by Rosenberg that involves the transfusion of T lymphocytes—has been touted as the best direct evidence that the immune system is capable of curing patients with cancer. Indeed, growing large numbers of these tumor-infiltrating lymphocytes (TILs) in vitro and activating them ex vivo before infusion has proven successful in some patients with metastatic melanoma, even those with extensive tumor burdens who have been heavily pretreated.

Rosenberg also pioneered the groundbreaking yet controversial technique involving the administration of genetically modified lymphocytes to treat metastatic melanoma. In his biographical book, Rosenberg recalls his excitement prior to the first treatment with genetically modified cells: "Infusing gene-modified TIL into [the patient] would open a door in medicine. The possibilities of gene therapy are extraordinary. Manipulating genes creates an entirely new and almost unlimited way to deal with disease that could change the way medicine is practiced in the twenty-first century."

In this technique, lymphocytes are genetically engineered to express T-cell receptors (TCRs) that recognize tumor antigens or to express other molecules that increase antitumor activity. Using genes encoding TCRs that recognized the melanoma-melanocyte differentiating antigens MART1 and gp1000, Rosenberg and his colleagues provided the first example of the successful treatment of patients with genetically

modified lymphocytes; up to 30% of patients who received cells containing these TCRs had regressions of their cancers.

Exciting Developments

Rosenberg has tremendously advanced the area of ACT, opening the door for several new and exciting cancer treatments. He notes, "When I came to the NCI, I started a whole new area of research trying to develop these cell transfer therapies, which are now becoming a very significant part of modern oncology…. This whole area of cell transfer therapy is going to be a very important part of cancer treatment in the future."

"Now that we can genetically modify lymphocytes and give them new properties that they haven't normally had or that lymphocytes haven't had in the course of the evolution of the immune system, we have enormous flexibility in terms of manipulating these immune reactions. So we're working daily on ways to genetically modify lymphocytes to have better and more effective antitumor properties."

Rosenberg notes, "I have over the door of one of my labs a modification of a saying, I think it was originally by Louis Pasteur who said, 'Chance favors the prepared mind.' But I modified that to be, 'Chance favors the prepared mind, but only when the mind is at work.'" And based on Rosenberg's impressive list of accomplishments and the numerous lives he has helped to save, we can safely assume that Rosenberg's mind has been hard at work.

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Robert A. Kyle, MD

MYELOMA

Robert A. Kyle, MD

Mayo Clinic

Myeloma survivors owe much to Robert A. Kyle's reluctance to perform autopsies or to undergo cardiac catheterization. Those natural aversions led Kyle to choose hematology over two other research options toward the end of his Mayo Clinic residency, and launched Kyle on a course of research that has transformed our understanding of dysproteinemias, the family of plasma cell disorders related to multiple myeloma (MM).

The 85-year-old doctor, who has now been at the Mayo Clinic for 60 years, not only discovered how such disorders progress to serious diseases such as MM, but also worked out the appropriate medical response at every step. Those and hundreds more breakthroughs stemmed from a unique combination of clinical practice, data mining, and sheer effort. Kyle has put in nearly 80-hour weeks for six decades now, and colleagues say he's still working close to full speed.

"It would be nearly impossible to overstate Robert Kyle's impact on multiple myeloma research and treatment," said Kenneth C. Anderson, MD, Harvard Medical School, Jerome Lipper Multiple Myeloma Center, and LeBow Institute for Myeloma Therapeutics. "He is my hero, my inspiration, my role model. He is a giant."

A Landmark Paper

When Kyle began to study dysproteinemia in 1960, routine blood tests frequently found monoclonal gammopathies in patients with no symptoms of MM or other disease. Researchers had tracked some of those patients for a few years, found no tendency to develop disease, and dismissed the condition as benign.

Kyle began the work that would change all that in 1964, when he saw that a patient had developed MM 19 years after first being diagnosed with what was then called "benign monoclonal gammopathy." He wrote up that single case and published it, along with a warning that doctors might want to follow up on patients they diagnosed with a condition that might not be so benign.

He returned to the issue 14 years later with a landmark paper which demonstrated that the condition, while sometimes genuinely benign, was also the precursor to dysproteinemia ranging from MM to Waldenström's macroglobulinemia and primary amyloidosis. This finding definitively demonstrated the need to monitor, rather than simply ignore, the misunderstood condition, which, Kyle later demonstrated, afflicts 3% of

European Americans and 6% of African Americans who are 50 years and older.

Unfortunately, that same paper, which mined data from thousands of patient files, did not find any way to determine which cases would progress to which diseases over what timetable. Indeed, the analysis specifically found that there was no way to make predictions in individual cases, which is why Kyle rechristened the diagnosis *monoclonal gammopathy of undetermined significance* (MGUS).

Two years later, Kyle and his protégé, Philip R. Greipp, MD, professor of Laboratory Medicine and Pathology at Mayo, traced the next step on the road to MM with a paper on six unusual patients. Those patients had lab results that would then have prompted an MM diagnosis, but none of them had any symptoms, even after five years without treatment. Kyle and Greipp differentiated their condition from full MM with the label *smoldering multiple myeloma* (SMM).

"All of those papers, and hundreds more I've published, began with a clinical observation," Kyle said. "I noticed something I could not explain and then went back into the records looking for patterns."

A Treasure Trove of Data

When Kyle talks of going back to his records, he speaks of an incredible asset. Kyle's longevity and work ethic, combined with some early success with data mining, led him to amass an unprecedented collection of patients with dysproteinemia and to invent breakthrough strategies for teasing insight from their files.

His data management efforts began in the 1960s, when no doctors kept files on computers, with an early IBM punch card system and progressed from there. The system now has records on more than 46,000 patients seen by Mayo's dysproteinemia group, which now numbers 12 physicians. The database includes over 26,000 patients with MGUS, more than 8000 with myeloma, and nearly 4500 with AL amyloidosis.

Better still, the data on many of those patients spans decades because Kyle set up a research survey system that automatically requests updates from every patient who hasn't been to Mayo Clinic in a year. If the patient doesn't respond, then a second letter goes out, and if the patient doesn't respond to that, someone places a telephone call.

Kyle's "files" also include serum samples—every single one that he and his colleagues have collected since the 1960s. The group now has 250,000 samples, frozen in storage, and fully correlated with corresponding patients' medical records, often from first diagnosis to death. Mayo officials once begged Kyle to discard those samples, but recent advances in biological analysis have made them an obvious treasure trove.

Unique Value of the Mayo Clinic

In addition to mining records from his own patients, who all have dysproteinemias of some type, Kyle made a series of discoveries about the incidence and development of such conditions in the general public by taking advantage of Mayo Clinic's unique standing as a large medical institution in a small community.

"All of those papers, and hundreds more I've published, began with a clinical observation, I noticed something I could not explain and then went back into the records looking for patterns."

One way or another, Mayo Clinic provides medical services to most people who live in Olmsted County, Minnesota, and that has given Kyle access to what amounts to a random population sample, numbering in the tens of thousands, that sends every case of dysproteinemia to Mayo.

What's more, because he has been at Mayo for so long, Kyle has often been able to trace the incident or absence of disease through several generations of the same family. "We've used that data to figure out how common various dysproteinemias are in many different populations and how quickly they progress," said Kyle, who added that the numbers illustrate why doctors and patients must resist the urge to treat early-stage problems rather than simply monitor them.

"We've figured out that whenever a doctor diagnoses an MGUS, it has, on average, existed inside the patient for 15 years and will probably never cause any problems at all. It's less of a risk than any treatment we have now."

A Precocious Mind Destined for Medicine

Kyle was born in Bottineau, North Dakota, on March 17, 1928. He grew up with four brothers on a farm six miles outside of town and attended a one-room elementary school, where a single teacher juggled 15 to 20 kids in all eight grades. On most days, particularly when there was snow on the ground, he rode a pony to class.

Kyle moved on to high school in Bottineau when he was just 12 years old and, during winters, rented a room in town and did his own cooking rather than dealing with weather—40-degree-below-zero temperatures and

deep snowfall—that often made the short commute home impossible.

Science interested Kyle throughout school, and he always had a vague inclination toward medicine, but his interest grew serious when one of his younger brothers got meningitis. The two were sharing a room in Bottineau that winter and, when Kyle rose one morning, his brother could hardly speak. The 16-year-old Kyle took his 14-year-old brother to a doctor, who made the diagnosis and treated him with sulfa. The doctor gave Kyle detailed nursing instructions, which he helped carry out for two full weeks. His brother recovered and, when Kyle graduated from the University of North Dakota, he decided to go on to Northwestern Medical School, and in 1953 to a residency at Mayo Clinic.

Myeloma Breakthroughs

"My plan, right up until the end of my residency, was to go to Southern California, set up as an internist and enjoy a comfortable life in paradise, but I got hooked doing research on plasma disorders," Kyle said. "It's been a much colder life than I planned, but a much more interesting one."

Kyle's first hematology research, the research he chose over pathology or cardiac physiology, spurred him to sign up for a clinical hematology rotation. During that rotation, he became interested in the use of serum protein electrophoresis as a diagnostic tool, so he studied the electrophoretic patterns from more than 6000 patient tests performed at Mayo Clinic between 1956 and 1959 and correlated them to the size of the serum spikes. His work showed that if the height was more than four times the width at the midpoint of the peak, that patient very likely had myeloma or macroglobulinemia. If, however the ratio was lower, the patient most likely had a chronic infection or chronic active hepatitis, rheumatoid arthritis, or some other inflammatory process.

That rotation also marked the first time Kyle connected amyloidosis with MM. A single patient came to the hematology department with a diagnosis of "scleroderma," but she also had visible skin thickening, so a consulting dermatologist did a skin biopsy that disclosed amyloid.

Kyle realized from that result that some patients with smaller spikes in their electrophoretic patterns had systemic amyloidosis. He then reviewed all 81 cases of primary amyloidosis seen at Mayo Clinic from 1935 to 1959, and published a paper that made the point that all of these patients had abnormal plasma cells in the bone marrow, and that some had symptomatic MM.

"Back when he first started his research, our understanding of the relationship between various plasma disorders was virtually nonexistent," said Morie A. Gertz, MD, chairman of Internal Medicine at Mayo. "He has spent a lifetime changing that, not only through his research but also by training quite literally thousands of clinicians and researchers over the decades."

A Man of Many Interests

When his four children were young, Kyle led local chapters of both the PTA and the Boy Scouts, but his only long-standing hobby, one begun when a bad back kept him bedridden for 40 days, is stamp collecting. He has a huge collection of medically themed stamps and has written hundreds of monographs on the subject.

Kyle's other nonmedical passion is travel. He still spends three weeks every summer driving the American West, and still flies more than 125,000 miles a year to conferences and gives lectures all around the globe.

For most of his life, Kyle's working day began when he reached his office at 7:30 AM, where he stayed for 11 hours before going home to eat dinner with his family. After the kids went to bed and his wife Charlene settled in to read a book, he'd wedge in another two hours of work before going to bed at 11:00 PM. He has worked slightly shorter weeks since turning 80 but, according to colleagues, not much shorter.

"I'm very excited about the work I'm now doing on how smoldering multiple myeloma progresses," he said. "About half of all cases become full myeloma in five years but a third haven't progressed in 10 [years], which suggests it may actually be two different conditions. The trick will be differentiating them in advance."

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Charles L. Sawyers, MD

PROSTATE CANCER

Charles L. Sawyers, MD

Memorial Sloan-Kettering Cancer Center

During his undergraduate years at Princeton University, Charles L. Sawyers, MD, studied history. Now, well into his career as a physician and translational scientist, Sawyers is busy making it. Now chair of the Human Oncology and Pathogenesis Program at Memorial Sloan-Kettering Cancer Center and Howard Hughes Medical Institute investigator, he has played a seminal role in the discovery of three groundbreaking cancer drugs. And in developing these drugs, he has helped to create an approach to the treatment of cancer that has transformed cancer research.

Although Sawyers's most recent discovery is for his work in developing enzalutamide, a drug therapy for the treatment for metastatic castration-resistant prostate cancer (mCRPC), he applied many of the same scientific methods he developed while working with leukemia earlier in his research career. Sawyers, over the course of his career, had explored how signaling pathway aberrations in cancer cells could be exploited as targets for new drugs. And practice, as they say, makes perfect. In his work with enzalutamide, Sawyers focused on how prostate cancer cells develop resistance to drugs that target the androgen receptor (AR) pathway. To appreciate and understand his approach to solving scientific problems, one has to go back to when Sawyers began his career, first as an undergraduate, then as a medical student, and, finally, as a physician scientist.

History Provides a Lesson in Research

Sawyers was born and raised in Nashville, Tennessee, into a family of physicians: a grandfather, father, two uncles—all surgeons—and a mother, an anesthesiologist. As a young student, he excelled in mathematics and science, so one would have thought that a career in science, especially medicine, was inevitable. Yet, when he headed off to Princeton University for his undergraduate education, those areas of study were far from his mind. Instead, he chose to major in history. A liberal arts education, he felt, would broaden and enrich his outlook on life. Ultimately, he says, it contributed to his ability to isolate and analyze science problems.

"It exposed me to a certain style of research. You select a topic, investigate and master a body of evidence using original sources, and come up with a conclusion. You grab onto something you think is controversial or fascinating in some way, and try to get to the heart of it. I actually think that that's what research in science is all about, and frankly, that's how a liberal arts education works."

It was during this time that he encountered the work of science historian Thomas S. Kuhn, PhD. Kuhn, through his magisterial work, *The Structure of Scientific Revolutions*, which argues that scientific progress is the result not so much an *evolution* in ideas, but rather a *revolution* in

ideas—one led by "intellectual mutineers," insurgents who overthrow one conceptual worldview or paradigm to replace it with another; thus, Galileo and Copernicus upended astronomy, Newton rewrote physics, and Darwin revolutionized biology. The idea that new discoveries in science could result not from the logical extension of older ideas, but from an overturning of those ideas was intriguing to the young Sawyers, and ignited his interest in and passion for the scientific method and informed his life's work.

Learning to Be a Scientist

After graduating from Princeton, Sawyers enrolled in Johns Hopkins University School of Medicine in Baltimore. "Hopkins had an outstanding faculty made up of people who were involved both in teaching medical students and running a laboratory, combining research with clinical activity." At Hopkins, Sawyers was greatly impressed and influenced by Donald S. Coffey, PhD, a faculty member and researcher who worked on prostate cancer. "He is a man of great personal charm and charisma, with a renegade spirit that I greatly admire," said Sawyers. Coffey, according to Sawyers, also has a unique talent: to get students genuinely interested in a problem, to get them to dig into it, and to get them excited about biomedical science.

"It was inspiring. And don't forget, this was a time when the tools of molecular biology were just being broadly applied to questions in medicine. The ability to understand the genetics of a disease was leading to fascinating new insights. Cancer was a fascinating challenge. A lot of the features of biomedical science are part of cancer research, so you're pretty much in the mainstream of all research. You can draw on many different lines of investigation. Solving problems that arose from the research was incredibly interesting. The real question was whether I could stomach the clinical part of it."

That question, it appears, was answered when during his residency at the University of California, San Francisco (UCSF), Sawyers began a month-long rotation through the leukemia ward, caring for patients with cancer, many of whom were around his own age. "It was an incredibly rewarding month for me. Of course, there were sad moments. But the relationships with the patients and the families were incredibly driving and rewarding. I knew right then that that's what I wanted to do. It wasn't something that I could have predicted, that I'd have thought I'd have felt so strongly about in advance. But it just grabbed me."

Sawyers' interest in chronic myeloid leukemia (CML) ultimately led him to sign up for postdoctoral research in molecular biology at a lab led by Owen N. Witte, MD, at UC, Los Angeles (UCLA). Sawyers credits Witte with teaching him how to be a scientist. "He taught me scientific rigor, how to think like a scientist. Whenever I went to him with a problem, he'd say, 'Boil that down to a question you can test.'"

At the time Sawyers joined the UCLA lab, the group was concentrating on the Philadelphia chromosome, a mutant that is formed when pieces of two separate genes, the *BCR* and the *ABL*, break off and then rejoin to form the oncogenic BCR-ABL. He worked on elucidating how BCR-ABL triggers a cascade of intracellular

signaling that ultimately leads to CML. In the recesses of his mind, Sawyers tucked away an idea: perhaps a therapeutic strategy might emerge from an understanding of BCR-ABL activity, one that could be applied to other cancers as well.

Interestingly enough, it was his work here that, although not quite as disruptive of old ways as Kuhn had described, would ultimately transform cancer research and challenge and overturn established ideas on how to treat it. These new ways of thinking about cancer and cancer treatment resulted in groundbreaking approaches, at first derided by critics, but then increasingly adopted by the cancer research community.

A New Age in Cancer Treatment Begins

While Sawyers was studying how BCR-ABL signaling triggered cancer in blood cells, and trying to determine how abnormalities in the signaling pathways could be exploited as targets for new cancer therapies, physician scientist Brian J. Druker, MD, of Oregon Health & Science University, along with Ciba-Geigy (now Novartis) chemist Nicholas B. Lydon, PhD, were attempting to devise a completely new type of treatment strategy. They were looking for a drug that could disturb the signaling pathways driven by BCR-ABL, and thereby frustrate the culprit's ability to incite the deadly proliferation of cancer cells, but at the same time leave normal cells untouched.

The concept that such a drug might be efficacious against CML gained few immediate adherents. The objections of the proponents of conventional wisdom multiplied and concerns were raised: what if the drug that obstructed Bcr-Abl also injured other cellular components critical to life?

"You can draw on many different lines of investigation. Solving problems that arose from the research was incredibly interesting. The real question was whether I could stomach the clinical part of it."

Just as Sawyers would later not be dissuaded by critics of his approach to prostate cancer treatment, Druker and Lydon proceeded despite these objections. As they expected, imatinib first killed cancer cell lines that needed BCR-ABL to grow while sparing normal cells, then killed cancer cells taken from patients with CML without harming unaffected cells.

The results of their groundbreaking work are now the stuff of medical history. Gleevec (imatinib) was soon hailed as a miracle drug. A new age in cancer treatment—that of molecular targeted therapy—had begun. As these new strategies were being devised, Sawyers would make good use of these new tactics later in his career, when his research began to focus on prostate cancer.

Overcoming Obstacles

But progress is never simple…there are always obstacles to overcome. "The sad part was that many patients in the later stages of CML developed resistance and relapsed quickly. We eventually would learn that some patients treated in the early stage relapsed as well, and that CML cells were still present at low levels in patients in remission. So we set out to solve the puzzle of why some patients were developing resistance." This is what led Sawyers to begin investigating treatments for prostate cancer.

In collaboration with two of his trainees, Mercedes Gorre, PhD, and Neil Shah, MD, PhD, Sawyers identified the causes of resistance to Gleevec. "It was the work of structural biologist John Kuriyan that showed us how imatinib bound to BCR-ABL. That work helped us understand how mutations could prevent the drug's binding. Soon after that we found dasatinib, a new drug that inhibited BCR-ABL in its mutated form." Sawyers' efforts in CML would equip him to go on and try to conquer the next disease that caught his attention. "The work defined a path that has now been pursued again and again with other cancers. I applied the same strategy myself in developing a treatment for metastatic prostate cancer."

Developing Enzalutamide– With an Eye Toward Its Successor

Current thinking on the development of treatment resistance in prostate cancer holds that a patient relapses because the ARs on the tumor cells are no longer driving the disease. Sawyers, always one to challenge conventional wisdom with an eye toward overturning it, felt otherwise. "We thought that mutations in the androgen receptor might be the cause."

As it turned out, he was right. Cancer cells, he discovered, mutate and then go on to produce an abundance of ARs, which once again fire up the cell's signaling activity to rob a drug of its efficacy. He recognized his old adversary, the mutation, which he had encountered before. He knew from experience that what would be needed was a drug that could suppress the uprising of deviant signaling activity, shut down the mutinous ARs, and inactivate them.

In collaboration with UCLA biochemist Michael E. Jung, PhD, Sawyers and his team screened for and found a compound that was successful in shrinking drug-resistant tumors in mice. But would it work in patients with prostate cancer? Indeed it did. The drug that eventually emerged was enzalutamide.

On August 31, 2012, the FDA approved enzalutamide for the treatment of patients with mCRPC. The approval was based on a single randomized, placebo-controlled, multicenter trial in 1200 patients.

An old hand at ferreting out cancer's tricks, Sawyers is already one step ahead of his enemy and planning his next move against the disease's ability to circumvent its own annihilation. "We've already started thinking about resistance to enzalutamide; we started before we even saw it happen in patients. We knew it would eventually

become a problem. We've seen it happen with other targeted therapies."

Indeed he did, and now, thanks to Sawyers and others who have helped develop such targeted cancer drugs as imatinib, dasatinib, and enzalutamide and its successor (it's in the works), CML has been reduced to a manageable chronic condition, and patients with mCRPC are getting new leases on life.

On a Mission to Speed Up Combination Therapy

Sawyers' pet project now is to persuade both the FDA (which he considers sympathetic), and the business community to get behind combination therapy with these drugs. Right now, he argues, we are doing exactly what was done 70 years ago in infectious disease. "We give one drug, it works, and then it stops working. Then we give the next drug, it works for a while, then it stops working. Isn't it blatantly obvious that we need to give these drugs in combination?"

No one, he says, will argue that we shouldn't give combination therapy. "What I find somewhat amazing is that we're not doing it fast enough, we're not embracing it. It's sort of my mission right now to advocate for that. I'm pushing on all fronts."

With a record such as his, combination therapy is likely just around the corner.

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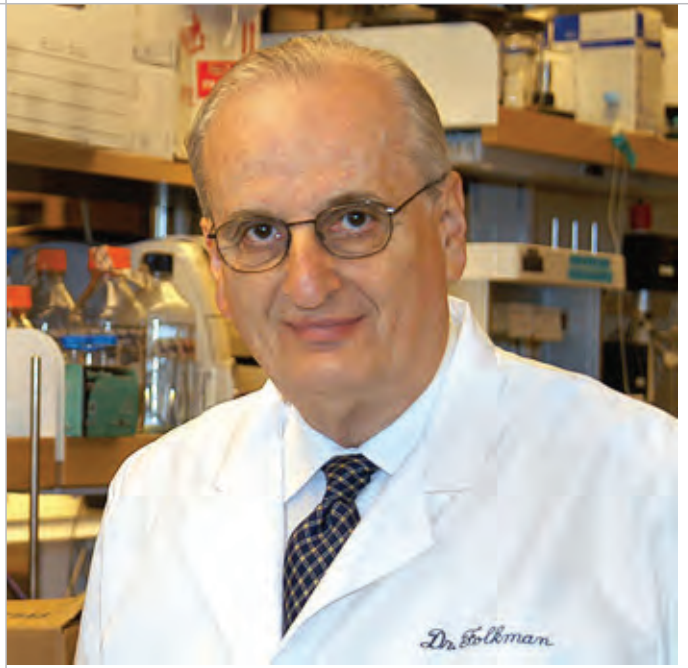

Judah Folkman, MD

Giants of Cancer Care™ inaugural class 2013

SCIENTIFIC ADVANCES

Judah Folkman, MD (deceased)

Harvard Medical School

Asked why Judah Folkman, MD, ranks among the greatest modern-day medical pioneers, Robert S. Langer, ScD, recalled the time he told Folkman the gist of a new paper involving ultrasound. Folkman asked why heat from the ultrasound wouldn't cause harm, and Langer explained how endothermic reactions could be used to keep things cool. Folkman pondered the technique and then, off the top of his head, began imagining how it could improve everything from cast design to hurricane management.

"Each idea was totally unorthodox and yet fully plausible. It was truly amazing," said Langer, then a postdoc in Folkman's lab, and now an MIT Institute professor who runs a storied biomedical engineering lab at the school. "More amazing, however, is the fact that I tell this particular story not because it was a creative apex for Judah, but because it was just a typical conversation that I happen to remember. He was just that creative. He was constantly pushing himself and others, consciously, to invent bold ideas—ideas that could change the world."

Over the course of a 74-year life cut short by his sudden death in 2008, Folkman changed the world repeatedly with bold ideas that ranged from implantable pacemakers and subcutaneous birth control to an entirely new field of medical study: how diseases like cancer recruit blood vessels from the body via a process called *angiogenesis*.

A Gift for Creative Thinking

Many strengths fueled Folkman's success. Colleagues from Harvard University—a school that has produced or employed 144 Nobel Prize winners over the years—say they've never encountered a smarter person. Langer—a man who has authored more than 1200 papers, won more than 800 patents, and launched more than two dozen companies—says he's never met a harder worker or a more persistent experimenter.

But none of Folkman's strengths stood out more than a consciously cultivated gift for creative thinking, one that repeatedly allowed him to see possibilities that others missed. The idea of fighting cancer by starving tumors of blood first occurred to Folkman in 1963, when he and Fred Becker were comparing possible substitutes for blood transfusions. During those experiments, the two young doctors injected adult mouse melanoma cells into isolated, perfused thyroid glands taken from dogs, and noticed that while tumors did form, they never developed blood vessels or grew beyond 2 mm in diameter.

Other researchers had already made similar observations, but Folkman's efforts to understand

his findings led him to complete a few more experiments and then to hypothesize, in a 1971 paper in *The New England Journal of Medicine*, several very new ideas:

- Tumors cannot grow dangerously large unless they develop vascular networks.
- Tumors can't build their own vascular networks, so they must trick their hosts into building such networks through angiogenesis.
- An angiogenesis inhibitor could therefore treat cancer effectively.

The article drew such negative response that it quickly made Folkman a pariah. Most top cancer researchers at the time thought tumor vasculature to be a mere response to inflammation rather than a necessary precondition for tumor growth. Even researchers who found Folkman's angiogenesis hypothesis theoretically possible attacked it as irresponsibly speculative.

Despite the criticism, Folkman decided to pursue the angiogenesis hypothesis, alone if necessary, until he confirmed or disproved it.

"It is tempting to say that Judah just ignored his critics at this point, but it's dead wrong," said Donald E. Ingber, MD, PhD, another Folkman protégé who now runs a major research institute, Harvard's Wyss Institute for Biologically Inspired Engineering.

"He considered every single critique and would have dropped the hypothesis had the critics advanced a valid argument based on experiments for doing so," said Ingber. "But they didn't, and Judah had the courage to proceed."

A Young Brilliant Mind

The years of (relative) isolation that followed this fateful decision marked a sharp departure from all that had come before. Folkman's father, a rabbi who regularly visited hospitals to comfort ailing congregants, made a habit of taking his 7-year-old son along. The plan was to nudge young Folkman toward a yeshiva (a Jewish educational institution), but the trips sparked a passionate interest in physical, not spiritual, health, and the boy decided on medicine.

By the time Folkman entered high school, he had set up a medical research lab in the basement of his family's house. His most impressive experiment: removing the heart of an anesthetized rat and keeping it beating for several days in a perfusion system of his own design.

Officials from the local high school, not surprisingly, decided shortly thereafter to send the precocious 15-year-old directly to Ohio State University, where he spent four years studying under the world-famous surgeon Robert M. Zollinger, MD, before enrolling, at age 19, in Harvard Medical School.

Folkman's years at Harvard Medical School saw him invent and install the world's first implantable pacemaker. (The school somehow permitted that radical experiment but lost out on a fortune when it nixed another of the young student's innovative ideas: patenting the design.)

After graduation, during a two-year stint in the Navy, Folkman and a colleague discovered that silicone rubber could be made to release chemicals at a predictable rate, and Folkman turned that insight into the world's first implantable birth

control device. (This time, he willingly gave away the patent rights, to the World Population Council.)

In 1967, just two years after Folkman completed his residency at Massachusetts General Hospital (as chief resident, naturally), colleagues at Harvard named him chief of surgery at Children's Hospital in Boston. He was 35.

Folkman somehow met all of the resulting commitments of that job—he was famous for returning every patient call—while he built and ran the laboratory that would test his controversial ideas about angiogenesis.

Passing Down the "Intellectual Adventure"

He also managed to squeeze in a happy family life. His widow, Paula, has described their marriage as a 48-year-long romance in the obituaries that followed Folkman's death. His two daughters described life with Folkman as an "intellectual adventure," filled with impromptu brain games such as inventing new uses for common items.

It was the same sort of game that Folkman played in his conversations with Langer and with everyone else he knew well. He had learned it from his father, who played it with him at the dinner table and helped build a mind that saw what others could not.

Partnering With Corporate America to Further Research

Folkman's many commitments naturally left him very short of time, but over the next decade, he was often shorter of the money he needed to do his research. Grant committees frequently declined to finance experiments that challenged their beliefs so directly. Folkman responded by challenging himself much as he would challenge his daughters—to devise creative funding ideas. His brain responded with a concept that would change academic research forever: corporate financing.

In 1974, he accepted a $23 million grant from Monsanto Corporation. Academics denounced Folkman for selling out, but Harvard Medical School's president supported him, and corporate funding has since become an invaluable component of scholarly research. Throughout the early 1970s, Folkman attracted enough money and talent to produce a steady stream of published findings.

His team found several angiogenesis "factors," compounds secreted by tumors that induce blood vessels from the host to rapidly extend into the cancer. Better still, team members also demonstrated the existence of at least one angiogenesis inhibitor with an elegant experiment that showed how growing blood vessels avoid cartilage. The team struggled to isolate any of the antiangiogenic compounds from the cartilage, however, so Folkman challenged his brain again, this time for ideas that would strengthen his team. His brain responded with another world-changing idea: bringing other types of scientists into medical research.

In 1974, Folkman hired Langer, who had just earned his doctorate in chemical engineering from MIT, and Langer proceeded to help the team take a big step toward isolating the angiogenesis inhibitor in cartilage. *Science* published the paper in 1976, the same year that *Nature* published an article by Folkman and Langer that is now credited

with helping create the field of controlled-release drug delivery. The inhibitor was not purified or identified until 1990, when it was published again in *Science*, by Langer and his postdoctoral fellow at the time, Marsha A. Moses, PhD.

Between 1980 and 1996, Folkman and his team found 12 angiogenesis inhibitors, and went on to show that several of them produced incredible benefits in cancerous mice. When one of those compounds excelled in animal studies and another seemed promising in early human trials, mainstream publications such as *The New York Times* speculated that Folkman's once-derided work would soon cure cancer.

The Angiogenesis Inhibitor Success Story

Skeptics enjoyed a brief resurgence when the compound in clinical trials stalled, but the tide by then had definitively turned. Other labs around the world had begun their own investigations into angiogenesis. In 2004, 33 years after Folkman predicted that angiogenesis inhibitors would one day become a mainstream cancer treatment, the FDA approved Avastin (bevacizumab) for use in patients with advanced colon cancer. Just four years later, there were 10 angiogenesis inhibitors approved in the United States and hundreds of labs looking for more.

With so many scientists now taking up the task of discovering individual inhibitors and turning them into drugs for mature tumors, Folkman focused more of his attention on the role angiogenesis plays in the earliest stages of cancer and in a range of other diseases.

His publications on angiogenesis and macular degeneration led to tests that proved angiogenesis inhibitors can restore vision lost to abnormal ocular neovascularization or exudative age-related macular degeneration, a condition that afflicts roughly 3% of Americans.

His publications on angiogenesis in other diseases may one day lead to new treatments for both the many diseases characterized by too much angiogenesis (psoriasis, rheumatoid arthritis, and more than 70 others) and several other ailments characterized by too little (stroke, coronary artery disease, chronic wounds).

A Passion That Will Live On

"He was still doing world-changing work—and was still consumed with the passion for discovery—on the day that he died," said Moses, another of the protégés who came to Folkman as a postdoctoral researcher and rose to international fame. Moses is director of the Vascular Biology Program founded by Folkman at Children's Hospital Boston.

Folkman and his research team in the lab at Harvard.

"He was also mentoring an incredible number of researchers from around the world who had, by that time, taken up the field he created. Much of that time went to veterans of his program who had gone on to run their own labs, but Folkman also mentored countless people who had no ties to him whatsoever.

"Some people would probably say that Dr Folkman was helping his competition, but such an idea was absolutely foreign to him," said Moses. "His only goal was pushing the science forward in order to improve the lives of the patients that he cared so much about. This is exactly what he did—and to an extent that very few others ever imagined. He truly was an amazing man, and we were honored to have known and worked with him."

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