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Giants OF Cancer Care™

2014

CLASS ALBUM

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SETTING A FOUNDATION UPON WHICH TO BUILD

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Exceptional cancer researchers and cancer physicians aren't born—they're made. Although they come from varied backgrounds, there is a common thread they all seem to exhibit: a dogged persistence in tackling and solving some of the most complex scientific challenges; a compassionate drive to improve the quality of life of the patient; drawing inspiration from mentors who came before them; and all too often, they have experienced the loss of a family member or friend from cancer. These attributes and experiences mark just some of what makes up an individual destined to thrive in the oncology field.

The Giants of Cancer Care initiative celebrates individuals who have achieved landmark success within the field of oncology. As Chair of the Advisory Panel, one of my goals was to build on the solid foundation that was set in 2013 with the inaugural class of Giants. The members of the 2014 Giants of Cancer Care class are as impressive as we hoped—an assembly of 16 esteemed oncology leaders who have distinguished themselves in their respective fields and who now join our 2013 inaugural Giants class in receiving this honor.

Another one of my goals was to add diversity to the Advisory Board by expanding its membership. The panel is now made up of 29 oncologists and hematologists renowned as leaders in the field. In selecting this year's Giants, the panel considered a nominee's body of work, including clinical impact, significant contributions, and overall accomplishments. The nomination process was opened to a national audience, and the categories were broadened, with the board evaluating nominees in 11 tumor type categories, including breast cancer, lymphoma, lung cancer, melanoma, and prostate cancer, as well as in five specialty categories.

With these first two classes of giants, this dynamic program has laid the groundwork for its future development and expansion, honoring not only the oncology trailblazers of today, but also cultivating the ideas and aspirations of a new generation—potential Giants of Cancer Care in the years to come.

TABLE OF CONTENTS

RECOGNIZING EXCELLENCE, BUT LOOKING AHEAD TO THE FUTURE

It wasn't too long ago that "cancer" was described as medicine's "black box." It was a great unknown. But with the investment this country has made in cancer research, we have a greater understanding of the molecular basis of cancer and innumerable new capabilities for detection, diagnosis, and drug delivery. In addition, refinements in surgical techniques and radiation delivery systems have resulted in targeted, focused therapies that improve the patient experience and outcomes. Patients are living longer and are leading healthier lives with and after a diagnosis of cancer.

But practicing oncologists and hematologists continue to face challenges—from current and projected demand for services and a slowly dwindling oncologist workforce supply, to an ever increasing range of economic, regulatory, and administrative pressures.

It is in the face of these challenges that we launched the Giants of Cancer Care initiative in 2013. Our inaugural class, which initially recognized the achievements of 12 pioneers in the oncology field, has expanded this year to 16 and includes not only tumor-specific categories, but also categories for education, supportive care, and genetics.

Giants are chosen by an exclusive advisory board made up of 29 oncology educators, clinicians and researchers. Advisory Board members have dedicated their valuable time to the program, providing guidance to OncLive as it further develops the program and, most importantly, selects the oncologists who will be named Giants.

In evaluating criteria for selection to the inaugural class of Giants, the Advisory Board considered individuals who have made a significant contribution to patient care, clinical trials or translational research.

The growth, support, and enthusiasm for the award has been remarkable among oncologists. It is our distinct privilege to honor these unsung medical heroes. It is our mission to continue recognizing the leaders in the oncology field for their remarkable achievements in research and clinical practice.

MIKE HENNESSY
CHAIRMAN/CEO
MJH ASSOCIATES, LLC

BREAST CANCER

DENNIS J. SLAMON, MD, PhD

UCLA JONSSON COMPREHENSIVE CANCER CENTER

The idea that one kind of cancer may include several subtypes, each marked by unique mutations that can be targeted with tailor-made therapies, is taken for granted these days.

Much of today's research is focused on identifying hallmarks of cancer subtypes and developing medications to target them, and more than 65 targeted therapies for various cancer types are on the market in the United States.

Follow that trend back to its beginning and you'll find Dennis Slamon, MD, PhD, standing on the starting line.

Slamon, now director of Clinical/Translational Research at the Jonsson Comprehensive Cancer Center at the University of California, Los Angeles (UCLA), conducted the laboratory work and testing that resulted in trastuzumab (Herceptin), the first molecularly targeted therapy for breast cancer. The monoclonal antibody made by Genentech helps counteract a mutation of the HER2 gene, which is found in about 25% of breast cancer patients. It reduces recurrence rates by half in specific types of early HER2-positive breast cancer and by one-third in metastatic HER2-positive breast cancer, and increases survival rates by about 35% and 30% in early and metastatic disease, respectively, according to the researcher.

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INDUCTEE

2014

The intravenously administered medication was approved by the FDA in 1998, and within 10 years, it had been used to treat 420,000 women worldwide. Its approval also marks the moment that the area of targeted therapies for cancer really began to take off.

"That's the area where things are moving the fastest—finding molecular heterogeneity and taking advantage of that to develop novel therapeutic approaches for subtypes, rather than one-size-fits-all approaches," said Slamon. "That's where a lot of effort is going on, not just by us, but in a number of labs around the world. Trastuzumab was one of the things that really broke that wide open."

It's an accomplishment that made Slamon the subject of both a Lifetime movie, *Living Proof*, and a book by Robert Bazell, *HER-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer*. His is a particularly intriguing story because the scientist had to fight for 12 years to get trastuzumab from development through approval, keeping the project alive despite a nearly crippling early lack of funding.

"We followed the data, and if it's there and it says your approach is right, it doesn't matter what anyone else's preconceived notion is," Slamon said. "We never gave up when people said we were wasting our time."

Those achievements have been heralded worldwide, and they are certainly appreciated by OncLive. For bringing the world trastuzumab, helping to launch an important new path for cancer research, and developing additional promising anti-breast cancer drugs during a career that has spanned about 40 years, Slamon has been selected as one of OncLive's Giants in Cancer Care™ for 2014, in the Breast Cancer category.

"I was honored, as I think were all the honorees, and I felt very good about being named among those peers," Slamon said upon learning he would receive the award.

STRIVING FOR FURTHER DISCOVERIES

These days, Slamon is continuing his fight against cancer through his roles at UCLA. Serving as chief of its Division of Hematology-Oncology and also as a professor of Medicine, the doctor devotes about 30% of his hours to administrative duties, including raising money for research; another 20% to seeing cancer patients; and a small percentage to teaching and giving lectures.

He spends the remainder of his time—nearly half—reviewing data and considering where it might lead.

"The highlight of my day is to meet with mid- and junior-level investigators and see this new stuff," he said. "With colleagues capable of pushing the agenda in a positive way, we can think about exciting ideas."

One of the most promising recent developments to come out of Slamon's lab has been palbociclib, an oral inhibitor of CDK 4/6 that was developed for the treatment of hematopoietic malignancies but was only mildly active in that cancer type. On August 18, Pfizer announced it had submitted a New Drug Application to the FDA for palbociclib, in combination with letrozole, as a first-line treatment for advanced or metastatic breast cancer in postmenopausal women.

Another project of Slamon's lab has involved BMN 673, a PARP inhibitor being developed by BioMarin that targets BRCA1/2 mutations in patients with locally advanced or metastatic breast cancer, but that also may have promise for the treatment of triple-negative breast cancer, some


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Cancer Care
2014
BREAST CANCER
Dennis J. Slamon, MD, PhD
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luminal breast cancers, and other malignancies, Slamon said.

The drug is being tested in a phase III clinical trial.

Not surprisingly, Slamon and his colleagues are also continuing to work with trastuzumab.

In 2010, the drug was approved by the FDA for use in HER2-positive metastatic stomach cancer, in combination with chemotherapy. Now, Slamon's group is considering potentially better ways to use the drug, such as in combination with other antibodies or other targeted agents.

"We're looking at what other pathways you might be able to block in combination with HER2 to be more efficacious in any malignancy where the alteration is—breast and gastric, although some ovarian cancers, 8% to 10%, have the alteration, as well," he said.

PAVING THE WAY TO A MEANINGFUL CAREER

The son of a coal worker and a homemaker, Slamon knew from the age of 5 or 6 that he wanted to be a doctor, inspired by the physician who used to make house calls to treat his family.

"He was very caring, very gentle, and very effective," Slamon recalled. "I thought it would be great to be able to help people like that and make a family feel so good."

In high school in New Castle, Pennsylvania, a student teacher fueled Slamon's interest by infusing his lessons about biology with enormous enthusiasm. Slamon moved on to Washington & Jefferson College, in his home state, excited to learn more.

"I took all but one of the biology courses the school had to offer, because I couldn't fit any more into my schedule," he said. "I loved the topic, the diversity of it, and the more I learned, the more I thought about combining my interests in biology and medicine."

Slamon did exactly that, simultaneously earning his medical degree and doctorate in cell biology in 1975 through a combined MD/PhD program at the Pritzker School of Medicine at the University of Chicago.

It was there that he began the research that paved the way for trastuzumab. In the lab of Winston A. Anderson, PhD, a cell

biologist in the Anatomy Department, and under the tutelage of Werner Kirsten, MD, of the Pathology Department, Slamon participated in research on retroviruses that caused cancer in mice.

"They were incredibly potent, more than anything we'd seen—acutely transformative retroviruses that caused cancer 2 to 3 weeks after injection," Slamon said. "We learned, ultimately, that they were carrying an oncogene," a gene with cancer-causing potential.

LONG BATTLE, LONG HOURS ON PATH TO TRASTUZUMAB

That work led to a breakthrough several years later as Slamon completed a fellowship at UCLA's Division of Hematology-Oncology.

"We realized that what these acutely transformed viruses were carrying that made them so potent were genes stolen from normal cells," Slamon said. Once stolen, the researcher found, those genes—known as proto-oncogenes—were altered, becoming abnormal and contributing to the growth of cancer.

Slamon built on that knowledge in 1986, when he was asked by a Genentech researcher to look for siblings to the epidermal growth factor receptor, also known as HER1, a protein that sits on the surface of a cell and can cause cancer if mutated. One of the six genes Slamon was asked to investigate was HER2, and the results intrigued him.

"In 25% of breast tumors, we saw an alteration of gene amplification, an overabundance of numbers of the HER2 gene," Slamon recalled. "Then, we realized that women whose tumors contained the alteration had a much different outcome. They had a more aggressive tumor that recurred more rapidly, and they died more quickly."

The chilling finding proved something that would help change the face of cancer treatment.

"It told us right away that we were not dealing with one disease in breast cancer," Slamon said, "even though the dogma at the time was that each disease was a monolith, defined by the tissue where it arose and treated with a one-size-fits-all approach."

To Slamon, HER2 looked like a perfect target for treatment with an antibody, but not everyone agreed.

"No one was interested in pursuing antibodies because so many had failed," Slamon said. "I was trying to convince Genentech to stay with the program based on the data, and it took a couple of years of hard sell. The company wasn't terribly enthused, but there was a core of people there who believed in the data and kept the project alive."

LINING UP PRIVATE FUNDING

Luckily for Slamon, there were also private funders who felt certain he was on the right track.

One was Lilly Tartikoff (now Lilly Tartikoff Karatz), whose husband, Brandon, then president of NBC's Entertainment Division, had been treated for cancer by Slamon. The other was Tartikoff's friend, Ronald O. Perelman, chairman of Revlon, whom Tartikoff approached for support.

Initially, Slamon recalled, Perelman donated $1.8 million to help with his research. In 1995, Perelman gave $7.5 million to establish the Revlon/ UCLA Women's Can-

cer Research Program, which Slamon still directs.

Millions more have been raised for Slamon's research, first through an annual Fire and Ice Ball founded by Tartikoff and Perelman, and now through the yearly Revlon Run/Walk. There's one Run/Walk in Los Angeles and one in New York, which together largely fund the translation of work from Slamon's lab into clinical trials, he said.

"Lilly told me what amazing work Denny was doing, and said that if he only had the funding, he could help many people," recalled Perelman, who also is CEO and chairman of MacAndrews & Forbes Holdings. "After meeting him and seeing the potential in what he was working on, I immediately wanted to get involved. Denny is one of the most brilliant and dedicated researchers in medicine today, and his work has saved many women's lives. I am so proud to have been able to help him accomplish that."

A major supporter of Slamon's preclinical work has been the US Department of Defense's Breast Cancer Research Program, through its Innovator Award, the doctor added.

With funding still difficult to come by for many scientists, Slamon wants to see every grant and donation used as effectively as possible. That's why the researcher spent 3 years as part of a Dream Team put together by Stand Up To Cancer, a project of the Entertainment Industry Foundation that utilizes the star power of celebrities to raise funds aimed at slowing the competition between labs and bringing them together to collaborate.

"The idea that one lab will make progress quickly is archaic," he said. "Putting funds behind the effort to bring labs together is a good experiment."

While Slamon's grant through Stand Up To Cancer has been completed, he remains convinced that collaboration between labs is essential.

"That's still the ideal way to do research, although I'm not sure we've yet mastered it," he said. "There are still improvements we can have on that model, but I think that kind of collaboration, team research, can be conducted and is the best way to approach problems on a given drug."

Regardless of the format, Slamon is committed to continuing the work that was his childhood dream—and the embodiment of the values he absorbed during those years.

"My parents taught us that doing something productive that could help others was the pinnacle of what you might want to achieve," he recalled. Accomplishing that through the development of trastuzumab was "enormously gratifying," he added. "It's what it's all about." ■

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People are at the heart of what drives Teva Oncology. With over 100 years of global pharmaceutical expertise, our mission is to develop and deliver solutions that advance cancer care and improve the lives of people affected by cancer.

We are built on a strong foundation—Teva Pharmaceutical Industries Ltd. Our parent company is one of the top 10 global pharmaceutical companies, with over 60 manufacturing sites and 34 R&D centers worldwide. Teva has a portfolio of over 1,000 molecules—with over 50 products in oncology.

Teva Oncology is a leader in cancer care and one of the top 10 oncology companies in the US.*[1] Our portfolio includes multiple offerings for hematologic malignancies and an approved product for supportive cancer care. We have a diverse oncology pipeline of small molecules and biologics in development for hematologic malignancies, solid tumors, and supportive care. Our expertise is continually improving to deliver more treatment choices for people with cancer.

We are committed to helping patients throughout their therapeutic journey. We provide educational programs and materials, reimbursement support services, and sponsorships to cancer support organizations.

Our vision is to change the course of cancer care—one patient at a time.

TEVA Oncology

We treat the person, not just the cancer

*Excluding supportive care.

Reference: 1. EvaluatePharma®, March 2013.

DRUG DEVELOPMENT

HOWARD A. "SKIP" BURRIS III, MD

SARAH CANNON RESEARCH INSTITUTE

"Participation in a clinical trial is the first step in fighting cancer, not the last."

This statement holds special meaning for Howard A. "Skip" Burris III, MD, who advances cancer therapies for patients through one of the largest drug development programs in the industry. With his more than 20 years of experience in the field of early-phase clinical research, Burris has seen first-hand how novel therapies can make a difference in the fight against cancer. Burris has ensured that this message is embedded into the clinical culture that he leads at Sarah Cannon, in Nashville, Tennessee, a cancer enterprise that pairs clinical research alongside comprehensive treatment from diagnosis through survivorship.

"We help thousands of patients—and I get great personal satisfaction in seeing even one person benefit from a clinical trial," said Burris, who serves multiple roles at Sarah Cannon. As the president of clinical operations for the care service line of his organization, and the chief medical officer and executive director for its drug development arm, Sarah Cannon Research Institute (SCRI), Burris has the advantage of seeing how the delivery of new treatments has elevated the standard of care for his patients.

"Back in the early 1980's there were not many therapy options for those facing cancer," said Burris. "It was the beginning of modern chemotherapy

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INDUCTEE

2014

with drugs like Taxol and Taxotere, which were starting to shrink tumors in a targeted way, but over the last 30 years, that definition of targeted has really changed in a big way."

CHOOSING A PATH

Burris was just starting out his medical career at this pivotal period of time for cancer therapies. A graduate of the United States Military Academy at West Point, NY, he originally had set his sights on becoming an engineer, excelling in chemical engineering and math. Yet all roads in his life kept pointing him in the direction of medicine. "At West Point, you are assigned a family sponsor, and mine just happened to be a physician," explained Burris. "I wanted to help make a difference with the path I chose post college, and seeing the impact that my sponsor made by helping patients was what really led me to reconsider my earlier ambitions."

Given such influences, Burris enrolled in medical school at the University of South Alabama in Mobile, but he does admit his lack of pre-medicine courses in college left him somewhat unprepared for medical school. Determined to make up for it, Burris tried to learn all he could.

"I did the book work. I stayed late when we began to take care of patients. I tried to be the person to open or close on surgeries, to be in the emergency room, and it helped me gain the experience about what to do later in life as a doctor," he said. Burris then pursued an internship and residency at Brooke Army Medical Center at Fort Sam Houston, Texas.

Though Burris was initially attracted to surgery, the experiences he had through his clinical studies and rotations helped form his deeper focus in the field of oncology. "In one of my rotations, I worked with a dedicated group of oncologists who really opened my eyes to how unique the specialty was," said Burris. "I witnessed something I had not expected–the patients were caring for the doctor just as much as the doctor was caring for them."

The patients also inspired him with their gratitude. "Cancer patients are those you really feel like you are partnering with, and taking the journey with," he said. And after caring for those patients, Burris chose to continue at Brooke Army Medical Center with a fellowship in hematology and medical oncology.

Burris eventually held positions as the director of clinical research for drug development of the Cancer Therapy and Research Center and the Institute for Drug Development, both in San Antonio, Texas from 1993 through 1996. He established the first community-based phase I drug development program in Nashville, Tennessee, in 1997, which eventually would become the SCRI.

FOCUSING ON CANCER RESEARCH

In his earlier research positions, Burris was surrounded by forward-thinking clinicians during one of the most critical turning points in the development of cancer treatments. His mentor at the Institute for Drug Development, Daniel D. Von Hoff, MD, FACP, who demonstrated just how impactful clinical research can be for cancer, was one of the pioneers of phase 1 research, and has been credited with initiating many of the novel targeted cancer studies in the United States. Noted Burris, "He helped me to see the value of seeking newer and more effective drugs, and working with a special set of patients who were interested


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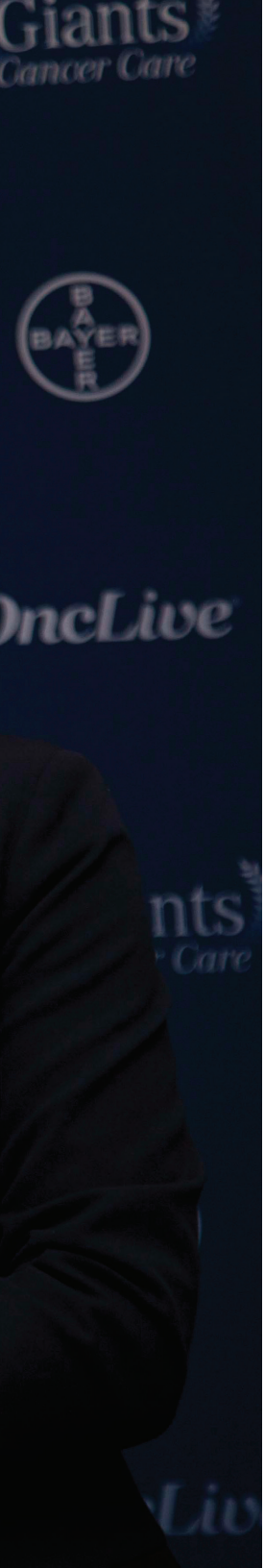
Howard A. Burris III, MD



in participating in clinical trials."

A pioneer in his own right, Burris has continued to advance phase I research and make his mark on novel therapies today. Among his many notable accomplishments, he led the first human studies for now-approved breast cancer drugs such as docetaxel, ixabepilone, lapatinib, everolimus and ado-trastuzumab emtansine. Beyond breast cancer research, Burris has been the lead investigator and author of randomized phase III trials leading to the approval of gemcitabine, which is used to treat advanced pancreatic cancer. Burris has also authored more than 300 publications and over 450 abstracts.

Through his oversight of the drug development programs at Sarah Cannon, the organization has conducted more than 140 first-in-human clinical trials and has held a leadership role in the development of more than half of the approved anticancer drugs over the last decade. Burris has also helped to expand Sarah Cannon's research expertise internationally. He has collaborated with partners in the United Kingdom to initiate an early-phase research program that opened to both public and private patients in 2010, as well as a molecular profiling lab that launched in 2013.

Colleague Jeffrey Patton, MD, the CEO of Tennessee Oncology, the physician practice where Burris is also a partner, commented that "having someone like Burris at the helm of these efforts makes such growth possible." Patton continued, "He is smart, fair, energetic, charismatic, a rainmaker—he's a superstar." Patton praised Burris for being one of the smartest guys in the room at scientific meetings, and noted that, "He also has a business mind, which people defer to, wanting and valuing his opinion." Most interesting, Patton said, is the distinctive ability that Burris has to be a research scientist as well as to handle the business aspects of medicine.

EXHAUSTED STANDARD TREATMENTS

In the oversight of Sarah Cannon's world-renowned programs for investigational drug development, Burris shared that "we see a record number of new cancer patients a year who are eligible for clinical trials—those who have exhausted standard

treatments and they have a particular mutation or abnormality." He further explained that Sarah Cannon has hundreds of clinical visits each month that span solid tumors like breast, lung, GI, but also blood cancers. "Within each of these cases, we see many patients who had prior treatment, but are no longer responding and need something new," he said. But it's not numbers or the business elements that drive Burris to continue his focus on early-phase studies: It's seeing countless patients come to Sarah Cannon having failed prior therapies and needing better alternatives.

COMMUNITY-BASED RESEARCH

Burris joined Sarah Cannon in 1997, which at the time was the first community-based research program that didn't have an academic center behind it. "While there are many more programs now, it was exciting to be a part of the team that stepped out to show that phase I research could be done if you had the right support system in place," said Burris. And community-based research is what has helped Burris to achieve such milestones in drug development.

"Over the last two decades, Dr. Burris has been devoted to the advancement of therapies for patients through innovative cancer research and care," said Sarah Cannon's chief executive officer, Dee Anna Smith. "His significant contributions to the development of new agents has transformed cancer treatment options worldwide."

Today, there are more than 100,000 new cancer cases diagnosed within Sarah Cannon markets across the United States and United Kingdom. "By reaching such a vast population of patients through our cancer care, we have the ability to also reach the subpopulation who are in need of and eligible for clinical trials," said Burris. "While a small minority of patients can afford to travel to sites across the country that may offer novel treatments, most face social and economic barriers that limit their access. And Sarah Cannon removes those barriers, so that patients can receive cutting-edge therapies closer to home."

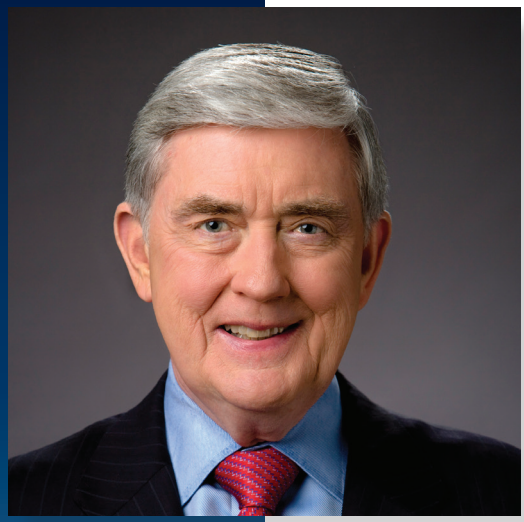
Burris knows all too well that without clinical research, he couldn't provide leading-edge therapies to his patients. Through his experiences, Burris has noted that targeted investigational therapies have really come a long way, with studies 30, 20, and 10 years ago that led to the approval of tamoxifen, Herceptin, and Gleevec, respectively. Burris added, "With the promise of immunotherapies and genomic sequencing over the last 5 years, these newer targeted methods are helping us better understand what is causing the cancer in the first place, and that's allowing me to offer more personalized options to my patients. It's really the best part of my week—being able to go into a clinic room and actively participate in a patient's journey in such a meaningful way," said Burris.

COMMITMENT TO ADVANCE

"While not every study can be a home run, we do learn from each investigational agent and end up further ahead than where we started," said Burris. He also acknowledges that it takes a village to make clinical trials successful. "Advancing therapies is a team approach, and I attribute my continued successes to the physicians I work with daily, the researchers I have the privilege of mentoring,

the partnerships we have forged with the largest pharmaceutical and biotech companies in the world, and above all the patients who are willing to participate in our work every day," he proudly stated.

"One thing about cancer—it's a humbling profession to be in for the successes and the failures. The patients who step forward and participate in clinical trials know that what they are doing is more likely to help someone else [than to help them], and seeing their strength is inspiring. I always feel the patients have given me the perspective, the motivation, and the energy to commit to this cause every day. Even uncertain of their futures, the patients come in for treatments, and are grateful to be a part of the process, which brings new perspective and inspiration to us all. We certainly couldn't advance therapies without their contributions and participation and I feel they've given me more than I've given them." ■



EDUCATION

JOHN R. SEFFRIN, PhD

AMERICAN CANCER SOCIETY

There are few words more associated with the American Cancer Society (ACS) than education, which made the choice for the Giants of Cancer Care™ award for education this year an easy one—ACS chief executive officer John R. Seffrin, PhD. The 2014 recipient says that eliminating cancer as a major public health problem requires both education and improved public policy, with an emphasis on elevating cancer prevention and ensuring access to quality health care.

"The ultimate conquest of cancer is as much a public policy issue as it is a medical and scientific challenge. The science alone is not going to be enough to eradicate the condition, especially if we don't deal with the issue of health disparities," Seffrin stated.

Seeing the big picture is what has propelled him since becoming CEO in 1992. It has led to a remarkable transformation of the ACS, going from an organization made up of 60 different boards to one that now has a standardized division operating model.

Seffrin initiated the transformation of the 100-year-old charity in 2010 that led to a complete restructuring, merging 11 corporate divisions into 1 central organization, and eliminating multiple governing bodies in favor of a single

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2014

board of directors. The transformation centralized virtually all back-office services, streamlined the fundraising portfolio, and realigned staffing resources.

"Reorganization has allowed us to standardize services and gain efficiencies. We have one fiduciary board of directors that is half the size of the former national board, with a much greater ability to direct the priorities, goals, and resources of the entire organization. Previously, each corporate division was governed by its own board, each with its own budget and program of work," Seffrin explained.

Implementing nationwide decisions was a slow, cumbersome process, but the organization's new structure allows it to be very nimble. He has fielded calls from other large nonprofit organizations, such as the YMCA, who asked just how he was able to accomplish it.

In his 2011 paper, *How the American Cancer Society Will Help Bring Cancer Under Control Earlier in the 21st Century: A Moral Imperative*, he pointed out that the world was changing and the previous operating model—how the organization was structured and governed, how decisions were made, and how the organization did business—fundamentally had not.

"Although we have made great progress with our current model, going forward it will allow, at best, for only incremental progress," he wrote. The ACS would not be able to make the kind of progress that it otherwise could if it did not change. He had data to show the progress made in research, treatment, education, and prevention that reduced cancer deaths over the years, but he also showed that there were thousands more lives that could be saved.

"Very few organizations have been able to publish data and show the kind of progress made in terms of reducing death rates and lives being saved. But, by the same token, we have lots of data to show that that number of lives saved could be a lot more if we were able to do business differently," Seffrin said.

EARLY INFLUENCES

Seffrin's first encounter with cancer dates to his childhood. His grandmother, who was living with his family at the time, died of cancer when he was 10 years old. He has since lost his mother to cancer, and his wife, Carole, is a breast cancer survivor.

A significant influence in Seffrin's life was his mother, who always believed he would do something important. She always saw the good in people, Seffrin said. "And she instilled in me the importance of being a forgiving person. In your professional life, if you can truly forgive, then you can move on. And this helps you stay the course and continue to lead."

The first step in forgiveness is understanding, and Seffrin's favorite novel, *To Kill a Mockingbird*, emphasizes the role of understanding the human condition. He said the level of writing in the novel is remarkable and is a key reason why he considers it a classic. "I grew up in the North, so it helped me better understand the Southern point of view," he said.

Another significant influence in Seffrin's life occurred when he was an undergraduate student in biology at Ball State University in Muncie, Indiana. A professor, William Bock, PhD, took an interest in his future plans and encouraged him to pursue a graduate degree. At the time, Seffrin's only intention was to graduate and get married.


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"I took his interest in me as a compliment," said Seffrin. "But I had no initial intentions of acting on his recommendation."

A week later, Bock caught up with Seffrin again, and handed him an index card with the names of 3 graduate schools he thought were the best. Bock wanted him to work on a master's degree in health education. He ended up going to the same school Bock had attended—the University of Illinois. Seffrin then went on to pursue and complete his doctoral degree at Purdue University. Looking back, Seffrin says that Bock's suggestion changed the path of his life.

PERKS OF THE JOB

Seffrin has been on the frontlines of the war against not only as CEO of the ACS, but—for many years before that—as one of the Society's roughly 3 million volunteers nationwide. Under his leadership, the ACS has become the world's largest voluntary health organization fighting cancer.

The organization didn't get where it is today without an energetic visionary at its helm. "I was in academia for 2 decades before leading the ACS," he said, during which time he had a number of opportunities to leave and join other nonprofit organizations. "Even if my career path had remained in academia, I'm certain I'd also have been engaged in a cause of one kind or another." Since joining the ACS, "the only constant in my weekly routine is travel. It is hectic and no 2 weeks are exactly alike."

One of the perks of the job is meeting with so many dedicated, gifted, and generous people, Seffrin said. That might include meeting with world-class cancer researchers at The University of Texas MD Anderson Cancer Center, holding a strategic meeting with volunteers, or engaging with ACS's intramural research scientists.

"ACS has a world-class epidemiology department—the largest in the private nonprofit sector—conducting a rich variety of ongoing research projects. Working with that team is part of what's so fulfilling about this career," Seffrin said.

"Right now, the team is following 300,000 participants over time, which will improve our understanding of cancer's causes, and how better to prevent and cure it," Seffrin said.

> *"The ultimate conquest of cancer is as much a public policy issue as it is a medical and scientific challenge. The science alone is not going to be enough to eradicate the condition, especially if we don't deal with the issue of health disparities."*

AVERTING A TSUNAMI

It has been a stellar career. Earlier this year, Seffrin announced his plans for retirement after 40 years with the ACS. A search committee has been assembled to find his successor.

Seffrin would like to dedicate the balance of his career to providing leadership on a global scale.

"I want to avert this tsunami of noncommunicable diseases, including cancer," he said. "We have an opportunity to create a world that will be both healthier and economically much more productive if we do the right things and bring cancer under control in this century."

The ACS has made so much progress in helping researchers understand how cancer develops at the intracellular level, and especially how it has become a major problem at the population level.

"This is an exciting time, especially if we can muster the courage and enlighten policymakers as they make their decisions. My hope is that I can play a role in getting our country, and other countries around the world, to make cancer control, research, and therapy a high priority," Seffrin said.

During the reception that honored all the recipients of the Giants of Cancer Care, Seffrin received a very meaningful compliment from Paul Bunn Jr, MD, recipient of the award for lung cancer, executive director of the International Association for the Study of Lung Cancer, and founding director of the University of Colorado Cancer Center. "I don't feel like a giant, but the ACS and John Seffrin have done more to save lives by pushing for a cigarette tax in Colorado than most of the scientists in the room," said Bunn. "They are the true giants." ■

GASTROINTESTINAL CANCER

GEORGE D. DEMETRI, MD

DANA-FARBER CANCER INSTITUTE/
HARVARD MEDICAL SCHOOL

For some cancer researchers, success means running your own laboratory independent of others, who might be viewed as competitors. Others, like George D. Demetri, MD, find success pursuing a career as a translational and clinical investigator, in which his goal is to bring other researchers together into highly functioning teams of global collaborations across academia, government, biopharma, and philanthropic enterprises. His collaborative leadership has led to remarkable advances in the treatment of sarcoma, particularly the sarcoma subtype known as gastrointestinal stromal tumor (GIST).

"I was once told by a well-meaning mentor, 'You are smart enough, you could run your own lab, but you are throwing your career away to be a clinical investigator.' Traditionally, laboratory investigators are set up as the *really smart* guys. But that was not the role I chose to pursue," said Demetri, recipient of the 2014 Giants of Cancer Care™ award in Gastrointestinal Cancer.

Rather than spending his time in the laboratory, Demetri views himself more as a matchmaker, "making connections between faculty members,

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INDUCTEE
2014

research nurses, and our various research teams in the experimental therapeutics program here at the Dana-Farber Cancer Institute, across Harvard Medical School, and extending into many other sectors of research, development, and care delivery. I bring people together and make sure that our projects and programs are moving forward—whether they focus on GIST or other subtypes of sarcomas, whether they are in early or late clinical trial stage, or in expansion cohorts to other diseases," said Demetri.

This approach to teamwork has been fruitful, says Demetri, who is the senior vice president for Experimental Therapeutics at the Dana-Farber Cancer Institute and a Professor of Medicine at Harvard Medical School in Boston, Massachusetts. This teamwork approach has extended to productive collaborations with start-up biotechnology companies such as Sugen and Plexxikon in the past, according to Demetri.

"Initially, this approach didn't appear to fit the outdated standard concepts in which academicians ask basic questions. Also, biopharma companies are in the business of implementing studies to get drugs approved," Demetri said. This non-overlap of separate worlds seemed inefficient and poorly designed for the modern era of mechanism-based drug discovery and more precise and predictive therapeutic development; he thought if academicians could drive the science behind the trials in collaboration with top-notch companies, then nearly magical efficiencies and effectiveness could be achieved.

"The foremost example of our team's work has been the sequential development of uniquely different tyrosine kinase inhibitors as effective therapies for patients with GIST. By targeting specific molecular structural variants of GIST, we have validated the concept that a human solid tumor can be treated by signal transduction inhibitors," Demetri said. He has designed and implemented a world-renowned clinical research center focused on the treatment of sarcomas, and his team is at the cutting edge of developing personalized cancer therapeutics for several uniquely defined subtypes of sarcomas.

Their efforts led to the development and subsequent FDA approval of imatinib mesylate (Gleevec) as the first effective therapy for patients with metastatic or unresectable GIST, and serves as the basis for ongoing research in other novel agents. The development of Gleevec, one of the first examples of a rationally-targeted oral cancer therapy for a solid tumor, was followed by research to overcome drug resistance through other targeted drugs, including sunitinib (Sutent) and regorafenib (Stivarga) for GIST as well as pazopanib (Votrient) for other sarcomas.

EVOLVING SARCOMA RESEARCH

Sarcomas are a paradigm of the complexity and heterogeneity of solid tumor oncology. Clinically important subsets of sarcomas are increasingly being defined by molecular signatures and biological characteristics rather than by the part of the body in which the disease arose. Demetri's team is translating this research about the basic biology of sarcomas into new therapeutics directed at novel targets.

"The biggest change in sarcoma research is that we have discarded the notion that there is one thing called 'sarcoma,'" said Demetri. Sarcoma has been parsed into hundreds of different diseases, Demetri continued. "If we really understand the wiring in all the tumors, we might be able to make some difference for patients," he said.

Looking back, he described sarcoma research before the 1990's as limited by a therapeutic nihilism: there was a sense that nothing could possibly make a big difference for patients. Clinicians met with infrequent treatment success, although advances in chemotherapy of certain sarcomas, especially the pediatric cases, such as Ewing Sarcoma and osteosarcomas, could indeed lead to cures. "But adults with metastatic soft tissue sarcomas typically did not do well. That nihilism associated with sarcoma was a barrier in building a sarcoma program, even at Dana-Farber and Harvard," he said.

Funding for diseases that affect a small population of people is often not forthcoming, making for small progress. Sarcoma is one such example, he said. "That made it frustrating, even if it was completely understandable," Demetri said. "But what has happened in sarcoma is now clearly being applied to more common cancers," he continued.

"We know there is no single thing called 'lung cancer.' Our field has parsed lung cancer into various clinically-important defined subsets. There is no *one* disease called 'breast cancer,' [because] there are lots of different kinds of breast cancers. I think that we are going to find that every form of cancer is an orphan disease, and—ultimately—that mixing and matching of these rare subsets are going to create new bins, new therapeutic categories that will allow us to study sarcomas and make a difference in subtypes of carcinomas and hematologic malignancies that match them," Demetri predicted.

TRANSLATING THE DRIVER MUTATIONS IN GIST TO NEW THERAPY

"Dana-Farber has a unique culture," said Demetri. "It's one in which basic scientists and clinicians work shoulder to shoulder on common challenges."

He relates an anecdote about a breakthrough in understanding the *KIT* mutation in GIST. Approximately 80% of all GIST contain a mutation in the *KIT* receptor tyrosine kinase that results in uncontrolled activation of this signaling protein.

In the early 1990s, Christopher D.M. Fletcher, MD, the renowned sarcoma

pathologist at Dana-Farber/Brigham and Women's Hospital, described various immunohistochemically defined subsets of these sarcomas of the intestinal tract. This led to many discussions within the team, as they struggled to understand whether these subsets might explain mechanisms important for this cancer. Eventually, another colleague from Dana-Farber returned to Japan and was part of the team that made the first *KIT* mutation discovery in GIST in 1998.

"And finally we had a mechanism," said Demetri. "In many ways it was the 'a-ha' moment, the idea that we had this class of tumor that we were arguing about. What is really driving it? The immunohistochemistry (without *KIT* at the time) wasn't really giving us any insights, but at last we had this molecular biology insight which brought everything together," Demetri explained.

Jonathan A. Fletcher, MD, a molecular biologist and pediatric oncologist at Dana-Farber/Brigham and Women's Hospital, had created some of the first GIST cell lines which enabled more collaboration between his lab, Demetri, and other colleagues including David Tuveson, MD, PhD, to test the new drug then known as STI-571 (now called Gleevec) to shut down the mutation.

Demetri said, "It was just a terrific and rapid movement from seeing this disease as a "black box" challenge to putting the basic science on top of it, to putting the functional validation together, and then ultimately saying, 'We have got to get this to patients to test this; it looks almost too good to be true, but it has got to be tested.'"

SCIENCE IS A REMIX

As the first in his family to attend college, Demetri set his sights on nuclear physics, but soon found that "all the physics seemed way too mathematical for me." Eventually, he found himself gravitating towards the molecular biology department at Harvard University.

There were giants in that molecular biology department—for example, James Watson and Matthew Meselson. "I was fortunate to be trained by such incredible people who could see the value in this new field," he said. "For example, in 1974, the polymerase chain reaction (PCR) hadn't been invented, our tools were primitive by today's standards," he said. The PCR is a biochemical technology in molecular biology used to amplify a single copy or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.

Throughout his academic and professional career, Demetri has brought teams together to use what has come before and improved upon it, built on it, and advanced the current thinking.

There's a lecture that Demetri is particularly fond of bringing up when he thinks about the work he has done in the GIST field. It's a TED Talk by Kirby Ferguson called, "Embrace the Remix."

TED, a conference where technology, entertainment, and design converge, is a nonprofit organization devoted to spreading ideas, usually in the form of short, powerful talks (18 minutes or less). TED began in 1984.

In his talk, Ferguson explains how everything is a remix

of something else, everything is sampled, everything is mixed together, postulating that there are very few, if any, truly original ideas on the planet in any field. Ferguson uses an example of how Bob Dylan used folk songs as the basis for some of his own compositions, but it could be applied to any field. "And I think that goes for science. Science is continually remixing things," said Demetri.

So whether he's receiving an award like the Giants of Cancer Care, or tracking how a particular kinase shuts off a crucial step in the cell cycle, Demetri is keenly aware of who and what has come before and all who have contributed along the way.

"I have mixed feelings about any kind of prizes and honors because there are so many people that need to be honored and deserve to be honored," he said. "Even in my field, even in GIST, I feel a little guilty being honored like this because it has been such a team effort," he said.

In 1999, when the researchers of imatinib met at the American Society of Clinical Oncology meeting they knew they might have something special, and they weren't just referring to the targeted agent.

"We said if we were all still talking to each other in 5 years, we will have succeeded. And here we are, 15 years later and we are all good friends, we are all talking to each other, there have been no major breakups, and I think we have all treated each other fairly. So, that to me is important, maybe not as important as having done so well by patients because that takes precedence over everything. But it is certainly second on the list. I can sleep at night feeling that it hasn't been all about me, I have treated people fairly, and I feel in many ways I have been fairly treated, too." ■

GENETICS

JANET DAVISON ROWLEY, MD

(DECEASED 2013)

UNIVERSITY OF CHICAGO

In a world where people often lament "you can't have it all," Janet Davison Rowley, MD, proved to be the exception to the rule.

Balancing a remarkable career capped by her seminal discovery of the role played by chromosomal abnormalities in blood cancers, Rowley was also a devoted wife and mother of 4 sons, a passionate gardener, an enthusiastic cyclist and swimmer, and an ardent advocate for research at the University of Chicago where she studied and worked for most of her 88 years.

Rowley, posthumous winner of the 2014 Giants of Cancer Care™ award for Genetics, continued to work in her laboratory right up until her death from ovarian cancer in December 2013. Given her reputation for scientific rigor, her determined work ethic until the end of her life came as no surprise to her colleagues at the university and beyond.

"Janet fostered and mentored investigators literally until the last few weeks of her life," said Everett E. Vokes, MD, winner of the 2013 Giants of Cancer Care award for Head & Neck Cancer and physician-in-chief at University of

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INDUCTEE

2014

Chicago Medicine. “Her labs never closed, her activities continued” in a manner emblematic of the “intellectual curiosity, intensity, and discipline” that she displayed throughout her career, said Vokes, who also chairs the Department of Medicine.

AN EARLY LOVE OF SCIENCE

These qualities were evident in Rowley early on. As she told the National Institutes of Health (NIH) for its profile of her: “I was always fascinated by science. I especially liked the orderliness of the classification of plants and animals in a logical phylogenetic tree,” presaging her later passion for the study of genetics, as well as for gardening.

With the strong support of her parents, both graduates of the University of Chicago, Rowley earned a scholarship when she was 15 years old to attend their alma mater. Upon graduating in 1944, “I realized that medicine would combine my interest in science with my desire to help others,” said Rowley, and she was accepted into the medical school—at age 19—but had to wait 9 months, because the medical school’s quota of 3 women already had been met.

Undeterred, Rowley went on to earn her medical degree, and married fellow medical student Donald Rowley—a trailblazer himself in experimental immunology—who shared her deep love of science and became a professor of Pathology at the University of Chicago. He, too, continued to conduct research extensively up until the time of his death, also in 2013, at age 90.

In fact, science was somewhat of a family business in the Rowley household, noted eldest son David B. Rowley,

PhD, a geologist and professor at the University of Chicago. “It was not uncommon for the kids to be excused from the dinner table and then come back an hour or more later to find our parents still sitting there, discussing medicine and science.

“They were both remarkable intellects,” he continued. “For them, work was never work. Work was always pleasure.”


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POSITING A GENE-CANCER CONNECTION

When Donald Rowley went on his first sabbatical to study at the University of Oxford's Dunn School of Pathology in 1962, Janet, with children in tow, took advantage of the opportunity and applied for her own NIH fellowship to study cytogenetics with Marco Fraccaro, who was then overseeing the new MRC Population Genetics Research Unit at Oxford, and to learn more about patterns of DNA replication in human chromosomes with hematologist Laszlo Lajtha.

Rowley credited her part-time work at a clinic for children with Down syndrome during the late 1950s with igniting her own interest in inherited diseases, coinciding at the time with the discovery by French scientist Jerome Lejeune that Down syndrome was caused by an extra copy of chromosome 21.

Upon her return to the United States from Oxford a year later, Rowley decided to seek part-time work again, but this time in genetics research, as she explained in a 2011 interview with the *New York Times*. She approached Leon Jacobson, MD, then director of the Argonne Cancer Research Hospital at the University of Chicago and a former professor from her medical school days.

"I have a research project started in England that I'd like to continue with . . . All I need is a microscope and a darkroom. And, by the way, will you pay me? I must earn enough for a babysitter," she told Jacobson.

For the next 10 years, Rowley focused her research on chromosomes in leukemia cells at a time when many researchers maintained that genetic abnormalities were the result of cancer, rather than the cause.

Rowley accompanied her husband to Oxford again in 1970, when she was able to study new banding techniques for studying genetic material by staining it for examination under a fluorescent microscope. This technique, Rowley explained, allowed investigators to observe subtle differences and identify different chromosomes.

When she returned to Chicago, Rowley deployed her new skills by analyzing chromosomes from patients with acute myelogenous leukemia (AML). She lined up the photographs of leukemia cell chromosomes on a table, "and told my kids not to sneeze," she noted in an article appearing in *U Chicago News*. Her approach worked, and in 1972 she identified the first known translocation of two chromosomes (8 and 21), which were broken and had switched ends. Later—while examining cells from patients with chronic myelogenous leukemia (CML)—Rowley observed that chromosomes 9 and 22 (also known as the Philadelphia chromosome,

discovered by Peter Nowell, MD, and David Hungerford, PhD, in 1960) each had breaks and swapped ends, marking the second translocation.

"At this point, I was very perplexed," Rowley wrote, recalling the discoveries in a commentary for *Nature Medicine* in 1998, the year she was honored with the Lasker Clinical Medical Research Award, alongside Nowell and Alfred Knudson, MD, PhD. "I now had 2 consistent rearrangements, the 8:21 and 9:22 translocations, each associated with a different type of leukemia. There was no precedent for such specific translocations, and the mechanisms behind them were mostly a mystery," she wrote.

More clues to the conundrum would be revealed, however, with Rowley's subsequent identification of a 15:17 translocation in acute promyelocytic leukemia.

"This third example of a translocation, and particularly one with such specificity, convinced me that the chromosome changes were an essential component of the leukemogenic process," Rowley explained in her *Nature Medicine* commentary, "and I soon became a 'missionary,' attending hematology meetings in the 1970s and early 1980s carrying the 'gospel' that chromosome abnormalities were an essential component of hematologic malignant diseases to which the clinical community should pay attention."

They did. Through her perseverance, Rowley finally persuaded earlier skeptics that cancer is a genetic disease. By 1990, researchers had pinpointed more than 70 translocations across varying cancers.

In the *New York Times* interview, Rowley was characteristically humble about her transformative discoveries.

"Looking down a microscope at banded chromosomes is not rocket science. If I hadn't found it, somebody else would have," she said. Her colleague Vokes disagrees.

"She believed in the value of a scientific question. Her hypothesis was that cancer is a genetic disease. She set out to prove it, and she did. This was a really major achievement," Vokes stated.

SUCCESS SHARED

How did Rowley find time to maintain a full family life, actively pursue hobbies like gardening, and mentor budding scientists, yet never stop her research? Although she attributed much of her success to luck, her work ethic and love of science most certainly played big roles.

Her son David noted that when Rowley was working in the garden, in the back of her mind she was always thinking about science. Those many hours in the garden, he said, gave her the time and space to mull things over.

"My mother typically wouldn't go to bed until between 11 and midnight. The time just after dinner until she went to bed was almost invariably spent reviewing manuscripts or grant proposals. And later on when she was on President [George W.] Bush's Council on Bioethics, she would often spend hours and hours reading and editing the committee reports to keep them aligned with the actual science as much as she could," her son recalled.

Despite having published some 500 journal articles,

Rowley appeared to have her priorities well in order, relishing outdoor pursuits and time spent at the family cottage on Lake Michigan—just a 45-minute drive from Chicago—which her sons and grandchildren still enjoy.

Not surprisingly, Rowley received many formal accolades in the United States and throughout the world for her groundbreaking discoveries. In addition to her Lasker Award, Rowley was awarded the National Medal of Science, also in 1998. In 2009, she received the Presidential Medal of Freedom from President Obama, and a year later, the Lifetime Achievement Award from the American Association for Cancer Research.

David Rowley remembers fondly how on these occasions the Rowley family invariably would be the largest contingent in the room. Hearing that there might be "only 4 tickets" available would not thwart his mother from sharing her success. "She loved to have her family around her, and she would fly us [children and grandchildren] to wherever in the world an honor was being bestowed."

Her generosity extended well beyond her family—not only in the laboratory, but to fellow members of the University of Chicago community.

"She participated actively in departmental and university-wide activities, which, for an accomplished scientist, isn't always the case. She cared about the home base, and was very much involved," Vokes said.

Her support for young scientists was equally unyielding, and she routinely advised them never to give up: "Take risks. Do something different if it looks interesting. I didn't do anything noteworthy until I was 50," she told them.

"She has inspired a generation of translational research scientists, impacted hundreds of thousands of lives, and her spirit will live on in all of the people who have benefited from her work," Brian J. Druker, MD, director of the Knight Cancer Institute at Oregon Health & Science University and winner of the 2013 Giants of Cancer Award™ for Leukemia, said in an interview with the University of Chicago at the time of her death.

Rowley donated her own peripheral blood for her early investigations at Oxford, as well as biopsies from her cancer to the University of Chicago for research, including work by her husband as part of his own immunology studies. In an interview with the *Chicago Tribune*, David Rowley noted: "She approached her cancer as a scientist. Even in death, she had arranged to have an autopsy done so that her colleagues could actually learn about her disease."

Vokes recalled how Rowley famously would swim in Lake Michigan well into the autumn months when others would find the water far too cold, as well as a time just a year before she died when he was attempting to navigate a Chicago crosswalk in the middle of a big snowstorm, only to look up and see Rowley pedaling her bike home as she routinely did, undaunted by the weather.

"She really was somebody who lived life to the fullest," he said. ■

GENITOURINARY CANCER

PHILIP W. KANTOFF, MD

DANA-FARBER CANCER INSTITUTE/
HARVARD CANCER CENTER

If he had to choose another career, Philip W. Kantoff, MD, said he'd really enjoy being in a classic rock band or playing professional basketball.

"I love Led Zeppelin, the Grateful Dead, the Allman Brothers, AC/DC, Queen," he said excitedly in a phone interview. "I still go to concerts. One of the most fun things I ever did was when I took my son to London to see Eric Clapton at the Royal Albert Hall in London about three or four years ago."

But Kantoff, 59, knows where his strongest talents lie.

"I really enjoy music," he said. "I play the piano—but with no proficiency. I also play basketball, tennis and golf, again with no proficiency. It's a good thing I have my day job."

LEADING AND PIONEERING

But piano skills aside, Kantoff has proven to be a rock star in that day job—as a giant in the oncology world.

He is a leader in the field of prostate and genitourinary cancer research, and holds several different titles at the Dana-Farber Cancer Institute/ Harvard Cancer Center in Boston, Massachusetts. Known for his work in identifying genetic markers of prostate cancer, his research has also helped

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INDUCTEE
2014

bring several prostate cancer drugs to the market, such as chemotherapy mitoxantrone and vaccine sipuleucel-T. Kantoff is currently the director of the Lank Center for Genitourinary Oncology, chief of the Division of Solid Tumor Oncology, and the head of the prostate cancer program, all at Boston's Dana-Farber Cancer Institute/ Harvard Cancer Center—all programs he has developed from their infancy into the robust areas they are today, with about 20 physicians and scientists and many more postdoctorates and fellows involved. He also oversees the prostate cancer SPORE (Specialized Program of Research Excellence), a multimillion dollar grant from the National Cancer Institute for the past 12 years that funds a number of different projects.

Such variety means Kantoff's weeks are never dull. He spends about half his time on research activities, and divides the rest between administrative and clinical tasks. The time spent with patients, he said, is the most rewarding.

Currently, he sees patients with prostate and testicular cancer, which is a departure from an earlier time in his career when he also saw patients with urinary, kidney, and bladder cancers. Watching patients get well is "one of the great moments when you are an oncologist," he said. "Taking a very sick testicular cancer patient and curing them is one of the most remarkable feelings. It's such a rewarding part of what we do."

Kantoff has also earned praise from others for his ability to teach and heal.

"In addition to his brilliant research career, Phil embodies the finest attributes of a physician and mentor," said Lee Marshall Nadler, MD, the dean for clinical and translational research at Harvard Medical School in Boston. "Every one of us refers our friends and families to Phil because he truly cares about his patients. He also deeply cares about his colleagues, faculty, trainees and staff. Everyone who works for Phil knows that he will treat them with respect, and remain loyal to them even when they leave his program. This has been true from the time he was a junior faculty member until today."

THE BIRTH OF A MOLECULAR BIOLOGIST

Kantoff's interest in science and medicine sprouted as a child, learning from his father, Sidney, who studied and taught entomology as a young adult before working in the clothing business, while living in Forest Hills, New York. "My father had wanted to be a doctor but did not get a scholarship to go to medical school and as an orphan, couldn't afford to go," he said. "Instead, he studied insects, and spent a lot of time with me as a kid teaching me what he knew."

Father and son pored over bug classifications, and soon, young Phil was hooked on molecular biology, reading books about early science and medicine such as *Microbe Hunters* and *The Citadel*. "These were fascinating accounts about people who moved from different fields like math or physics into biology and became early scientists who studied molecular biology, which led to the evolution revolution in biology."

Growing up in the New York area, Kantoff also recalled a "fantastic, inspirational" seventh-grade biology teacher, Michael Krutoy, who inspired him to pursue a science career. He also spent a summer at the The Jackson Laboratory in Bar Harbor, Maine, studying mouse genetics,

where Kantoff made an important decision. "That was the point where I said 'This was for me. I want to be a scientist.'"

After high school, Kantoff attended Brown University for both college and medical school through a special 6-year program, and did his internship/residency and chief residency in internal medicine at New York University/Bellevue Hospital. He focused on oncology because "it seemed to be the most molecularly approachable area when I entered the field 25 or so years ago," he said. "I had wanted to apply molecular biological approaches to cancer, but it was very hard to do at the time. Not until the past 15 years has it been doable."

IDENTIFYING A PASSION

After medical school, Kantoff did a 4-year post doctorate stint at the National Institutes of Health, researching gene therapy, then came to the Dana-Farber Cancer Institute in Boston, as a medical oncology fellow. While there, he saw an opening and went for it.

"Phil was a fellow when I was chief of medical oncology at Dana-Farber," said George Canellos, MD, who is now the Institute Physician of Dana-Farber Cancer Institute and also the William Rosenberg Professor of Medicine at Harvard Medical School. "He did an excellent job as a fellow, but I thought he would return to the NIH where he previously worked on a new area of gene therapy. Instead, he shocked me by applying for an opening we had in the area of genitourinary oncology as the only staff member."

Landing the job in 1988 set Kantoff on a new path. "I went into genitourinary oncology not because I was driven into that particular area of oncology, but mostly because there was an opportunity," he said. "It was a great field for me to go into. On one hand, we have one disease, testicular cancer, where we cure people almost all the time. On the other hand, we also have prostate cancer, which has developed tremendously over my career, from a disease that no one was interested in to a disease that is very fascinating, both biologically and clinically. I've spent a lot of my career trying to understand the heterogeneity of the disease and develop better treatments."

Prostate cancer has subtle issues of biology, heterogeneity, patient interaction and patient values and psychology that Kantoff finds enthralling. "The whole mix makes the area a life's work for me," he said. "There's so much to it—I enjoy studying the disease and taking care of patients. There's so much there, and so much still that needs to be done."

Kantoff's devotion to growing the department and contributing to the research in the genitourinary field was notable. The department "started off with a bang, as there were much data on testicular cancer, which was a topic for compilation and investigation," said Canellos. "The rest is history, as Phil slowly expanded the staff commensurate with the growth of the genitourinary patient volume. He was also successful in training and nurturing and expanding a set of experts in that field. His scientific experience allowed him to expand the scientific side of

tumor biology related to genitourinary cancer. His unit is one of the strongest in the field and he has expanded his talents to serve as a leader in the Dana-Farber Cancer Institute program in solid tumors. He is a success story of the Dana-Farber Cancer Institute. He began his career as a young man with great potential, which found a successful outlet at Dana-Farber Cancer Institute, and in the process contributed to its growth and distinction in the cancer research field."

Growing and sustaining his relationships with others is, in fact, one of Kantoff's guiding principles. "I try to create a work environment that's respectful," he said. "I've tried to create a horizontal environment here, where nurses, physicians, administrative assistants—everyone—feels part of the community and part of the mission. I'm very proud of that. And I'm very proud of the people I have trained through the years who have gone on to be outstanding clinicians and investigators here and elsewhere."

These are attributes that Kantoff, who lives in Brookline, Massachusetts, has tried to convey to his own children. He is the proud father of Aaron, 29, a newlywed who works in the venture capital field; Emily, 27, who is studying to be a nurse practitioner; and Sydney, 21, named in honor of Kantoff's father and a student at Tulane University.

And such traits have been lauded by others. "Phil is more than a giant—he's a gentle giant," said Edward J. Benz, Jr, MD, president and CEO of the Dana-Farber Cancer Institute and the Richard and Susan Smith Professor of Medicine, Pediatrics, and Genetics at Harvard Medical School. "While it is true that his contributions to cancer and research are gigantic, it is who Phil is that makes him so special. He is caring and kind to his patients and their loved ones, supportive and loyal to those whom he leads, and a wonderful colleague, friend, leader and institutional citizen. He has built a world-class program for the care and study of genitourinary neoplasms, trained and mentored a generation of outstanding physicians, and scientists, and for thousands of patients, he has made their journey through cancer as good as it could possibly be."

TRANSFORMING CANCER TREATMENT

Kantoff has witnessed the changes in cancer treatment through the years. "When Gleevec was developed, it was a paradigm that we all felt was going to be *the* paradigm, that if we understand the genetics of a cancer, we'll be able to cure cancer," he said, referring to the drug approved by the FDA in 2001 that was among the first cancer medications to work by stopping a particular cancer-causing protein within the cells of people diagnosed with acute myeloid leukemia, and one of the first targeted cancer therapies. But that approach has been more difficult for solid tumors, both the ones Kantoff works with as well as solid tumors in general, he said. "While I still believe in genetics as a path to better treatments, I think immunotherapy is extremely promising as well. At the same time, focusing more on early detection and prevention for all cancers, but particularly prostate cancer, will

also help reduce the number of patients with cancer," he said.

It's likely Kantoff will be on the forefront of such advances, or at least collaborate with others to help find new forms of treatment. "He has become one of a small group of international innovators in the study of genitourinary oncology and prostate cancer," said Bob Mayer, MD, currently the faculty vice president for academic affairs at Dana-Farber Cancer Institute, and who served as the director of Kantoff's medical oncology fellowship training program. "He has the unique knack of being able to define the truly important research questions to ask and then bringing together colleagues from different disciplines to effectively address these challenging issues," he said.

In the future, Kantoff said he'd love to help patients live longer by using "multi-modality therapy for early prostate cancer. I think within the next five to ten years, we'll be able to do it," he said confidently.

Most people who die from prostate cancer walk in the door with early disease, then die 10 to 15 years later. "There's an opportunity there to use multi-modality therapy to minimize the odds that people will relapse," he said.

No matter what setbacks might occur, Kantoff said he'll just keep looking forward. "I can't remember not being knocked down," he said. "Whether it was patients who you take care of and become friends with, who pass away, and it drains the living soul out of you, or writing a paper or grant that gets rejected—just getting up and moving on and just saying okay. Defeat is part of this whole thing, but success is absolutely about being persistent. The ability to keep on going, despite defeat, is part of the business of science and medicine. Anyone who tells you otherwise is deluding themselves." ■

HEAD & NECK CANCER

KIE KIAN ANG, MD, PhD

(DECEASED 2013)

THE UNIVERSITY OF TEXAS
MD ANDERSON CANCER CENTER

When an oncology patient finishes his or her radiation treatment at The University of Texas MD Anderson Cancer Center in Houston, that patient rings a bell.

It's a custom that dates to 1996, when a patient who was a Navy admiral told his radiology physician, Kie Kian Ang, MD, that the Navy tradition was to ring a bell to signify a job being complete.

The patient brought a brass bell to Ang's clinic, rang it loudly upon completing his radiation therapy, and then donated it to Ang and his staff. The tradition stuck, as other MD Anderson head and neck physicians and their patients began to follow suit. More than 15 years later, some 5 to 10 MD Anderson patients each day sound a bell for the very same reason.

The tradition is just one of the many things Ang, a professor and vice president for global academic programs at MD Anderson who died in 2013 from cancer, left as his legacy to helping improve radiation care. Ang, who was 63, was a standout researcher, physician, colleague, family man, and friend, and his life exemplified a personal and professional commitment to new understandings about radiation oncology for head and neck cancers.

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BREAKING GROUND

Known as Kian to friends and colleagues, Ang was a highly respected physician and scientist who made incredible inroads in radiology and head and neck cancer.

"He was someone who had a unique ability to be an outstanding clinical care provider, an outstanding clinical researcher, and a translational researcher—an MD/PhD who had independent lab studies," said Thomas A. Buchholz, MD, the executive vice president and physician-in-chief of MD Anderson. "He took problems he might see in his patients and made discoveries in the laboratory that he could bring back to help patient care."

One example was understanding how the human papillomavirus (HPV) affected the responsiveness of patients with head and neck cancer. Ang discovered that patients with head and neck cancer who were infected with HPV were more responsive to radiation therapy than non-infected patients with head and neck cancer. Specifically, such patients were more responsive to a less aggressive form of radiation.

Ang and his colleagues published their findings in the *New England Journal of Medicine* in 2010, supporting the approach that each patient's case should be treated individually.

To help make radiation more effective with resistant tumors, Ang's laboratory worked to locate and understand the molecular changes that made such cancers resistant, and then mixed radiation therapies with molecular targeted agents to make them more likely to respond to treatment.

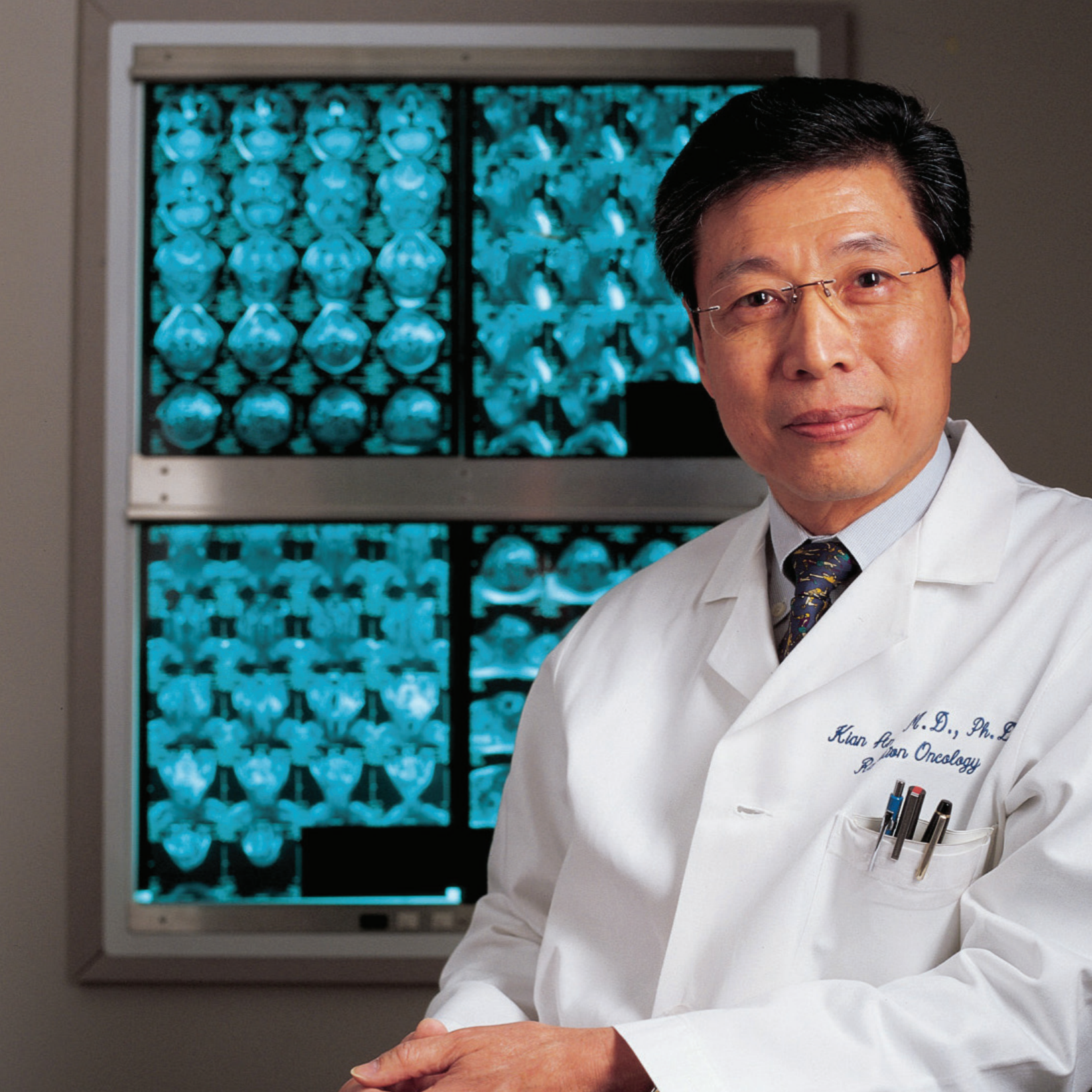
He shared his knowledge widely. Ang cowrote, with James D. Cox, *Radiation Oncology: Rationale, Technique, Results*, one of the leading radiology oncology textbooks in the field. In addition, he wrote or cowrote more than 350 peer-reviewed articles, more than 50 book chapters, and edited 7 textbooks.

His insights weren't limited to medicine, either, recalled Paul M. Harari, MD, the Jack Fowler Professor and chair of the Human Oncology Department at the University of Wisconsin School of Medicine and Public Health in Madison. Harari spoke at a September 2013 memorial for Ang at MD Anderson.

"I met Kian at a Radiation Therapy Oncology Group (ROTG) meeting 22 years ago and I was very respectful of him," Harari said. The ROTG is backed by the National Cancer Institute and works on finding new radiation treatments through clinical trials research. Ang chaired the Head and Neck Cancer Committee from 1999 to 2012.

"He was several years my senior and I was fresh out of my training and was sitting with him. He was engaging me to be involved in a ROTG committee in a way that was very graceful and diplomatic. He described to me how he wished for me to take over producing the minutes for the meeting we had just come out of. [He] said it in such a way that I was just flattered and honored. It was only until later that I realized, 'I guess he's asking me to be his secretary.'"

At the memorial, the audience of Ang's colleagues, friends, and family laughed at Harari's recollection of his "light bulb" moment.


M.D., Ph.D.
Radiation Oncology

"But something about the style of Kian made that come through so that I found that very important, and I have always held on to that lesson and used it many times myself. So I thank Kian for that," said Harari.

AWARDS AND ACCOLADES

Ang's personal and professional biography spanned the globe. Born in 1950 in China, Ang was raised in Indonesia. He graduated from Catholic University of Leuven in Belgium with a medical degree in 1975 and a doctorate from the same institution in 1984. In Belgium, while working with Professor Emmanuel van der Scheuren, MD, and Professor Albert van der Kogel, PhD, Ang researched rat spinal cords and published papers on how normal spinal cord tissue responds to radiation.

In 1984, Ang was asked to join MD Anderson. He began working in the Department of Radiation Oncology as an associate professor of radiology, and it was there that he began to focus specifically on head and neck cancer treatments. In 1990, he became a full professor and was later named deputy department chair and deputy division head, and was both the Robert R. Herring Professor of Clinical Research and later appointed to the endowed Gilbert H. Fletcher Distinguished Memorial Chair. In 2012, Ang took on the role of MD Anderson's vice president for Global Academic Programs, where he oversaw professional collaborations between MD Anderson and 26 top academic programs around the world.

These and other international connections helped make Ang a revered figure in the world of head and neck cancer radiation.

"I traveled many times with him, to the Far East and elsewhere in the world, and there was always a line of people outside his hotel room waiting to talk to him," recalled Buchholz, who considered Ang a mentor. "Within the professional circles, he had really close ties, and was one of the most respected radiation specialists worldwide."

Ang also held many professional leadership roles. He was a trustee of the American Board of Radiology from 2004 to 2012. He was also the president of the American Society for Therapeutic Radiology and Oncology in 2005 to 2006, the chair of its board of directors from 2006 to 2007 and he earned

the Society's highest honor for career contributions, the ASTRO Gold Medal, in 2011.

According to an article about Ang published on the website of the International Federation of Head and Neck Oncologic Societies, those who nominated him for the Gold Medal wrote: "Kian Ang is unique. There is no one in the United States, or even in the world, who has distinguished himself as [such] a master clinician and teacher, a long-term funded laboratory investigator, and a creative clinical investigator whose work has changed the practice of cancer care."

AT PLAY AND AT HOME

Ang also deeply valued his leisure time and family ties. "He was a fantastic athlete—an avid skier and tennis player—and a connoisseur of good food and wine," said Buchholz. "He loved good French food and dim sum. He enjoyed the best of what every place had to offer."

But his loved ones were who brought him the most happiness, said Harari at the September 2013 memorial.

Ang and his wife Sunny were the proud parents of Angelica and Dimitri, now adults, and the family had cherished annual barbecues and Christmas parties.

"The greatest joys Kian would express to me were when we would talk about one another's families," said Harari, who said that he traveled to the same head and neck committee meetings in the United States and around the world as Ang did.

"I always looked forward to connecting with Kian, and often Sunny, who traveled with Kian for dinners and events. These colleagues become such close friends that you end up seeing them more than you do some colleagues at your own institution. Kian knew my 4 children by name and although I'd only met them once or twice, I knew all about Angelica and Dimitri—their school successes and challenges and the excitement of their marriages. These were things that brought tremendous joy to Kian. It was so obvious that that was the highlight, that that was the legacy. He leaves a beautiful family, a talented family, over and above the tremendous academic achievements." ■

LEUKEMIA

HAGOP M. KANTARJIAN, MD

THE UNIVERSITY OF TEXAS
MD ANDERSON CANCER CENTER

Hagop M. Kantarjian, MD, has built the nation's largest clinical leukemia practice, in part to ensure that leukemia studies are completed efficiently and in a timely manner. This helped him become one of the most productive clinical translational cancer researchers of all time.

"My clinic is my research laboratory, and nearly every patient is participating in a study," he said. "The goal is to give patients something better than current standards of care and then, when the regimens we devise become standards of care, to look for regimens that are even better."

This attitude has revolutionized the treatment of many types of leukemia, extending the lives not only of many thousands who have come to the leukemia program at MD Anderson Cancer Center in Houston, Texas, but also of millions who have received care elsewhere.

Kantarjian spent decades developing the new research protocols that transformed chronic myelogenous leukemia (CML) from a death sentence to a manageable condition. He helped create the hyper-cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimen for treating acute lymphocytic leukemia (ALL) in adults. He found lifesaving uses for

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drugs that had been abandoned, important medications such as clofarabine (Clolar) and decitabine (Dacogen). He pioneered the use of epigenetic therapy in leukemia.

In all, Kantarjian has authored or coauthored more than 1200 peer-reviewed articles, many of them describing breakthrough studies that rank among the most important in the history of leukemia research.

PHOTOGRAPHIC, ENCYCLOPEDIC MEMORY

Why has Kantarjian achieved so much success? Colleagues say it starts with remarkable mental talents.

"He has a photographic, encyclopedic memory unlike any other I've ever encountered. He can absorb huge quantities of information and remember it all forever," said another giant of cancer research, Emil Freireich, MD.

According to Freireich, who helped invent the very idea of combination chemotherapy, Kantarjian's incredible facility for acquiring, storing, and retrieving knowledge helps his protégé in 2 key ways.

First, it gives Kantarjian a deep understanding of leukemia, and that understanding helps direct his research in fruitful directions. If some study from 1972 suggests an interesting possible follow-up for work that was just published yesterday, Kantarjian knows it, because he remembers the study from 1972.

Second, and more important, Kantarjian's breadth of knowledge makes him a natural leader of large teams. He knows enough about every specialty to manage specialists, and he knows enough about how different specialties mesh to combine their efforts effectively.

"He isn't a lab researcher at all," Freireich said. "He does his research in his head. Then he assembles the proper team for the project and keeps that team running efficiently—all while he's managing half a dozen other research teams and running his department. It's an incredible talent, and it makes him more productive than any traditional researcher could ever be."

Kantarjian gives a different explanation for his success. He says that he owes much of it to the lessons he learned from mentors such as Freireich, Michael J. Keating, MB, BS, and Kenneth McCredie, MD.

Chief among those lessons was to ignore tradition, challenge every idea, and dare to seek improvement.

Indeed, Kantarjian said, this is the ethos that permeates MD Anderson and made his career possible.

"Most places expect deference based on seniority or prestige or tradition. Anderson expects the opposite. From the day I arrived, they encouraged me to question the assertions of the most senior people," said Kantarjian, who expects the same from his youngest researchers.

"Even if new ideas prove wrong—and most of them do—they are the only possible path to improvement, so you must keep investigating them. Nothing is ever good enough."

TINKERING

Shortly after his arrival at MD Anderson, a young Kantarjian helped to run some of the first studies that pitted interferon against CML. The team discovered, in relatively short order, chemo-interferon regimens that significantly improved on existing standards of care, but Kantarjian kept on experimenting.

He spent years tinkering with different medications, in different doses, on different schedules—eking out little


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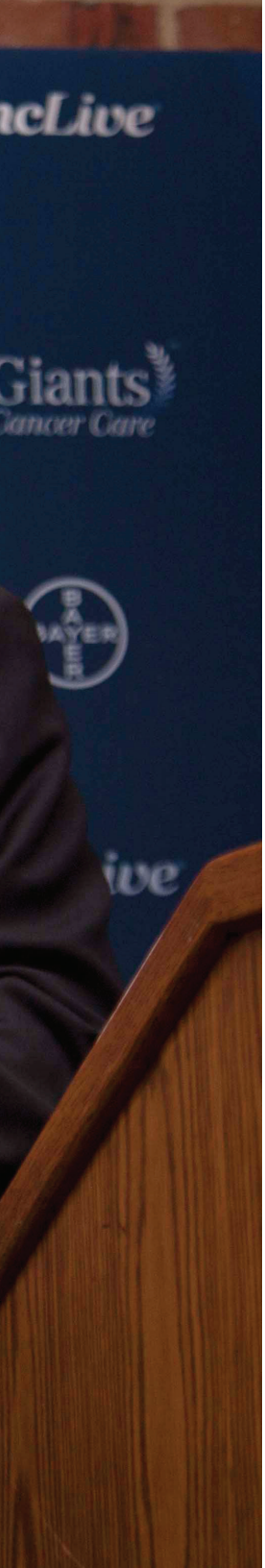


gain after little gain and waiting for the next big jump.

That jump came years later when Kantarjian helped develop treatment protocols for first-generation kinase inhibitors such as imatinib (Gleevec). The next leap followed a few years after that, when he did the same for second-generation kinase inhibitors that are the current standard of care.

Those clinical studies helped transform CML from a fatal disease to a chronic ailment. CML once killed most victims in 5 years and 80% of them in a decade. Now, as long as patients take their medicines every day, most people can survive it for many years.

Kantarjian's hunt for new ideas extends far beyond promising new drugs such as imatinib. It extends all the way to previously rejected medications. Decitabine, for example, was first developed in 1964 by researchers who expected big things from its unique activity. It floundered in trials, however, in part because its prolonged myelosuppression made it difficult to determine the preferred dose and schedule. Eventually, concerns about its toxicity led researchers to abandon it.

Kantarjian knew of those studies but decided, in 1992, to try decitabine again with new dosing and schedules. He brought the drug to the United States on an investigator IND and, in collaboration with Jean-Pierre Issa, MD, developed it as an epigenetic low-dose therapy for myeloid diseases.

In 2006, after a phase III trial led by Kantarjian, the FDA approved it for the treatment of myelodysplastic syndrome (MDS). In 2013, after another trial led by Kantarjian, European regulators approved the drug for use in newly diagnosed or secondary acute myeloid leukemia (AML) in older patients who are not candidates for standard induction chemotherapy.

Similarly, clofarabine was "neglected by everyone" when Kantarjian undertook its development as an investigator IND in 1992. He conducted the animal toxicology studies and followed them with phase I, II, and pivotal studies. It took years, but Kantarjian's trials eventually led the FDA to approve the drug for use in children with ALL who had already failed on 2 other treatment regimens. Now, there are more than a dozen

trials under way that pit the drug—as monotherapy or in combination with other drugs—against a host of cancers.

Kantarjian's efforts to create the hyper-CVAD regimen show that persistence in action. He first borrowed from the original VAD regimen in myeloma and from the Burkitt pediatric regimen to create a hybrid hyper-CVAD regimen for adult ALL in 1991. He continued to tinker with the regimen, later adding tyrosine kinase inhibitors for the subset of Philadelphia chromosome–positive (Ph+) ALL, and monoclonal antibodies for the subset of pre-B-cell ALL.

Today the hyper-CVAD regimen and its derivatives are standard of care in adult ALL, curing more than 50% of patients. Kantarjian hopes that the recent addition of novel monoclonals such as inotuzumab to chemotherapy can further escalate the cure rates to greater than 70%, thus closing the cure gap in adult ALL to approach that for pediatric ALL.

EARLY UPHEAVAL

Kantarjian's professional life has been a model of stability. He came to MD Anderson as a fellow in 1981, and he has remained there ever since.

His early years, on the other hand, unfolded amid massive upheaval.

Kantarjian was born in 1954 and raised in Beirut, Lebanon, in a time of peace and prosperity. Beirut was then known as the Paris of the Middle East and widely considered to be one of the most cosmopolitan cities of the world.

Things changed abruptly in 1975, just as Kantarjian was completing his bachelor's degree at American University of Beirut and preparing to begin his medical studies at the same school.

A civil war broke out between Lebanon's Christians and Muslims and transformed Beirut into a battleground. Roughly 60,000 city residents died during the first 2 years of the war, which lasted until 1990.

In the midst of all the fighting, Kantarjian continued his medical education.

"During the early years of the war I lost several people I was close to, and I often felt afraid for myself and my loved ones. I coped by doing my best to ignore the things I could not control and focused on living my own life in the best and most productive way possible. For me, that was school," he recounted.

"I'm sure the experience made me stronger—it made everyone who survived it stronger—but beyond that, I cannot really say what impact it had on me. I don't think the war really taught me anything except that people need to feel physical safety to thrive."

Kantarjian isn't sure when he decided to become a physician. He didn't aspire to the profession in childhood, so he assumes the idea came to him in college. The desire to specialize in leukemia, however, probably dates to meeting Freireich in 1978 when Kantarjian came to MD Anderson for a 4-month elective as a medical student.

Freireich was then leading the Department of Developmental Therapeutics and was one of the most inspiring cancer researchers in medicine.

"He seemed like another bright-eyed kid who wanted to change the world by curing cancer," Freireich said. "It

wasn't until he came here that we all saw he might have something valuable to contribute. He had incredible purpose and discipline for one so young. When he first got here, for example, he had a habit of being slightly late to meetings, and I called him on it. He hasn't been late to a meeting in 3 decades," Freireich said.

LOOKING BACK, LOOKING FORWARD

Looking back at his life, Kantarjian sees both a lot of hard work and a lot of luck.

"Being a leukemia specialist over the past few decades has been the most satisfying job imaginable because of the incredible strides we've made in treating patients, but there's no way I could have predicted those improvements when I chose to specialize.

"I could have just as easily stumbled into some field where there was no money for research or one where the research just hit dead end after dead end and patients kept dying a few weeks after diagnosis....As things are, I'm smiling when I walk into work each morning and smiling when I walk back out."

When Kantarjian's workday does end, usually about 12 hours after it began, he relaxes by painting in the styles of his favorite artists, Matisse and Cezanne, or by reading authors like Salman Rushdie, Philip Roth, and Graham Greene, or by jogging through Houston's parks.

He has also stayed very close to his family. Indeed, both of his parents and 4 of his siblings eventually followed him from Beirut to Houston. His parents have passed away, but he gets together with his brothers and sisters at least once a week.

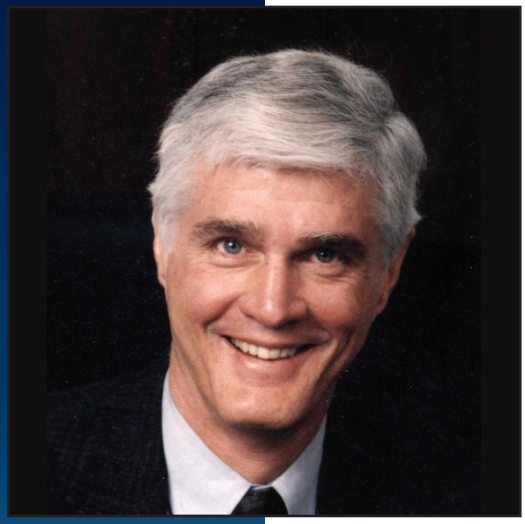
"My wife says we meet way too much," said Kantarjian, whose 30-year-old son also lives in town. "But that's the culture I come from. We value family, particularly those of us who felt ourselves in danger of losing that family."

Looking forward, Kantarjian plans to focus his efforts in several areas.

He is particularly excited about the potential of using monoclonal antibodies to treat ALL. The addition of rituximab to combination chemotherapy has already produced encouraging results, and newer medications also seem promising. For example, an anti-CD22 antibody called inotuzumab ozogamicin has produced significant single-agent responses in relapsed and refractory ALL.

He is also excited about improved epigenetic therapies with better hypomethylating agents (SGI110) and immune-oncology strategies in AML and MDS.

In addition to his research, Kantarjian plans to continue writing and speaking about issues such as chemotherapy drug shortages, the high cost of cancer drugs and cancer care, and broad health insurance coverage of patients with cancer. ■



LUNG CANCER

PAUL A. BUNN JR, MD

UNIVERSITY OF COLORADO
CANCER CENTER

When Paul A. Bunn Jr, MD, arrived at the University of Colorado School of Medicine in 1984, there was no National Cancer Institute (NCI)-designated cancer center in the region. The Division of Medical Oncology had only four medical oncologists associated with the facility and a handful of patients participating in clinical trials.

Today, the center boasts 55 faculty members in its Division of Medical Oncology alone and an overall clinical trial enrollment of more than 6000 patients a year. And, the center is among the nation's premier research hubs, which includes serving as an NCI-designated consortium for the growing Mountain State region and as a principal site for developing emerging therapies for patients with lung cancer.

These milestones have been reached in no small measure thanks to the efforts of Bunn, who served as the center's first director for more than 20 years. Yet Bunn's impact upon cancer care extends far beyond the programs he helped build in Colorado.

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Over the years, Bunn has served as president of the American Society of Clinical Oncology (ASCO), the International Association for the Study of Lung Cancer (IASLC), and the Association of American Cancer Institutes, and as chairman of the FDA's Oncology Drugs Advisory Committee.

He was the federal government's principal expert witness in the *United States of America v Philip Morris USA*, the landmark legal battle against the tobacco industry in the 2000s.

And, the research team he helped build at the University of Colorado Cancer Center has investigated many of the new therapies approved in recent years for patients with lung cancer.

In recognition of his achievements, the Giants of Cancer Care™ advisory board honored Bunn in May as the 2014 winner for Lung Cancer.

From his vantage point, Bunn takes an optimistic view of the progress that has been made against lung cancer during his career.

"When I was a young man, we did trials in non-small cell lung cancer [NSCLC] at the NCI with 12 drugs in a row that no one responded to," Bunn recalled in an interview. "The median survival at the time was 5 months. That was grim. Now, if you have a molecular driver, the chance that a pill will bring you benefit is about 80%. The average survival of those patients is 3½ years.

"So if you said to somebody, 'You're going to die in 3½ years,' it might not make them very happy—rightfully so," Bunn continued. "But if you said that a few years ago it would have been 5 months and that now it's 3½ years, you would say that some of our investment in cancer research is paying off."

At the same time, Bunn sees many remaining challenges. "Making the cure rate higher is a major unmet need," he said, as is improving the time for moving new treatments into curative settings.

A PUSH TOWARD ONCOLOGY

If it had not been for the Vietnam War, Bunn might never have explored a career in oncology research.

In 1971, shortly after the expiration of the education deferment that allowed young men to avoid the draft, Bunn obtained his medical degree from Cornell University Medical Center in New York City.

"When I was in medical school, I knew that I wanted to do something with internal medicine, but I didn't know what," Bunn said. He discussed his options with one of his professors, Richard T. Silver, MD, who today is director of the Leukemia and Myeloproliferative Center at New York Presbyterian-Weill Cornell Medical Center. Earlier in his career, Silver had worked at the NCI.

"When I suggested to him that I was interested in research and I was not interested in Vietnam, he said you could kill 2 birds with 1 stone and go to the National Cancer Institute, be in the public health service, meet your

military obligation, and do research," related Bunn.

After an internship and residency at HC Moffitt Hospital at the University of California, San Francisco, Bunn was able to do just that. He prevailed amid stiff competition to land a position as a clinical associate in the NCI's Medicine Branch under the direction of Vincent T. DeVita Jr, MD, a 2013 Giants of Cancer Care award winner, and others.

For Bunn, it was the beginning of a quest to understand the biological and molecular underpinnings of cancer. He concentrated on preclinical studies delving into the biology of lung cancers and cutaneous T-cell lymphomas with many mentors and colleagues. Notably, Bunn's work at the NCI frequently involved the use of what were then new technologies such as cell culture to establish new cell lines and flow cytometry to analyze their DNA.

THE MOVE TO COLORADO

Bunn advanced to become head of the Cell Kinetic Section at the NCI, but after 11 years he felt it was time to choose between spending his career in the public health sector and pursuing other options. "I was looking for an academic place that wanted to build a first-rate cancer center that would be a good academic program and a good place to raise a family," Bunn related.

So he accepted a position as head of the Division of Medical Oncology at the University of Colorado Cancer Center in 1984. Three years later, he also became the center's first director, a position he held until 2009.

In many ways, the changes that have transformed the care provided at the center reflect those that took place throughout the field. "At the time, the infusion center had two chairs," Bunn recalled of his arrival in Colorado. "One oncology nurse more or less mixed and administered the chemotherapy. Now, there are more than 60 infusion chairs."

Such growth, Bunn said, "is not only true in Colorado, it is true in many places. Oncology care is way different than it used to be. There has been a tremendous amount of growth and a tremendous amount of subspecialization."

Under Bunn's leadership, that growth in Colorado has produced one of the nation's most successful lung cancer research programs. The key ingredients, Bunn said, include "basic scientists who are interested in lung cancer and preclinical models, and pathologists who are interested in biomarkers and molecular analyses." There are other important players: pulmonologists, radiologists, and translational researchers.

Bunn himself has coauthored more than 300 peer-reviewed journal articles. Asked to cite his most important research milestone, Bunn noted the development of the "biomarker concept" in NSCLC.

Starting in the late 1990s, Bunn and colleagues explored multiple biomarkers for molecularly targeted therapies for NSCLC. Their work aided in the development of EGFR tyrosine kinase inhibitors for patients with that mutation, originally with gefitinib (Iressa) and later with erlotinib (Tarceva), which the FDA approved for patients with NSCLC in 2003 and 2004, respectively.

The evolving understanding of the biology of lung cancer has enabled clinicians to move beyond the more toxic

chemotherapy regimens that were formerly standards of care. "In the past, what we did had no scientific basis," said Bunn. "Now, we're only beginning to harness the immune system and these molecular drivers, and it's all based on science. I'm optimistic that in the next decade we can make more advances than we did in the past decades."

LEADING THE WAY

In the oncology community, Bunn and the program he helped establish are leading players in national and international research circles.

In 1992, the University of Colorado Cancer Center was awarded the federal government's first Specialized Program of Research Excellence (SPORE) grant in lung cancer. The grant, which totaled $2.4 million last year alone, has been funded every year since then and is believed to be the longest continuous SPORE project.

Currently, Bunn serves as principal investigator for the SPORE lung cancer grant, which includes four major projects involving early detection, chemoprevention, novel treatments, and resistance to EGFR inhibitors.

The center was among the largest contributors to the National Lung Screening Trial, which culminated last year in new guidelines endorsing the use of low-dose CT screening for people ages 55 to 80 at high risk for developing lung cancer.

And, the center's Fred Hirsch, MD, PhD, a translational researcher who explores biomarkers, is serving as a co-chair for the recently launched Lung-MAP trial.

Throughout his career, Bunn has received many honors, including a leadership award from the American Association of Cancer Research and the IASLC in 2010, given at the first Molecular Origins of Lung Cancer conference; the Caine Halter Hope Award in 2012; the IASLC Merit Award in 2003; and the American Italian Cancer Research Foundation Award in 2002. He became the 71st Distinguished Professor in the history of the University of Colorado system in 2013.

FAMILY'S INFLUENCE AT WORK

At first glance, the arc of Bunn's career might seem unsurprising. His father, Paul A. Bunn, MD, was a respected infectious disease specialist who became one of the first full-time professors at Syracuse University and a civic-minded resident of the nearby town of DeWitt, New York, where he raised his family. Members of Bunn's extended family also were physicians.

Bunn was impressed by his father's dedication to medical ethics. He recalled that his father contracted tuberculosis as a result of treating patients as a medical student and had little patience in later years with doctors who did not want to care for individuals with HIV. His father's philosophy, and one that Bunn shares, is "If you're a physician, the Hippocratic Oath says anybody who comes into your house, you're going to take care of."

Yet when Bunn entered Amherst College, he did not plan to follow in his father's footsteps and instead intended to pursue political science. He changed his mind, though, after he did well in required math and science courses, and ended up graduating in 1967 with a Bachelor of Arts in biology.

Like his father, Bunn also has displayed a community spirit in his approach to lung cancer research. In addition to his full-time academic positions at the University of Colorado Cancer Center and a 10-year tenure as IASLC executive director, Bunn has held what he calls "volunteer administrative jobs."

He was president of ASCO from 2002 to 2003, of IASLC from 1994 to 1997, and of the American Association of Cancer Institutes in 1996. He also chaired the FDA's Oncology Drug Advisory Committee from 1992 to 1996.

These days, Bunn has stepped back from his various administrative roles partly so that he has more time to spend with his family.

"One's family is the most important thing in one's life," said Bunn. "It is a difficult balancing act. Fortunately, I have three wonderful children, a wonderful wife, and four terrific grandkids. It is one of the reasons not to have administrative jobs right now."

Although his schedule might not be quite as packed these days, Bunn still serves as a faculty member at the University of Colorado School of Medicine and as principal investigator for the SPORE grant; he also still treats patients, including individuals diagnosed with cutaneous T-cell lymphoma.

As far as his research goals are concerned, his plans are straightforward and succinct: "My future research goals would be to develop better treatments for lung cancer patients," he said. "That hasn't changed." ■

LYMPHOMA

RICCARDO DALLA-FAVERA, MD

COLUMBIA UNIVERSITY MEDICAL CENTER

The race began in 1976, right after Harold Varmus, MD, and J. Michael Bishop, MD, showed that normal cellular DNA from several bird species contained sequences similar to the SRC oncogene from Rous sarcoma virus.

Eminent scientists from around the world set off to claim a place in history by finding similar sequences, called proto-oncogenes amid normal human DNA, but they all lost out to a junior researcher who had just begun a fellowship at the National Cancer Institute (NCI).

Riccardo Dalla-Favera, MD, still ranks that first breakthrough among his best work, but it has plenty of competition. He has since helped to discover a good portion of everything that's known about the genetics of lymphoma.

His research has already improved the diagnosis and has the potential to influence the treatment of that disease, the most common of all the hematologic malignancies.

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DISCOVERIES KEEP COMING

"Even before the discovery of that first oncogene," Dalla-Favera said, "it was pretty clear that a condition like lymphoma would only occur after mutations in many different genes, so I never saw the challenge as finding only one mutated gene. I saw the challenge as finding them all and figuring out how together they drove the disease."

Dalla-Favera came to the NCI 2 years after Varmus and Bishop published their landmark paper.

Like many other researchers, he figured that if healthy bird genomes contained SRC homologs, then healthy human DNA might also contain proto-oncogenes, long sections of code a mutation or two away from genes found in tumors.

Confirming this hypothesis amidst the entire human genome would obviously be impossible, but Dalla-Favera knew how he could narrow the search.

Earlier research had already demonstrated that the few genes of any virus would pair with whatever human genes were the closest match. Therefore, Dalla-Favera figured, an oncogene inside a virus would likely pair with the most similar proto-oncogene inside human cells.

FORTUITOUS TIMING

Dalla-Favera's timing was fortuitous. The first technology capable of testing his idea had just arrived at research facilities, and Dalla-Favera had just gone to work in a laboratory that stored many cancer-causing viruses.

He requisitioned everything he needed and, within a few months, discovered human cellular sequences that are homologous to the v-MYC oncogene found in the avian myelocytomatosis virus.

He then followed up with research that showed where the gene localized and demonstrated that it sometimes translocated to other chromosomes.

Dalla-Favera's work was a key step in confirming the hypothesis that Varmus and Bishop put forward years earlier and in creating the modern understanding of how cancer develops.

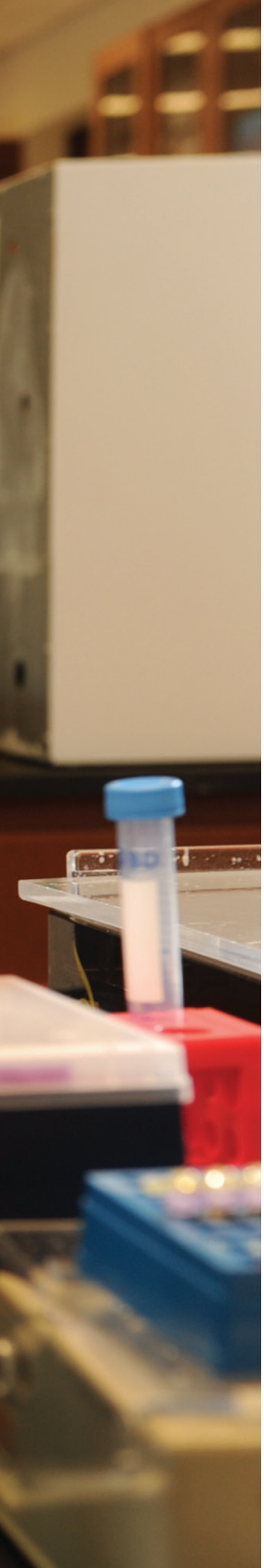
Indeed, the discovery of proto-oncogenes helped solve mysteries—some decades old, some even centuries old—such as why carcinogens and viruses trigger cancer in some people but not others, why the propensity to some cancers is hereditary, and why the risk of developing cancer increases with age.

It was a sign of things to come.

"Riccardo was exceptional even by the standards of people who do research at NCI," said Robert C. Gallo, MD, who ran the NCI's Laboratory of Tumor Cell Biology during Dalla-Favera's fellowship.

"He had a natural gift for conceptual science that made him insightful, but his biggest gift was his focus. When he set his mind on a goal, he worked relentlessly toward it. Each time he took a step forward, he immediately identified the next step and focused on that," Gallo said.

Why?



"Asking why top researchers spend 80 hours a week investigating arcane problems is like asking why rodents run on wheels. It's just in their nature," Gallo said. "It's not a sacrifice for them, though it is for their families. It's what they're compelled to do. We're addicts who lucked into a socially acceptable addiction."

RESEARCH BECKONS

Dalla-Favera was born in 1951 and raised in Milan, Italy, where his father and several other family members practiced medicine. Their influence inspired him to enroll in medical school, but he never planned to follow them into the clinic. The research laboratory was already beckoning.

Dalla-Favera chose to concentrate on lymphoma for largely pragmatic reasons. Italy's hematology departments got substantial funds from a government that shortchanged other research areas. That money allowed those departments to do some of the only world-class research in all of Italy, and most of the cash naturally went to study hematologic cancer.

Still, despite the relative strength of Italy's hematology programs, Dalla-Favera set off for the United States after completing his residency at the University of Milan. Americans spent more on science than did Italy, and they clearly led the world in cancer research. Dalla-Favera figured he'd spend a few years studying with the masters in America and using the technology before he returned home for good.

That was 36 years ago.

"I was probably naïve in thinking that I'd return, given how much I wanted to do research and how much better the opportunities were here," Dalla-Favera said. "I missed my family and friends. I missed my native culture. I missed my soccer team. I still do. But I'd have probably been willing to move to Antarctica if that had been the best place to do research. I'm very lucky that I ended up someplace as nice as New York," he said.

Dalla-Favera arrived in the city in 1983, when he took a job at New York University, and his only move since then has been uptown, to Columbia University.

ONCOGENES

When he began his work, he found oncogenes by looking at chromosomes under the microscope, trying to detect minute differ-

ences between cancerous and healthy cells.

It may sound primitive to modern ears, but the technique proved surprisingly productive. Dalla-Favera kept making significant discoveries throughout the 1980s, about how oncogenes mutated and how different mutations produced different results.

He collaborated, for example, on a number of papers about the genetics of Burkitt lymphoma. His work explored topics such as how c-MYC mutations differed in the endemic and sporadic forms of the disease and how the expression of a c-MYC oncogene causes the tumorigenic conversion of of human B-lymphoblasts infected by Epstein-Barr virus.

The same period saw him contribute to a number of papers that explored the relationship between viruses—particularly the AIDS virus—and various forms of lymphoma.

The steady production helped him rise through the ranks, from assistant professor to associate professor to full professor. During that time, he kept distractions to a minimum. He saw no patients. He ran no drug trials. He did no administration.

In 1992, life became more complicated. Columbia awarded Dalla-Favera an endowed chair, put him in charge of the Division of Oncology in the Department of Pathology & Cell Biology, and made him a deputy director of the Columbia-Presbyterian Cancer Center. In 1999, Columbia made him director of its Institute for Cancer Genetics, a title he still holds.

Dalla-Favera now oversees the work at 15 separate research laboratories, but he has always maintained a team of his own and managed to devote most of his professional life to its efforts. (He still doesn't see patients or run drug trials.)

The stream of new discoveries has continued to flow.

"The thing that really illustrates his commitment to lymphoma research is his willingness to let go of promising discoveries if their potential importance lies with other diseases. He has repeatedly allowed his team members and others to take things out of his lab rather than working on them in-house and diffusing his team's concentration," said Michael Shelanski, MD, PhD, chairman of Columbia's Department of Pathology & Cell Biology.

"That focus alone would produce a fair amount of success, but he really has all the tools. He has a keen eye for talent, and he makes consistently excellent hires, both for his own team and the others he oversees. He does drive people very hard, and that reputation scares some people, but he's a great boss for people who share his passion for the work. He has an innate sense of what path will prove the most productive when there are many directions a project could take, and he guides his team members in the most productive directions," Shelanski stated.

CITED EXTENSIVELY

Dalla-Favera's research has always won space in the most prestigious journals and respect from colleagues who understand its true importance. Dalla-Favera's scholarly works have already been cited more than 39,000 times, and the rate of citation keeps increasing as the implications of his discoveries emerge.

Moreover, time has begun to reveal practical applications for the work. For example, some antibody tests that

provide specifics about each patient's cancer trace their origins back to discoveries that Dalla-Favera and colleagues made about B-cell lymphoma 6 protein.

Such advances have already improved the diagnosis of lymphoma, but Dalla-Favera believes the future holds much more important applications.

"We've finally reached the point where we know most of the genes that are responsible for producing different types of lymphoma. Now we want to learn more about the importance of each and group them by functions such as cell reproduction or cell suicide," Dalla-Favera said.

Further information in those very basic areas may help others create rational ways to determine which medications, among the dozens that are currently approved, will work best for different tumor types in general and individual patients in particular.

It may even underlie the development of treatments that can reverse a few of the most important genetic mutations and cause tumors to collapse.

PASSIONATE ABOUT BIOLOGY

But Dalla-Favera and the team he leads won't be doing any of the development work, and they certainly won't be doing clinical trials.

"The skills needed to perform biological research and to develop new treatments appear completely different to me. I have spent decades developing my skills in the first area, so I can be much more productive by concentrating my efforts there and leaving drug development to the experts," said Dalla-Favera, who added that he feels much more passion for biology than for chemical engineering.

"There's no way to do good work over any period of years without true passion. Research is frustrating. Many days—perhaps even most days—are entirely unproductive. You need passion to work at problems long enough to solve them," Dalla-Favera explained.

Passion has kept Dalla-Favera working 80-hour weeks for nearly 4 decades now. For much of that time, he relaxed by playing soccer and squash, but his body began to rebel when he turned 60. He now contents himself to read about professional soccer and other sports taking place in Italy.

Colleagues say that, despite his long residence in the US, Dalla-Favera remains true to his roots in many ways. He dresses, for example, with a level of sophistication that's unusual among American researchers and displays an enthusiasm for fine dining that's as stereotypically Italian as his enthusiasm for soccer.

Looking back, he counts himself lucky to have had so many opportunities, but he does not look back often. There are still so many questions he wants to answer.

"Those early years were golden years because new technology gave you the opportunity to do things that no one else had ever done before," he said. "But the same is true today. We can now do more of some kinds of work in a day than we once could do in a year, and that opens up incredible possibilities." ■

MELANOMA

JEDD D. WOLCHOK, MD, PhD

MEMORIAL SLOAN KETTERING CANCER CENTER

Before the Internet and global interconnectedness, advancements in science and medicine were usually slow and incremental, with research and findings conducted by solo researchers, and shared over time.

"The idea of team science is something that evolved quite a lot in the past few years. It used to be that this idea of large groups was rarer than it is now. It has become quite the norm to assemble large groups to solve problems more quickly, and I'm all for it," said Jedd D. Wolchok, MD, PhD, the recipient of the 2014 Melanoma Giants of Cancer Care™ award. Wolchok is chief, Melanoma and Immunotherapeutics Service, and Lloyd J. Old Chair for Clinical Investigation at the Memorial Sloan Kettering Cancer Center in New York City.

The collaborative effort, in which all the researchers involved play a role to accomplish a common goal, can only succeed with a keen understanding of interpersonal dynamics. For Wolchok, this kind of group dynamic is well

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2014

demonstrated in a favorite book, *American Prometheus*, the classic biography of J. Robert Oppenheimer written by Martin J. Sherwin and Kai Bird. The coming together of colleagues from multiple disciplines toward a vital and common goal was evident in the Manhattan Project and subsequently in the efforts to find more peaceful and controlled application of the atomic science.

Once a group comes together, good decisions can be made based on logic, reasoning, and instinct, with the good of a group sharply in focus. Approaching problems analytically, logically, and with calmness has gotten Wolchok this far.

SUMMERS AT MEMORIAL SLOAN KETTERING

The death of a loved one is often the inspiration for a budding scientist to pursue a career in cancer research. In Wolchok's case, the death was his grandmother's, but his passion for clinical research was gradual, fueled by the summers away from Princeton University, where he completed his undergraduate studies.

"By the time I finished college, the research experiences I had during summer breaks while working at Memorial Sloan Kettering in the translational laboratories fueled my interest," said Wolchok. "I saw incredible possibilities that existed in terms of moving research from the laboratory to the clinic, and taking those successes and failures back to the laboratory for refinement. That was a very inspiring set of experiences for me."

Wolchok was mentored by Lloyd J. Old, MD, considered the father of modern tumor immunology, and Alan Houghton, MD. The Houghton Laboratory brings together a mix of molecular biologists, immunologists, medical oncologists, and surgeons. The participants understand that this type of environment encourages cross-fertilization of scientists and clinical investigators. The laboratory, which Wolchok now runs, is interested in 2 fundamental questions: "How does the immune system recognize cancer, particularly mutations?" and, "How does the immune system reject cancer?"

Wolchok considers it an incredible honor to continue his mentors' work, although he would much rather have Houghton actively engaged in the ongoing research. Houghton suffers from amyotrophic lateral sclerosis and Lloyd Old died from prostate cancer in 2011.

IMMUNOTHERAPY AND MELANOMA

Until about 3 years ago, there were no medications that improved survival in patients with metastatic melanoma. Immunotherapies were considered complicated and marginal. They were only administered at a few cancer centers. In addition, immunotherapy's low success rate and low tolerability, with only otherwise healthy patients as candidates, made it a difficult clinical treatment to pursue.

"I think one had to be persistent in both immunotherapy and in melanoma treatment because there was so much failure until recently," said Wolchok. "There were so many trials that did not meet expectations. There was so much questioning of the validity of the underlying science because of that." But he pointed out that persistence in this field has paid off. Researchers stuck with it until agents were developed that could modulate the immune system in a potent enough manner to impact tumor growth.


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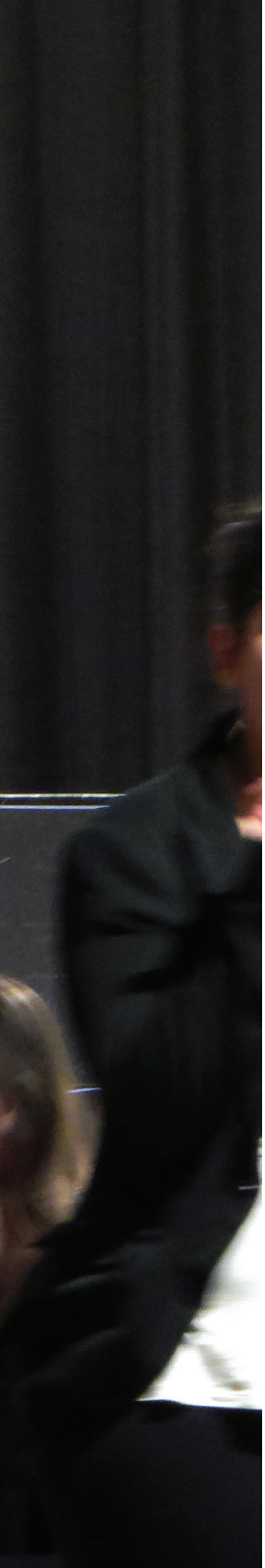

"In my mind, the science was never in question. Because many ideas were explored in the clinic, but failed to meet expectations, there was a characterization of the field as being speculative in nature. That was a challenge," Wolchok said.

He recalled that much of the focus of discussions with patients was about the hope and promise of clinical trials. With the approval of ipilimumab, vemurafenib, dabrafenib, and trametinib following advances in the understanding of melanoma biology and tumor immunology, "the tenor of those patient conversations now has some concrete source of hope."

Wolchok discussed one patient who participated in a phase II trial involving ipilimumab in which an initial set of imaging scans suggested that the disease had gotten markedly worse since treatment began.

"Yet the patient told me that he felt better. It caused my colleagues to rethink the way we judge the clinical efficacy of this kind of cancer therapy," said Wolchok. It also gave him a newfound respect for the complex biology that exists between the patient and the tumor, and the fact that when treating the immune system, the patient's condition might not improve on schedule.

"That patient had another set of imaging scans performed 2 months later with no further therapy and showed that almost all the disease had regressed," Wolchok said. In the official documents filed for the trial with the FDA, that patient was scored as a drug failure. "In that instance, I realized that we need to rethink the way we judge the clinical activity of novel anticancer therapies.

"My lab research is very linked to clinical care, either in forming new clinical trials or helping to understand current clinical trials. There is nothing that can possibly be more thrilling than to help a patient improve the state of his or her health. That is the number one thing that buoys me but there is a lot of laboratory science that feeds forward and feeds back from that," said Wolchok.

THE COLLABORATIVE EFFORT

Wolchok values the collaborative effort—whether it's working on a vexing problem in the laboratory with many team members or mastering a challenging musical piece

> *"With the approval of ipilimumab, vemurafenib, dabrafenib, and trametinib following advances in the understanding of melanoma biology and tumor immunology, "the tenor of those patient conversations [about the promise of clinical trials] now has some concrete source of hope."*

in the Brooklyn Wind Symphony where he plays tuba. He pointed out that "there aren't many career opportunities for professional tuba players," but even if there were, he still would not consider a change in career paths.

The Giants of Cancer Care award is given for individual accomplishments, but Wolchok understands that success stems from a team effort and from others who have come before. When accepting the award during a reception in Chicago, he noted that some people there "have been mentors and role models to me, like Dr. James Allison. Having a former fellow from Memorial Sloan Kettering, Dr. Jason Luke, present me with the award—I felt acknowledged in a 360-degree way. That was very meaningful to me." ■

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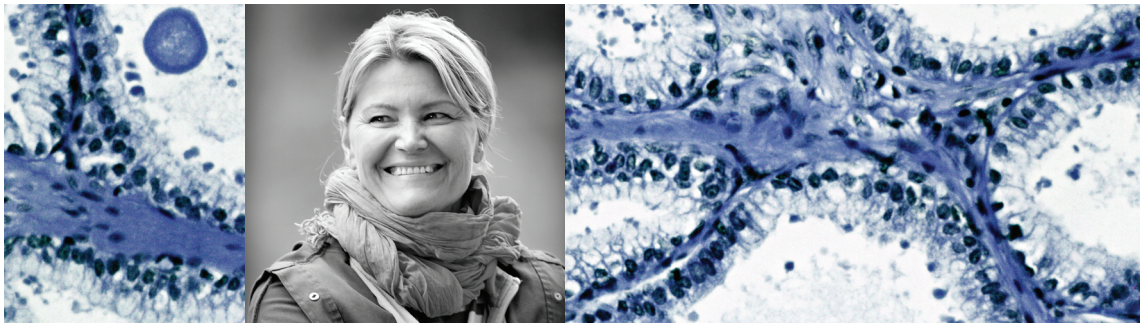

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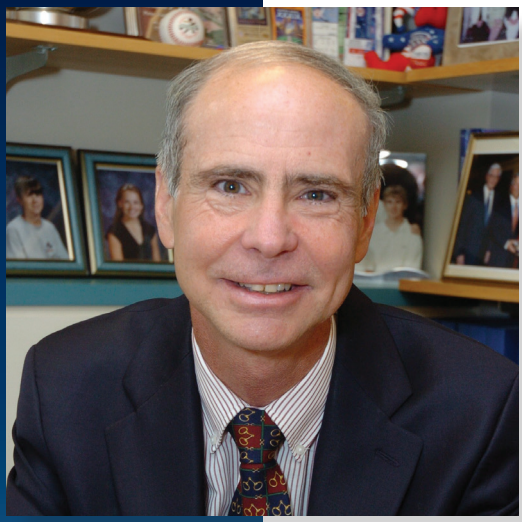

MYELOMA

KENNETH C. ANDERSON, MD

DANA-FARBER CANCER INSTITUTE/
HARVARD CANCER CENTER

When Kenneth C. Anderson, MD, began his studies at Johns Hopkins Medical School, he fully intended to abandon the basic biological research he loved and focus instead on the sort of general clinical practice that would provide "real benefits to real people."

Then he met Richard Humphrey, MD, a legendary pathology professor, who convinced him that research could provide even greater benefits to real people, if Anderson always followed 2 simple rules: make science count for patients, and treat patients like family.

Humphrey could not have imagined at the time how right he was. The discoveries that Anderson has made over the past 34 years at the Dana-Farber Cancer Institute have helped spur a revolution in the treatment of multiple myeloma—9 new treatments in less than 15 years.

When Anderson began that work, multiple myeloma was not only incurable, it was basically untreatable. Now, for many, it's a chronic disease.

"I've always enjoyed the intellectual challenge of discovering how the

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disease works and what can disrupt its workings," said Anderson, who is now the director of the Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics in Boston.

"But the real joy has come from watching patients live long enough to enjoy birthdays and graduations and other milestones they would have missed," Anderson said.

PRACTICAL GOALS

When Anderson came to Hopkins, Humphrey was culturing multiple myeloma cells in test tubes and bombarding them with potential treatments. The effort did little to change myeloma care, but it did change Anderson's life.

That one experiment illustrated that very basic research could have very practical goals. It also convinced Anderson that myeloma research might prove particularly fruitful.

By that time, bone marrow aspirations made it easy to gather myeloma cells from patients, and even the simplest cultivation techniques kept those cells growing. Myeloma thus ranked among the easier cancers to study in the laboratory, but when Anderson turned his attention to the disease, virtually no one was doing so.

After completing his internal medicine residency at Hopkins, Anderson began a medical oncology fellowship at Dana-Farber in 1980, pitching in with ongoing efforts there to develop and test treatment protocols for the first generation of monoclonal antibodies.

Anderson first used antibodies to deplete tumor cells from bone marrow taken from multiple myeloma patients, which was then returned to them to restore blood and immune function after high-dose therapy.

Fewer cancer cells in the transplanted marrow led, in turn, to fewer relapses for transplant patients.

Such work illustrated the breakthrough potential of treatments that prevented tumor cells from interacting normally with their microenvironments and inspired Anderson to embark upon a multidecade quest to understand and model the workings of multiple myeloma.

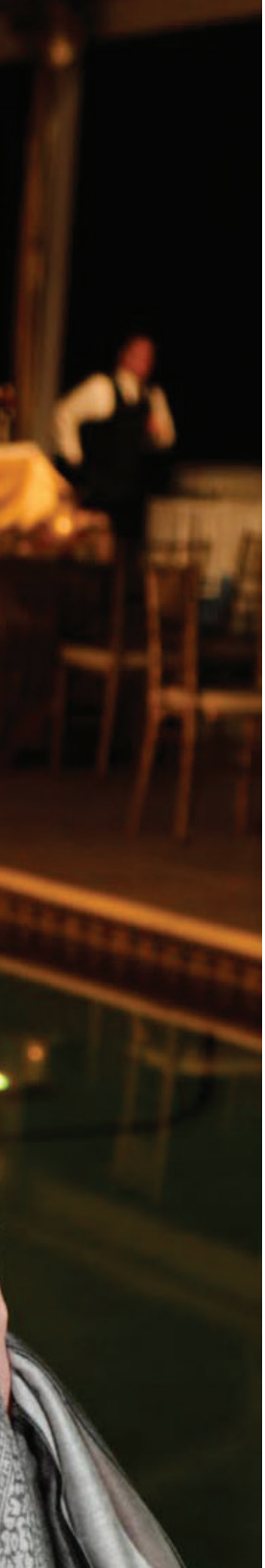
For example, Anderson and his colleagues slowly discovered how multiple myeloma cells used cytokines to develop resistance to many treatments, and they speculated that a cytokine-inhibiting substance could retard the development of drug resistance.

THALIDOMIDE

The problem was finding a drug that could interfere with cytokines. Anderson gathered as much information as he could about existing and experimental compounds. He tested possible candidates. Nothing offered much promise—until 1997, when Anderson heard that Bart Barlogie, MD, PhD, had undertaken a trial of thalidomide on 84 patients with previously treated multiple myeloma.

The idea for using thalidomide as a cancer treatment came from one of Anderson's most eminent colleagues at Harvard, the pioneering angiogenesis researcher Judah Folkman, MD, a recipient of the Scientific Advances award of the 2013 Giants of Cancer Care™.

Folkman believed the chemical would slow disease progression by depriving cancer of blood. The results, however, far exceeded anyone's dreams, and Anderson soon suspected that thalidomide acted not only as an angio-



genesis inhibitor but also as an immunomodulator, one that prevented the cell-signaling mechanisms that lead to drug resistance.

Research at Anderson's laboratory confirmed that thalidomide does interfere with cytokines and does delay drug resistance. Better still, all that Anderson had learned about multiple myeloma's biology over the years enabled him to create models of myeloma in its bone marrow microenvironment that helped predict how to administer the drug for maximum effect, first in animals and then in human patients.

Those models also helped Anderson's team to demonstrate preclinical antimyeloma activity of lenalidomide (Revlimid), a more potent thalidomide analog.

UNDERSTANDING THE BIOLOGY

Anderson and his team led both the preclinical and clinical trials that preceded FDA approval of lenalidomide in 2006. Then, using advances in both their own models and other research, they repeated the process 6 years later by leading the trials of pomalidomide (Pomalyst), which is more effective and well tolerated.

"When I started out in my career, very few teams did everything from basic research to late-stage trials, and I think my experience has demonstrated some real value in that. Understanding the biology improves your ability to predict what experimental compounds to test and how to optimize their usage. Performing drug trials on real patients gives you ideas about the underlying workings of the disease, which, in turn, gives you better ideas about fighting it. It's a positive cycle," Anderson said.

"The other thing my career demonstrates is the value of focusing on the same subject for long periods of time. You will run into brick walls, but if you keep old ideas on the back burner, you will be ready to capitalize when technology improves or new discoveries take place or you simply get an inspiration," Anderson explained.

Anderson grew up in Auburn, Massachusetts, a small town in the center of the state. He developed his interest in medicine by talking to his mother, who was a nurse, and the town doctor, who befriended Anderson during grade school and encouraged his aspirations.

Anderson studied biology at Boston University and, in 1973, became the first member of his family to earn a college degree. He then set off for Johns Hopkins, intent on becoming the sort of small-town doctor who

might inspire other precocious kids.

While Anderson ended up as a world-famous researcher at Harvard, he has still proven an inspiration to precocious youth. A good percentage of all the world's top myeloma researchers started their medical careers in Anderson's laboratory, learning the keys to effective medical research: make science count for patients, and treat patients like family.

Anderson, in turn, credits his gifted students and colleagues with much of "his" success. His colleagues disagree.

"He always gives credit to others and talks about 'we' rather than 'I' because he is a modest man and because he genuinely regards his team as a family that succeeds together," said Nikhil C. Munshi, MD, director of Basic and Correlative Science at the Jerome Lipper Multiple Myeloma Center.

"His generosity and obvious sincerity inspire people to give their all and to work together for the common good, and that produces results," Munshi stated.

BORTEZOMIB

Still, like all great researchers, Anderson has benefitted from serendipity.

In the mid-1990s, for example, Anderson discovered that the protein complex nuclear factor κB (NF-κB) performed several vital functions that enabled myeloma cells to survive and grow. That discovery might have had little practical impact, but for the fact that another team at Harvard happened to develop the first chemical that inhibits NF-κB at almost the same time.

Anderson quickly tested the compound against myeloma and saw dramatic results. Human trials proved equally encouraging, and the FDA approved bortezomib (Velcade) just 3 years after it was first tested in humans.

The speed of bortezomib's approval and the powerful effects it had on patient outcomes dramatically illustrated the power of Anderson's seminal idea: basic biological research can reveal the weaknesses in even the most powerful of diseases.

No other approach had yielded a single truly novel myeloma treatment in decades. Anderson had not only found a novel treatment but also gotten it through trials in record time because he understood its mechanisms well enough to use it properly from the start.

It was, to be sure, a triumph that had taken many years of work to attain, but that work provided the basis for a series of breakthroughs that followed soon after. It uncovered the mechanisms whereby novel agents work and thus informed their optimal use both alone and in combination. That, in turn, helped bring about FDA approval for the second-generation proteasome inhibitor, carfilzomib (Kyprolis), and the immunomodulatory drug pomalidomide.

MANAGING RELATIONSHIPS

The sheer speed of change says much about Anderson's scientific skills, but it may say even more about his ability

to manage relationships.

"Bringing a compound from the lab to the clinic requires cooperation among a lot of organizations: the National Cancer Institute (NCI), the FDA, pharmaceutical companies, biotech companies, academia, and, most importantly, patients," Anderson said. "Patients are the inspiration for all that we do."

"We've had success at moving things quickly because we've reached out to all the team members over the years and figured out how to best work together. For example, we've spent years talking to folks at the FDA about myeloma and what are the correct trials to evaluate novel agents to rapidly provide the data needed for their approval. They have been wonderful and worked tirelessly to help patients get access to novel life-prolonging treatments," Anderson explained.

Anderson has already been given a number of lifetime achievement awards, but he thinks that his most valuable work may still lie ahead of him. New discoveries in genomics and other areas have combined with improving technology to allow for in-depth understanding of myeloma biology, which in turn identifies new targets for next-generation treatments.

Dozens of new compounds are under development for the treatment of multiple myeloma, and Anderson hopes to shepherd the best ones to the clinic and, more importantly, to discover how they should be used in combination with other treatments.

Recent studies in his group have shown that myeloma is very heterogeneous at diagnosis and that genetic mutations and evolution are associated with disease progression. These findings suggest that, as with infectious diseases such as tuberculosis or HIV, combination therapies will be needed early to make the most impact.

MULTIDRUG COMBINATIONS

Anderson currently recommends a 3-drug combination—bortezomib, lenalidomide, and dexamethasone—along with stem cell transplantation and lenalidomide maintenance therapy for all eligible patients. Looking further ahead, however, Anderson believes that 4-drug or 5-drug combinations will become the new standards of care, standards with curative potential.

The challenge, of course, will lie in determining which 4 or 5 drugs should be given, at what dosages, on what schedule, and to which patients.

The sheer number of possible combinations will prohibit researchers from simply trying every combination, so the work of deciding which combinations to test will most likely rely on those laboratory models that Anderson has spent the last 3 decades building.

Anderson hopes those models will soon be able to move beyond predicting which combinations will be best overall and begin to use information about patient and tumor DNA to predict which will be best for individual patients. Targeted therapy has obviously proven very successful against other tumor types, and Anderson believes it will prove equally valuable in fighting multiple myeloma.

"Combinations of targeted therapies against those abnormalities present in a given patient are the greatest hope for the future," he said.

Medical profiles necessarily focus more on breakthrough discoveries than on clinical practice, but it is clinical work that motivates Anderson to do all the rest.

He spends as much time asking patients about their work and hobbies and family life as he spends discussing symptoms and treatments. He celebrates their victories. He sympathizes with their troubles. He works for them.

"My patients have placed their lives in my hands, and that is a sacred trust. I do everything I can to give every single patient every possible day," he said.

"I still mourn every patient I lose, but I feel incredible joy whenever I consider how much things have improved. I used to know patients for months. Now I know most of them for many years, and I celebrate milestone after milestone with them. They are my heroes and inspiration. It has been a privilege and a blessing for me to help change the natural history and treatment paradigm of myeloma. Providing the gift of life and hope to our patients, working with teams of selfless researchers, watching them become world leaders in myeloma, keeping them as lifelong collaborators and friends—it doesn't get any better than this," Anderson said. ■

OUTREACH

EDITH A. PEREZ, MD

MAYO CLINIC

Coping with challenges is part of the human condition, but self-awareness can have far-reaching results. Just ask Edith A. Perez, MD, about her experience attending medical school.

"I always thought I would do something… it wasn't something that I could totally articulate, but I knew I was going to do something different," Perez recalled.

The desire to do something different started in elementary school in Puerto Rico. She talked about a classmate who boasted to the class of someday allowing people to live forever. When her turn came, not wanting to be outdone, Perez proclaimed that this would require finding a way to expand the world (which she would do).

Her intellectual appetite has turned out to make a marked difference for patients with breast cancer everywhere. Every day, she puts her mind to finding better treatments for the disease and to conducting research that will help others in the oncology community move forward with science aimed at improving people's lives.

Much, although not all, of her work has concentrated on the study of compounds designed to fight HER2-positive breast cancer, leading to a 2005 discovery that changed the way the disease is treated. A study that Perez led and helped design showed that the use of trastuzumab (Herceptin), a monoclonal antibody that helps counteract a genetic and protein alteration of HER2, in concert with chemotherapy—rather than

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chemotherapy alone—resulted in a 52% decrease in the recurrence of HER2-positive breast cancer in patients who had undergone surgery for the condition, and improved their survival by 33%.

"It was a real breakthrough for patient management and I knew it would apply to thousands of patients in the United States and throughout the world," said Perez. "We presented those data at the largest meeting ever of the American Society of Clinical Oncology, with about 16,000 people in attendance," Perez recalled.

More importantly, she "realized that not too many physicians have the opportunity to affect that many lives to this degree, no matter how dedicated they are or how incredibly good their ideas. To see the eyes of the patients, and their gratitude for the results of the work that we have done, is very humbling and it has been quite powerful."

Using tumor and blood samples collected during the study, Perez and her colleagues have continued to consider the potential applications of trastuzumab. "I routinely explore things that I hope will be more efficacious and lower toxicity," Perez said, "because that's huge for people's lives."

MANY ROLES AT MAYO CLINIC

Perez accomplishes that through a variety of roles at Mayo Clinic in Jacksonville, Florida, including her role as director of the Breast Cancer Translational Genomics Program. For more than 2 years, she has served as Deputy Director at Large of the Mayo Clinic Cancer Center based in Rochester, Minnesota, and also is director of the institution's Breast Specialty Council. The Council brings together researchers from all Mayo Clinic sites to review research opportunities related to breast cancer prevention, treatment, and survivorship.

She is a Serene M. and Frances C. Durling Professor of Medicine at the Mayo Medical School; the first Mayo Clinic physician to serve on the Board of Scientific Advisors of the National Cancer Institute (NCI); and, in 2007, was given her institution's top honor for investigators when she was named a Mayo Clinic Distinguished Investigator.

Finally, Perez helped launch a fundraising marathon that led to the January 2009 creation (and continued funding) of Mayo's Breast Cancer Translational Genomics Program, which aims to unravel, categorize, and catalog relevant molecular alterations present in breast cancer. The goals of the work include gaining a better understanding of what drives the disease's growth, learn-


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ing what may predict sensitivity or resistance to different treatments, and identifying targets that can be used to develop new treatments, according to Perez. The event—called 26.2 with Donna, the National Marathon to Finish Breast Cancer—also includes a 5K, a half-marathon, and a relay. It attracts more than 10,000 participants, involving people from patients to elite runners, and helps raise funds not only for genomic research but for underserved women diagnosed with breast cancer.

RESEARCH PART OF HER HECTIC RACE

Her myriad roles make for a whirlwind schedule of workdays that stretch 10 hours or more. In addition to her clinical trial and translational laboratory work, Perez's schedule includes organizing, attending, and speaking at meetings all over the globe; participating in conference calls; conducting grant reviews on behalf of the National Institutes of Health (NIH); advising scientists and companies throughout the world on studies, research, and patient care; writing manuscripts; mentoring younger scientists; and making videos for YouTube to explain her current research.

Perez also heads Mayo Clinic teams in conducting basic research projects funded by the NIH, including one focused on tissue biomarkers for responsiveness to adjuvant trastuzumab and another project aimed at understanding the role of the immune system in response to anti-HER2 therapies—trastuzumab, pertuzumab and lapatinib (Tykerb)—in adjuvant, neoadjuvant, and metastatic settings. In large part, the projects involve analyzing the proteins and genes in tissue and blood specimens and

correlating them with patient outcomes.

Perez does not consider her heavy workload a burden on her private life. "My work doesn't feel like a lot of sacrifice. It's what I can do best," Perez said. "Although I would like more hours to play tennis, run on the beach, read, be with good friends, and volunteer my time, it's not a sacrifice at all."

Perez also manages to find time to see breast cancer patients, including a few who periodically return for follow-up care, and new patients who are seeking second opinions about diagnoses.

Seeing patients routinely would be difficult, Perez said, because of her travel schedule. Those she has treated, though, remain fixed in her memory.

"Some of their stories are really amazing," Perez said. "I just respect what they have to go through, because most of them thought they were healthy until, one day, this happened to them."

Perez was moved recently when she received an email from the husband of a deceased patient. "She died before Herceptin was available, and I thought, 'If she had lived a few more months, we would have had this novel treatment,'" Perez recalled. "This kind of experience has served as my inspiration all these years. Whenever I see a patient, I wonder, 'Is this the patient I'm going to help next?'"

INSPIRED BY A LOVED ONE'S DEATH

A similar thought inspired Perez to study medicine. She was a 16 year old freshman in college when her grandmother died suddenly. "I thought, 'If I had been a doctor, I could have helped her,'" Perez recalled.

Growing up on the east coast of Puerto Rico, close to the beach and the rainforest, Perez exhibited all the skills she would later need to pursue a medical degree.

"I really enjoyed science very early in my life, although I was going to be a mathematician, not a physician," she said. "I was really good at math, which I got from my father. Even when I was in college, I took a calculus class, and in the whole semester, I missed one question in one test. I could see the solutions easily."

By the time Perez was an intern, she was considering a specialty in breast cancer.

"It was interesting because it was evolving and complex, it had to do with people, and I realized that someone who liked to read could do well," she said. "I thought I could be doing this for a while, and I was right."

The daughter of a father who owned a grocery store and a mother who was a teacher-turned-librarian, Perez started school early, advanced an extra year during high school, graduated in two years, and, at 16, enrolled as a premedicine student at the University of Puerto Rico, Rio Piedras campus, where she earned a bachelor of science degree in biology 3 years later.

Perez stayed at the university to earn her medical degree, then completed her residency in internal medicine at Loma Linda Uni-

versity Medical Center in California. Having decided to pursue oncology, Perez began a fellowship in hematology and oncology at the Martinez Veterans' Administration Medical Center, affiliated with the University of California—Davis, School of Medicine. There, she did work related to lung cancer and began to explore breast cancer.

Then, one evening in 1995, a telephone call accelerated her path to the top of that field.

"I got a call asking if I'd be interested in transferring to the Mayo Clinic," she said. "I was extremely happy, and I accepted the opportunity. I was very fortunate because it's a great institution."

NEW COMPOUNDS IN FOCUS

Before moving to Mayo's facility in Jacksonville, Perez spent six months working at the institution's Rochester, Minnesota, location, where she devoted mornings to laboratory research and afternoons to patients.

In Mayo's laboratory, her focus was combinatorial chemistry, Perez recalled, "treating cancer cells with different medicines or new compounds and seeing how you can best kill tumor cells—is it best to combine medicines or use one? These are ideas I carry today when I do lab bench work that can be translated into clinical trials."

Since moving to Jacksonville, Perez has bolstered Mayo's breast cancer program by attracting continuous grant funding from Evelyn Lauder's Breast Cancer Research Foundation, becoming a founder of the genomics center, and helping to make numerous discoveries about the mechanisms of the disease.

For instance, "many people thought that the more copies a patient had of the HER2 gene, the better their response would be to Herceptin," Perez said. "But we found that, up to a threshold, more copies of the gene didn't make for a better outcome."

Perez is proud of the progress she has made during her time at Mayo Clinic, and she is eager to build on it.

"I love what I do, and I want to do more," she said. "These days, I'm much more productive than I ever was, and I'm having more fun than ever. It's all very interesting to closely work with outstanding collaborators here at Mayo Clinic and other institutions around the world."

One accomplishment Perez hopes she has achieved is having her research results translated into the community so it can improve the lives of patients worldwide. "It's about more than being in the laboratory," explained Perez. "It is more than being in front of my computer answering email. Ultimately, the impact I have will make a difference for people all over the world." And so the elementary school dream voiced years ago continues today. ■

PROSTATE CANCER

PATRICK C. WALSH, MD

JOHNS HOPKINS UNIVERSITY

Until the mid-1970s, the radical prostatectomy ranked among the most dreaded of all surgeries in men. Each procedure entailed a frenzied effort to navigate uncharted anatomy and avoid copious bleeding and following surgery, these men faced a lifetime of virtually certain impotence and probable incontinence.

The vast majority of prostate cancer patients thus made the understandable choice to forgo surgery in favor of radiation treatments that, at that time, rarely produced cures.

Then, in 1974, Patrick C. Walsh, MD, took charge of the Brady Urological Institute at Johns Hopkins University in Baltimore, Maryland, and spent the next few decades refining the radical prostatectomy into a safe, effective, and tolerable procedure, one that has not only extended countless lives but has also preserved quality of life.

"The survival numbers for prostate cancer have improved more in the past 20 years than those of any other major type of cancer," Walsh said. "Deaths have fallen 40%, and I thank God every day for giving me a role to play in that story."

Hugh Young, MD, the initial chief of urology at Hopkins, performed the first-ever radical perineal prostatectomy in 1904. Despite all its problems, the surgery represented a huge improvement over existing standards of care, and Hopkins became a world leader in prostate cancer care.

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In the 1960s, however, Malcolm Bradshaw, MD, developed techniques for treating prostate cancer with high-energy radiation. The bloodless procedure quickly became the treatment of choice.

REVERSE THE TREND

Walsh could not have known, when he moved to Baltimore, that his discoveries would eventually reverse the trend, but he did see a major opportunity to improve those prostate surgeries that still took place.

Anatomy texts from the period provided little information about the area around the prostate because following death, the abdominal contents settle into the pelvis, compressing the bladder and prostrate into a thick pancake of tissue that defied study.

Surgeons operated without a guide, blind in a sea of blood. Patients suffered the consequences.

Walsh decided to study the veins surrounding the prostate in hopes of finding some way to prevent the blood loss. He used the operating room as an anatomy laboratory, noting whatever he could see through the blood as he raced against the clock. Eventually, he deduced that there must be a common trunk that entered the pelvis over the urethra, so he decided to ligate it.

"All of a sudden, the bleeding nearly stopped. It was like someone turned off the tap," Walsh said. "I could see more of what I was doing and more of the surrounding area. I could also proceed at a more deliberate pace and, as a result, the operation became a safer, more complete cancer operation."

Walsh's technique for reducing blood loss transformed the radical prostatectomy from a dangerous operation to a safe one, but it did not inherently reduce the risk of impotence. Indeed, everyone at the time believed that the nearly universal incidence

of impotence among patients who underwent radical prostatectomy indicated that the nerves responsible for erections ran through the prostate.

Walsh learned otherwise in 1977, when one of his patients reported that he had regained sexual function shortly after his surgery.

That one report proved that the nerves responsible for sexual function do not run through the prostate and that all prostatectomy patients could experience full recoveries—if only Walsh could complete the map and perfect the surgery. The answer was not in any textbook.

So that's what he set out to do.

PASSED ON THE WINDMILL MUSEUM

Walsh was at a conference in the Netherlands when he finally traced the nerves that control sexual function, the nerves he'd need to avoid. He had just given a presentation, and his friend,

Pieter Donker, MD, who was head of urology at the University of Leiden, wanted to show him around town.

Donker talked up the local windmill museum, but Walsh said he'd rather tour Donker's laboratory, so that's where they went. At the time, Donker was performing dissections on a stillborn male infant to map the nerves to the bladder. Walsh explained his related interest in tracing the nerves that control erections. Donker said they should look together, and, in just 3 hours, they mapped the relevant anatomy and noted that it lay entirely outside the prostate. But these nerves were microscopic—how could they be identified in the male pelvis?

The next breakthrough came back in Baltimore. Walsh was operating on an adult patient when he noticed a group of blood vessels that took exactly the same path past the prostate as the nerves he and Donker had found. He hypothesized that the nerves were part of the cluster and that he could avoid the nerves by avoiding the blood vessels. He tested the theory during a radical cystectomy on a 67-year-old man. There were no reports of anyone regaining potency after such an operation, but 10 days after losing both his bladder and prostate, that man was able to have a normal erection.

A month later, on April 26, 1982, Walsh performed the first intentional nerve-sparing radical prostatectomy on a 52-year-old professor of management. It took several months for the patient to make a full recovery, but he has remained fully functional and cancer-free ever since.

"Once the first patient [in 1977] regained sexual function and proved that such a procedure was possible, it was only a matter of time until Pat figured out how to do it [inten-

tionally]. His focus is incredible. He will work relentlessly to accomplish anything he decides must be done," said Mani Menon, MD, a protégé who now runs the Vattikuti Urological Institute in Detroit, Michigan.

SELF-SUFFICIENT CHILDHOOD

Walsh was born in 1938 and raised in Akron, Ohio, where his father owned a tobacco shop. He was a standout student from the his first days in school, the sort of boy who spent his spare time observing animals to learn biology and taking apart household electronics to see how they work.

Walsh did not have nearly as much spare time as other boys, however, because his father believed kids should learn to be self-sufficient as soon as possible. He began delivering newspapers in elementary school and later supplemented that job with stints as a construction worker and a parking-lot attendant.

Walsh received full scholarships for both his undergraduate work and his medical degree at Case Western Reserve University and then began an internship at Peter Bent Brigham Hospital in Boston. He went to Boston with the intention of becoming a neurosurgeon but switched to urology a year later after deciding that urology would allow him to perform both diagnosis and surgery and then let him follow patients for years after.

Walsh's talents stood out, even at a hospital affiliated with Harvard Medical School. Francis Moore, MD, who was Brigham's surgeon-in-chief and the Moseley Professor of Surgery at Harvard, approached Walsh toward the end of his internship and said that he wanted Walsh to spend a few years doing additional training and research at UCLA before coming back to take over Brigham's urology department.

Walsh dutifully went to UCLA to study under Willard Goodwin, MD, and then spent 2 years fulfilling military obligations in San Diego.

In late 1972, Hopkins asked Ben Gittes, MD, who was Walsh's mentor in San Diego, to succeed William Wallace Scott, MD, as the director of the Brady Institute. Gittes declined the job and recommended his 35-year-old mentee. Hopkins interviewed Walsh and made the offer. Harvard countered by interviewing him for the same post at the Brigham. Ultimately, Walsh's wife, Peg, convinced him to take the Hopkins job—even though she preferred Boston over Baltimore—because she thought it was a better match for his interests and skills.

"If you want to succeed in academic medicine, you need a spouse who inspires and supports your dreams despite all the sacrifices, and my wife, quite simply, is a saint," Walsh said. "The Brady Institute hasn't been my life for the past 40 years. It has been *our* life."

Walsh's first nerve-sparing radical prostatectomy was a medical milestone, one that might seem like the end of the story, but it was really just the beginning.

Subsequent operations sometimes resulted in the sort of complete recovery experienced by the first patient. But other patients never recovered sexual function or full bladder control.

HONING HIS SURGICAL TECHNIQUE

Walsh realized that minute and almost imperceptible differences in his technique were producing huge variations in results, so he dedicated himself to noting the smallest details of each procedure and evaluating how variations affected outcomes.

He built a database that stored his initial observations and de-

tailed notes on his surgical technique for each patient, along with frequently updated reports on the patient's health and quality of life.

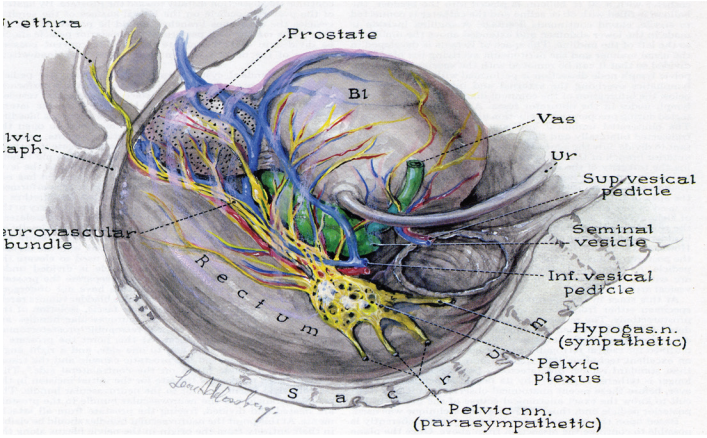
He also enlisted help from the noted medical illustrator Leon Schlossberg, who watched procedures and made ever-more-detailed notes about the anatomy around the prostate, its variation among patients, and the possible implications of the surgery.

"His biggest concern was that his effort to maintain [sexual] potency might be compromising cancer control, that skeptics might be right in calling it a 'cancer-sparing' surgery," said Herbert Lepor, MD, another Walsh protégé who now runs the urology department at New York University's Langone Medical Center.

"He asked pathologists to meticulously examine the data after 100 surgeries and he kept reexamining after that, ready to pull the plug on the procedure if there were any concerns at all. He knew the surgery was going to be his legacy one way or the other, but he searched more aggressively than anyone else for problems because he felt responsible," Lepor said.

Eventually, the quest to hone his surgical technique inspired Walsh to give himself another view of the procedure by videotaping each one. Professional athletes and their coaches have long found videos among the most powerful tools for enhancing performance. Walsh believes they're just as valuable for surgeons.

"When you're actually performing a surgery, the only thing you really see is the area around your own fingertips. When you're watching a video, you see everything," Walsh said. "You learn an unbelievable amount about the impact of what you are doing on surrounding structures."



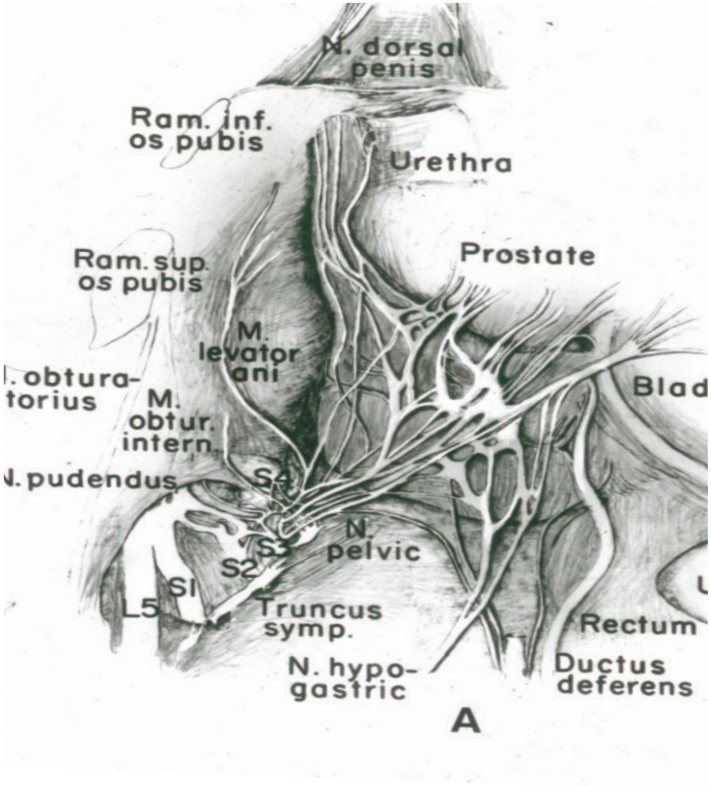
28 SIGNIFICANT CHANGES

Over the next quarter century, the process of testing potential improvements one at a time led Walsh to make 28 significant changes in the original nerve-sparing radical prostatectomy.

After 100 surgeries, for example, he realized that was it possible to widely excise the neurovascular bundle on one side of the prostate to produce a wider margin of excision than was previously possible using the perineal technique.

He learned that mucosal eversion at the bladder neck would reduce bladder neck contractures, that direct division of the posterior striated sphincter would improve surgical margins, and that using the McDougal clamp often was associated with inadvertent entry into the anterior prostatic tissue or excessive excision of the striated sphincter.

In 2011, after 4569 nerve-sparing prostatectomies, Walsh stopped performing surgery. He had, by that time, refined the procedure to the point that 94% of his patients regained sexual function and only 2% of them needed to wear any sort of sanitary pad.



Walsh's legacy extends far beyond the patients he treated himself. The advances he made to the prostatectomy transformed what was a fringe therapy into a mainstay of treatment, extending countless lives.

Prostatectomy is, for many patients, a more effective treatment than radiation. It is also a treatment that helps doctors evaluate the need for follow-up therapy in a way that radiation cannot, by providing tissue samples for analysis.

Nevertheless, it took Walsh's procedure many years to win the sort of widespread respect and usage it enjoys today. Some urologists read the initial reports of prostatectomy patients regaining their sexual function and concluded that Walsh's technique must leave cancer behind. Others resisted the procedure simply because it's far more difficult than radiation.

Walsh initially believed that any urologist who performs surgery could learn the technique. Indeed, he spent 5 years producing a 105-minute DVD and gave 50,000 of them away free of charge. In recent years, however, he has come to believe that only specialists who perform the operation regularly should perform it at all.

Walsh has spent his entire professional career working as hard as a resident. In addition to his research and his clinical practice, he spent 3 decades running the Brady Institute, teaching students, editing a major urology textbooks, reviewing 150-200 new papers each week, and writing 4 books for laymen. Asked what he did during his spare time, Walsh responded by asking what spare time was.

Now that he has retired from both administrative duties and surgery, he continues to teach students, perform research, and follow his 4569 patients. He is also writing a book about the history of the Brady Institute and providing ministry to prisoners who are awaiting trial or sentencing.

"The challenge isn't finding worthwhile things to do with my time," he said, "it's finding time to do all the worthwhile things that need to be done." ■

SCIENTIFIC ADVANCES

JAMES P. ALLISON, PhD

THE UNIVERSITY OF TEXAS
MD ANDERSON CANCER CENTER

James P. Allison has never hesitated to buck the system. As a teenager, the pioneering oncology researcher refused to take biology at his small-town Texas high school because the theory of evolution had been omitted from lessons for religious reasons. Instead, Allison took a university correspondence course, working alone in an empty classroom.

"I'd already decided that I wanted to be either a doctor or a scientist, and I knew that Darwin is to biology as Newton is to physics, so I refused to take the course. It got me into trouble with some of the teachers," said Allison, who went on to earn a doctorate in biological science and launch a nearly 40-year career dedicated to stimulating the human immune system to fight cancer. In November 2012, he left several leadership positions at Memorial Sloan Kettering Cancer Center, in New York, to step into the chairmanship of the Department of Immunology at the University of Texas MD Anderson Cancer Center.

Allison's readiness to challenge the status quo has never left him. It certainly showed itself as he made discoveries about the workings of T cells, which help protect the body from pathogens. Spurred also by personal and familial experience with cancer, Allison was willing to probe his theories even amid skepticism in the scientific community.

A case in point emerged when Allison began to suspect that the molecule CTLA-4

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(cytotoxic T-lymphocyte-associated antigen 4) inhibited antibody response. He weighed that idea in the face of theories to the contrary: In textbooks, CTLA-4 had been categorized as a molecule that stimulated immune response.

Allison pursued his idea anyway. The result was ipilimumab (Yervoy), which was approved by the FDA on March 25, 2011, as a treatment for unresectable or metastatic melanoma.

Allison's years of work on that project reaffirmed his guiding philosophy.

"Let your mind lead," advised Allison, a member of the National Academy of Sciences and the Institute of Medicine who in his free time enjoys playing blues harmonica and sailing. "Don't pay attention to conventional wisdom if you've got data that show otherwise. Sometimes it's hard to go against the system, but you have to do it if something needs to be accepted."

Over the years, Allison's discoveries have led not just to ipilimumab, but to a growing interest within the scientific community in creating other immune checkpoint blockades for tumor therapy. Another research group has developed nivolumab, which works by blocking an inhibitory molecule known as programmed death-1 (PD-1). That Bristol-Myers Squibb drug recently received a Breakthrough Therapy Designation from the FDA as a potential treatment for Hodgkin lymphoma. And researchers reported in May 2013 that, in a phase I study, combining ipilimumab and nivolumab led to deep tumor regression in approximately one-third of patients with advanced melanoma, and more quickly than would typically be expected with immunotherapy.

For developing ipilimumab and sparking the burgeoning field of immune checkpoint blockades for tumor therapy, Allison has been chosen by OncLive to receive one of its Giants of Cancer Care™ awards for 2014, in the area of Scientific Advances.

"Winning the Giants of Cancer Care award meant a lot to me," Allison said. "For a basic scientist to be acknowledged by an award for cancer care is really fulfilling and amazing to me. For a while, I was considered an ivory-tower, pointy-headed intellectual pursuing these arcane ideas about immunology. I think this gives basic scientists credibility in the cancer-care community."

THE APPROVAL OF IPILIMUMAB

The drug that started it all, ipilimumab, is an antibody that targets CTLA-4, a molecule on the immune system's T cells that impedes their ability to fight cancer. Once stimulated, T cells can protect the body from disease by attacking alien proteins, or antigens, such as tumor cells.

Normally, after a time, that attack is halted by CTLA-4, even though dangerous cells may remain. Ipilimumab is designed to eliminate CTLA's "stop" message, so that T cells can continue to fight indefinitely.

Administered intravenously, ipilimumab, also known as CTLA-4 blockade, works best if an anticancer therapy—such as radiation, chemotherapy, freezing, or targeted therapy—is used first to stimulate T cells to go on the attack, Allison said. Once that has been accomplished, the scientist said, the drug can be widely useful.

"You're treating the immune system, not the cancer, so it can be used, potentially, against every kind of cancer," he explained.

A phase III clinical trial of ipilimumab demonstrated improved overall survival of previously treated patients with metastatic melanoma, one of its authors announced during the annual meeting of the American Society of Clinical Oncology in June 2010. The study compared the efficacy of ipilimumab, the synthetic


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James P. Allison, PhD

peptide cancer vaccine gp100, and a combination of the two. Investigators reported that 46% of patients treated with ipilimumab were alive at 1 year, as were 44% of those treated with the combination and 25% of patients treated with vaccine alone. At 2 years, 24% of patients treated with ipilimumab alone were alive, as were 22% of those treated with the combination and 14% of those treated with gp100 alone. Progression-free survival was roughly the same in all groups.

Ipilimumab has also been approved by the European Medicines Agency and other health authorities worldwide, for a total of 41 countries, according to Bristol-Myers Squibb.

EXPLORING NEW APPLICATIONS FOR IPILIMUMAB

Now that ipilimumab is a standard of care for melanoma, it is being explored for the treatment of additional stages of the disease—such as completely resected stage III melanoma—and in other cancers, including metastatic bladder cancer, gastric cancer, breast cancer, and metastatic castration-resistant prostate cancer. Allison looks forward to the drug being tested in diseases such as glioblastoma and pancreatic cancer, which have been "resistant to traditional treatments," he said.

There are also numerous studies being conducted that are testing combinations of ipilimumab and other agents—although that process should be made easier, Allison said, through the removal of some of the economic and political barriers involved in including two drugs made by different companies in a single clinical trial.

While Allison told *OncologyLive* in 2011 that many sci-

entists were still resistant to the idea that immunotherapy could work in cancer, the idea has been gaining speed ever since. That same year, in fact, the National Institutes of Health created its Cancer Immunotherapy Trials Network, a collaboration between academia, industry, and philanthropic organizations that is helping 27 research sites across North America to develop immunotherapeutic anticancer agents that have been discovered but not yet approved for use in patients.

CANCER HAS TAKEN A PERSONAL TOLL

For Allison, all of that progress is meaningful on more than a professional level. Like the patients he's dedicated to helping, the scientist and family man has lost much to cancer.

When Allison was 10, his mother died of lymphoma. Two of her brothers also succumbed to cancers, one to melanoma and the other to lung cancer. Then, 6 years ago, Allison's brother died of prostate cancer, around the same time that Allison underwent a prostatectomy as he fought the disease himself.

The scientist was in graduate school at the University of Texas at Austin when he vowed to investigate treatments for cancer.

"I just thought, 'This is a terrible thing, and there's got to be a better way than chemotherapy and radiation,' which my mother and one of my uncles had," Allison said. "I saw all the negative effects."

In 1982, Allison was working at the University of Texas System Cancer Center when his research sparked a discovery that has been at the heart of his work ever since: He became the first scientist to figure out how T cells recognize alien proteins within the body.

"We [identified] the antigen receptor on T cells," Allison said. "That was important because it's like the ignition switch on T cells, the thing that recognizes peptide or bacterial protein or tumor antigens."

Six years later, at the University of California, Berkeley, Allison was working among researchers who realized that T cells needed to do more than recognize invading pathogens to start their attack. They needed a co-stimulatory signal, another molecule, to act as a gas pedal and make them go. Allison's group determined that the co-stimulatory molecule was CD28.

The final piece of the puzzle fell into place in 1996, when Allison and his fellow researchers noticed a gene that was structurally similar to CD28—CTLA-4—and started experimenting to see what it did.

"We found that if you delete CTLA-4, the T cells keep dividing. It's like you take the brakes off going downhill and can't stop," Allison said. "So I thought, 'Maybe this molecule shuts down T cells and keeps you from getting a strong enough immune response to deal with a tumor, and maybe if we block that molecule we can get the immune system to kill cancer cells and not cause side effects in mice.' And that's exactly what we found. With many

tumors, injecting this one molecule was enough to get a tumor rejected."

COMING FULL CIRCLE

By moving recently to his posts at MD Anderson, Allison was, in a way, returning to his roots. A native of Alice, Texas, where his father was a country doctor, Allison earned his bachelor's degree in microbiology and his doctorate in biological sciences from the University of Texas at Austin. After his postdoctoral fellowship at Scripps Clinic and Research Foundation in California, Allison's first faculty appointment was at MD Anderson's Science Park – Research Division in Smithville, Texas, for 8 years.

Allison next moved to the University of California, Berkeley, where he was a professor in the Division of Immunology and director of the Cancer Research Laboratory. Then, in 2004, he moved again—this time to Memorial Sloan Kettering Cancer Center (MSKCC), where he took on roles as the David H. Koch Chair in Immunologic Studies, director of the Ludwig Center for Cancer Immunotherapy, and attending immunologist in the Department of Medicine.

MSKCC was among the 150 sites where clinical trials of ipilimumab were being conducted. There, Allison was able to analyze the immune responses of study participants to help predict which categories of patients would most likely benefit from ipilimumab, and under what circumstances. That work also helped Allison hatch ideas for second-generation drugs.

"As I saw my drug developing, I wanted to be a part of it," he said. "I wanted to learn more about what went on in the clinic and to offer advice, because this was a totally new concept. You can't approach it the same way you would if you were giving a drug that will go into a tumor cell and kill it."

Three years ago, Allison landed at MD Anderson with the help of a $10 million scientific recruitment grant for established investigators given by the Cancer Prevention and Research Institute of Texas.

He plays an instrumental role in MD Anderson's relatively new Moon Shots Program, aimed at dramatically accelerating the pace of the conversion of scientific discoveries into clinical advances that reduce cancer deaths. The program is designed to attract philanthropic funding to expedite efforts already underway to develop new treatments to improve patient survival, reduce complications, and enhance survivorship and quality of life, according to the institution's website.

"The main reason for coming to MD Anderson is the opportunity offered by a clinical community that's open to using immunological approaches to treat cancer combined with other therapies," Allison said when his role there was announced.

"We plan to build a large platform where basic scientists interested in mouse models of cancer work side by side with physician-scientists who treat patients to analyze tissues from those

patients and truly understand the mechanisms involved," Allison said. "We can accelerate the transition of new combinations of drugs into the clinic beyond phase I clinical trials and broaden our focus beyond melanoma and prostate cancer to other types of cancer."

"We all know that no single drug will cure cancer," he added. "I think this is where we'll start getting cures, or at least long-term survival of patients. There's lots of enthusiasm for this approach at MD Anderson, and I'm really excited about it."

A particular goal for Allison in the years ahead is to further increase the percentage of patients who are able to gain long-term survival from immune checkpoint drugs.

"In the past, we've focused on moving median survival over a few months, and that's been sufficient to get drugs approved," he said. "What we know from immunological studies is that you can do that, but you also get a tail of the curve: After a certain point, a fraction of patients with melanoma—20%—have durable responses that can last a decade. So the median looks like a few months, but that 20% could be considered cured. By combining these [types of medications], you can move that [group of patients who have durable responses] to 40% or 50%, so my goal is to raise the tail of the survival curves to as close to 100% as we can get them, and to extend these therapies to as many different types of cancer as we can, because there's no reason immunotherapy won't work against many different types of cancer, if not all."

Along with that should come a new paradigm for measuring the efficacy of drugs and registering them that would move more quickly than the typical 5 years it takes to track overall survival in clinical trials, Allison added.

Also ahead is a potential opportunity for Allison to help shape the scientific talent of the future.

In December 2013, Allison's work earned him the Breakthrough Prize in Life Sciences—given by a group of American entrepreneurs including Facebook CEO Mark Zuckerberg—which came with a $3 million award.

As a potential use for part of that award, Allison was considering launching a program for high school students and college undergraduates designed to foster their interest in biomedicine, MD Anderson said in a press release at the time.

If that happens, those students might someday know the rush Allison experiences whenever he makes a discovery—the thrill that drew him to science in the first place.

"I enjoy the feeling," he said, "of being the first one on the planet to figure something out." ■

SUPPORTIVE CARE

JIMMIE C. HOLLAND, MD

MEMORIAL SLOAN KETTERING CANCER CENTER

Giants of Cancer Care™

INDUCTEE

2014

Cancer has been around for centuries, but talking about it is something relatively new.

As recently as the early 1970s, cancer remained an illness cloaked behind whispers and closed doors—as Jimmie C. Holland, MD, found when she began working in oncology. While the young doctor's goal was to help patients cope with their cancer, she discovered that was nearly impossible, since most were never even told they had the disease.

Forty years later, physicians and others who treat cancer are not just encouraged, but in some cases required to speak with patients about how the disease is affecting their lives—thanks in no small measure to the efforts of the pioneering oncologic psychiatrist described as the "mother of psycho-oncology" in a 2004 interview published in the *Journal of the National Cancer Institute*.

Holland played a vital role in the transformation by founding the nation's first full-time psychiatric program in an oncology center at Memorial Sloan Kettering Cancer Center (MSKCC) in New York City in the 1970s. Now 86, she is still treating patients and conducting research at the institution, where she has held the Wayne E. Chapman

Chair in Psychiatric Oncology since 1989. Along the way, she helped create the first quality-of-life questionnaires used to monitor the distress level of cancer patients, and founded two societies—still in existence—dedicated to the support of her field.

For her contributions, Holland has been chosen by OncLive to receive its 2014 Giants of Cancer Care™ Award in the Supportive Care category.

"I'm honored," she said, "and honored to be the first [to receive the award in the Supportive Care category], which is very nice."

WITNESSING AN EVOLUTION

It was 1997 when Holland first saw solid evidence that psychosocial medicine had become a widely recognized part of cancer care. That was when the National Comprehensive Cancer Network wrote its first treatment guidelines for distress management. More recently, two leading medical organizations asserted in their own guidelines that quality routine cancer care should include attention to patients' psychosocial needs.

"We've seen an overall humanizing of medicine," Holland said. "The humanist aspects are much more respected now. We call it patient-centered medicine. Doctors are being taught how to talk to patients, how to give bad news, how to communicate about illness, and how to better understand patients' responses, which they were not taught for so long before that. So, it's coming."

It was 2007 when the Institute of Medicine, after a year of research funded through a million-dollar government grant, declared for the first time that the psychosocial domain should be integrated into routine cancer care. Holland, a fellow of the Institute, served on the panel that reviewed data from clinical trials and found that there was convincing evidence in the literature to support a range of psychotherapeutic and psychotropic drugs, but that many patients who needed them weren't getting them. The panel released its findings in a report titled "Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs."

"It was a big move forward," Holland said, "because it was the first national health policy organization that had endorsed the fact that the psychosocial domain must be integrated into routine cancer care."

After that, she said, the Commission on Cancer of the American College of Surgeons (ACoS)—which regularly reviews and accredits more than 1500 American cancer centers—passed a mandate stating that, by 2015, any center that wants to be accredited will need to have a program in place to identify patients experiencing distress and refer them, when appropriate, for psychosocial care.

"This is big stuff," Holland said. "We're very pleased this is happening, because now there's a stick, as well as a carrot, for doing this kind of work. It will make a difference."

As a whole, Holland hopes, her work over the years has not only helped individual patients, but also banished myths that made life more difficult for cancer patients as a group.

"There's a myth that you have to be positive to fight cancer," she said. "I call it the tyranny of positive thinking. There's no such thing as making cancer worse if you're depressed. We just want patients to say when they are distressed and need help."

FOCUSING ON OLDER CANCER PATIENTS

Holland's efforts to spread that message haven't slowed, despite her many years in the field. The doctor works a 12-hour day, devoting about a quarter of her time to seeing patients. Her only nod to her age is her interest in working with people of her generation.


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"Because I'm older, I see a lot of older people," Holland said. "We have a geriatric program, called 65+, to help older patients get through their cancer treatment, which can be hard for them because many are also facing a number of problems associated with aging."

In part due to her work with that program, Holland has written a book, published by Oxford University Press in September 2014, titled *Lighter as We Go: Virtues, Character Strengths, and Aging*. Among the inspirations for the book was Holland's Vintage Readers' Book Program, which she started 2½ years ago.The program gave Holland a chance to speak with a lot of older people, she said.

"Part of the reason aging is difficult is because of the stigma we put on aging people: 'It must be so awful to be old; it means you're about to die,'" she said. "We extol the value of youth and beauty, but we're not too good when it comes to handling older people, and that's part of what the book is about. Let's get better communication and appreciation of old age. It has benefits as well as problems, so we should make it something more balanced. It's not something to be afraid of."

Similarly, Holland's research within MSKCC's Psychotherapy Laboratory, and via clinical trials, focuses on psychotherapy for elderly patients with cancer. One study focused on a telephone-based psychotherapy technique that Holland and her colleagues developed for older patients, who often have trouble getting out of the house.

"We did a controlled trial of the psychotherapy, and it works," she said. "People who have gone through 6 or 7 sessions are less depressed, anxious, and lonely. Our data have been presented in poster form, and will next be

presented at a meeting of the American Psychosocial Oncology Society."

PASSIONATE FROM THE START

Holland grew up an only child on a cotton farm near Dallas, Texas, when the area was still countryside.

She had an ordinary Texas life and an ordinary Texas name—"Girls get boys' names and boys get girls' names," Holland said—but unusual aspirations.

She planned to become a nurse, until she realized that women could be doctors.

"There weren't many around," Holland recalled. "There was a woman doctor in Dallas that I knew by her reputation, although I didn't know her well. But I began to realize it was possible."

Holland met with acceptance in medical school, even though she was 1 of only 3 women in the class that started in 1948, competing with returning World War II veterans for the opportunity to attend.

"I had a minimal amount of problems," she said. "I found that, if indeed people recognized that I was working hard, they wanted to help me. I didn't feel a lot of that kind of bias that you hear about."

Holland's interest in the way patients dealt with the range of responses to illness developed during her medical training. "When I started my internship [at St. Louis City Hospital in Missouri]," she recalled, "I began to realize that I really liked the psychological aspects of patients: how they were coping with their illness or how they managed to deal with an acute heart attack or with polio, resulting in being paralyzed from the neck down."

So Holland switched her focus to psychiatry, and kept it there through her training as a resident and research fellow at the Malcolm Bliss Mental Health Center and Washington University School of Medicine, both in St. Louis, and then during a residency and fellowship at Massachusetts General Hospital in Boston.

IDENTIFYING A NEED

Holland met her husband, James F. Holland, MD, early in her career, and when they married, she moved to Buffalo, where he worked at the Roswell Park Cancer Institute.

Now the Distinguished Professor of Neoplastic Disease at Mount Sinai Medical Center in New York, her husband was a pioneer in the treatment of childhood acute lymphoblastic leukemia, and it was by learning about his work that Holland realized attention to psychosocial care was largely missing from routine cancer care. It wasn't adequately considered in patients, and it wasn't being studied. Social workers carried the front line, with the nurse and oncologist in second place.

She decided that she "would like to work with patients with cancer to see if we can understand how to help them cope with their disease, and get them through it," Holland said.

She saw an opportunity in the 1970s, when the stigma associated with cancer started to fade. Both Betty Ford and Happy Rockefeller had gone public about surviving breast cancer, and patients were no longer being kept in the dark about their diagnoses.

Holland encouraged her husband, then the chairman of the nation's first cooperative clinical trials group for cancer—Cancer and Leukemia Group B (CALGB)—to add a committee for psychosocial issues as the organization worked to adopt a multidisci-

plinary philosophy.

"We became involved in research here in this country to understand how people were coping, and that got easier after we could talk to people about their disease and begin to study distress," she said. "How many people needed help, and how many were struggling to get along, were things we didn't know at all. So that was our earliest research—the prevalence of different psychological consequences of illness."

FINDING HER WAY

Once married, Holland and her husband started a big family. He already had a daughter, and together the couple had five more children; now, they have 10 grandchildren.

But even while raising her children, Holland found time to establish a place for herself as a leader in her field. "I worked only part-time when the children were small, so it was a more sequential career than most young women today, who do both at the same time. Even so, I could not have done it without the help of my supportive husband," she said.

From 1956 through 1973, Holland moved up the ladder from clinical instructor to associate clinical professor in the Department of Psychiatry at the State University of New York in Buffalo. During most of those same years, she held roles at a teaching hospital, moving up from attending psychiatrist to director of the Department of Psychiatry.

The family lived in the USSR for the academic year 1972-1973. Her husband consulted with the Russian Cancer Institute, and Holland worked as a consultant to the Russian Psychiatric Research Institute on a Joint Schizophrenia Research Study. This was during the Cold War, but their work was part of a cultural exchange program between the two countries.

Back in the United States, Holland spent four years at the Albert Einstein College of Medicine and Montefiore Hospital, in the Bronx, New York, where she rose to the rank of associate professor.

Then, in 1977, she accepted the job of chief of the first Psychiatry Service at MSKCC, and became a professor at Weill Medical College of Cornell University in New York City. This began the building of the psychosocial care program at MSKCC, which has had national and international ripple effects on the care of patients with cancer.

PIONEERING A FIELD

Holland was hired because both the head of Neurology at MSKCC, Jerome B. Posner, MD, and the head of the cancer center itself, physician/philosopher Lewis Thomas, MD, "recognized that the time had come to give attention to the psychological problems of patients," she said.

Holland and the fellows who came with her started by making rounds with other doctors in order to learn what patients were experiencing. Soon, physicians at the cancer center were referring their patients to Holland's tiny group, Psychiatry Services.

Meanwhile, she and her colleagues worked to develop the tools they needed to help patients.

"We realized that if we didn't have some way to measure subjective symptoms like pain, fatigue, anxiety, depression, and delirium, we were not going to have a true science. We had to find a way to quantitatively measure these symptoms," Holland said.

"In the '80s we made our first big effort to develop and validate reliable patient self-report assessment tools, and today we have a valid way to measure people's level of functioning, anxiety, depression, pain, fatigue, and subjective symptoms."

The tools were all in the form of paper and pencil questionnaires, Holland pointed out, since "there's no blood test" to determine how people are feeling.

Such tools represented a big change in philosophy in the oncology world, the doctor added. "When I started in the field, there was a strong sense that doctors believed that the valid assessment of patients' symptoms was by observation," she said. "What patients said about their feelings was considered unreliable."

The next step, Holland said, was to begin implementing the tools in studies.

"We began to use these tools in clinical trials. We showed that, if we intervened with an antianxiety drug or talk therapy, we could reduce anxiety and make people less distressed," Holland said. "Out of that has come our field of psychosocial oncology with its own evidence base. Now, we're able to put forth standards of care and clinical practice guidelines about how you should manage patient distress.

It's been a wonderful journey for Holland, who is proud to have helped develop a vital area of cancer care, and happy to have been in the right place at the right time.

"I've been blessed with a wonderful husband, kids, and colleagues who worked hard with me," she said, "and I've been able to combine my personal and professional lives in a very pleasant way that's made for a very satisfying life. I could not ask for better at 86." ■


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INDEX

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Bernard Fisher, MD
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Bert Vogelstein, MD
Johns Hopkins Medicine

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University of California, San Francisco

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Lawrence H. Einhorn, MD
Indiana University

HEAD & NECK CANCER
Everett E. Vokes, MD
University of Chicago

LEUKEMIA
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Oregon Health & Science University

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Yale Cancer Center

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