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PRESENTS

Giants® OF Cancer Care

2017

Recognize Greatness. Recognize a Giant of Cancer Care.

OncLive® PRESENTS

Giants® OF Cancer Care

The *5th Annual Giants of Cancer Care®* campaign celebrates the achievements of leading physicians and researchers who have devoted their time, talent, and resources to improving care for the many patients and their families affected by cancer. Their discoveries have propelled the field forward and established the building blocks for future advances.

Recipients of the 2017 awards demonstrate the qualities that distinguish them from others: unlimited selflessness, compassion for their patients, and a desire to understand and develop life-changing treatments against a disease that affects so many.

MENTORS MAKING A DIFFERENCE IN THE EARLY CAREERS OF GIANTS

As I read the profiles of the 2017 class of Giants of Cancer Care®, 2 concepts struck me; first, the importance of mentors and mentorship, and second, the importance of receiving an award from your peers in the oncology field. The mission of Giants of Cancer Care® is to recognize individuals who have achieved landmark successes within the global field of oncology.

Many of these individuals attribute their success to mentors. Mentors took a keen interest, devoted time and effort, and fostered the growing curiosity of many of the Giants in the early days and throughout their careers. Several of this year's winners attribute their success to the mentors who took an interest. For example, Daniel P. Petrylak, MD (Genitourinary Cancer); Kanti R. Rai, MD (Hematologic Malignancies); and Charles S. Fuchs, MD, MPH (Gastrointestinal Cancer) offer accolades to their mentors—Alan Yagoda, MD; Arthur Sawitsky, MD; and Robert J. Mayer, MD (a 2015 Giants of Cancer Care® award winner himself), respectively. In the subsequent "paying-it-forward" scenario, many of today's Giants have themselves acted as mentors to potential future Giants. The profiles of Lewis Cantley, PhD (Scientific Advances), and Thomas F. Gajewski, MD, PhD (Immuno-Oncology including Cell-based Therapies), provide insight into the important role these Giants have played in influencing and nurturing the pioneers of tomorrow.

With this 2017 class, a total of 63 individuals have received this award, and all winners were determined by each Giant's peers in their respective fields. For many, that alone is a special characteristic that makes this award unique.

In an interview given after receiving his award, Cantley said, "It's a special honor for your peers to select you for an award like this. It means my peers—people who have worked in cancer in basic research for many years—have found my contributions important. It's the highest possible honor that one can have."

John L. Cameron, MD (Surgical Oncology), asked, "How important is it to receive an award that's given to you by your peers? I am greatly honored by it, and I'm humbled that my peers think I deserve this honor, so I'm personally very delighted."

I hope the stories of these individuals will inspire you and spur you to action. Nominations for the 2018 class are now open: **giantsofcancercare.com/nominate.** Was there a mentor who guided you and who deserves recognition? Cast your nomination today.

MIKE HENNESSY, SR
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TABLE OF CONTENTS

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ON THE SHOULDERS OF GIANTS

PATRICK I. BORGEN, MD
CHAIR OF THE DEPARTMENT OF SURGERY
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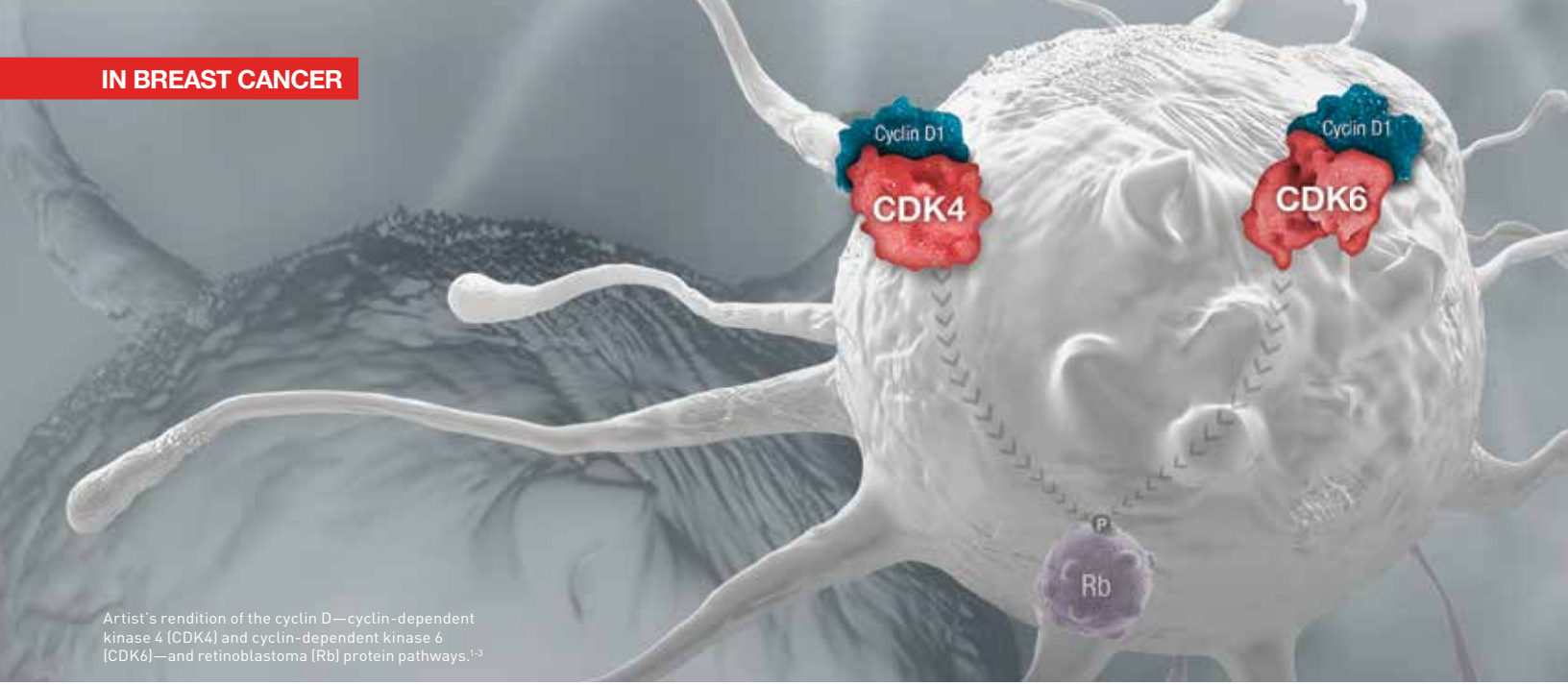
The metaphor of gaining perspective, insight, and advantage attributed to the phrase "the shoulders of giants" finds its origins many centuries ago, as far back as Greek mythology. In the English language, popularization of this trope is most commonly credited to Sir Isaac Newton who penned, in a letter to English physicist Robert Hooke, "If I have seen further, it is by standing on the shoulders of giants." Stephen Hawking reprised the figure of speech in his carefully curated compilation of work Copernicus, Galileo, Kepler, Newton, and Einstein, *On The Shoulders of Giants*. Countless contemporary authors have borrowed from Newton by repeatedly breathing new life into this timeless metaphor.

Giants of Cancer Care®, built solidly upon that richly symbolic foundation, was conceived and has thrived as a virtual "hall of fame," established to recognize and celebrate the individuals who have achieved landmark successes within the global field of oncology. Election to this rare circle of pioneers, innovators, researchers, advocates, and clinicians is coordinated by an advisory board, but the actual selection is made by a peer committee of more than 80 eminent oncologists. Nominees can come from any of the more than 30,000 active members of professional medical societies worldwide. From this very large pool of potential nominees only a small handful of individuals are nominated. In 2017, we inducted only the 50th member of this elite group of Giants. That makes election to the Giants of Cancer Care® (0.16% of candidates) more than 10 times rarer than election to the National Baseball Hall of Fame (317 inductees/15,213 total players in history, or 2.11% of candidates).

What can we report about this class of Giants of Cancer Care®? Collectively, they are responsible for more than 10,000 peer-reviewed articles covering a vast landscape of both solid and liquid tumor advances. Their trainees lead a staggering number of cancer research laboratories, clinical trial units and clinical departments. Their innovative spirit, which always challenges the status quo, has both fueled and accelerated progress against one of the largest threats to health the modern world has known.

It is not hard to remember a time when experts scoffed at the idea of eradicating cancer. The fact is, more and more patients are achieving functional cures or long-term remissions in diseases that were once uniformly lethal. None of these striking advances would have been imaginable without the truly pioneering efforts, insights, persistence and strong leadership of these Giants who often vigorously challenged time honored dogma, wisdom and beliefs to deepen our understanding of the true biology of cancer.

We proudly honor and recognize the members of this incredible group of Giants of Cancer Care®. Their sacrifices, struggles, victories and defeats must never be forgotten by future generations of men, women, and children who may never have to watch a loved one suffer or die from cancer. One of my strongest career goals has been that my children's children have no idea what I did for a living. That will only become a reality through the tireless efforts of today's and tomorrow's Giants of Cancer Care®. ■



Artist's rendition of the cyclin D—cyclin-dependent kinase 4 (CDK4) and cyclin-dependent kinase 6 (CDK6)—and retinoblastoma (Rb) protein pathways.[1-3]

Do CDK4 & CDK6 play different roles?

Historically, **CDK4** and **CDK6** were believed to be functionally equivalent[4,5]

Both play a role in cell cycle progression, gene transcription, and cell proliferation, primarily by regulating the Rb pathway.[5]

EXPLORATION INSPIRATION

Preclinical evidence suggests that the roles of **CDK4** & **CDK6** can differ[5-18]

	CDK4	CDK6
BREAST CANCER	Levels are increased in many breast tumors; required for tumor cell proliferation[9,10]	Levels are decreased in many breast tumors and breast cancer–derived cell lines[11]
PROLIFERATION	Plays a role in the proliferation of pancreatic and pituitary endocrine cells[12,13]	Regulates proliferation of T lymphocytes[14] and hematopoietic stem cells[15]
EFFECT ON STEROID HORMONE PRODUCTION	Upregulates enzymes responsible for steroid hormone production in a breast cancer cell line[16]	Downregulates enzymes responsible for steroid hormone production in a breast cancer cell line[16]
LEUKEMIC CELL DIFFERENTIATION	Does not block differentiation in leukemic cells[17]	Blocks differentiation in leukemic cells[17]
MALIGNANCIES	More likely to have preferential activity in epithelial cancers[18]	More likely to have preferential activity in mesenchymal cancers[18]

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Norman Wolmark, MD

National Surgical Adjuvant Breast and Bowel Project

He championed the evolution of large, randomized clinical trials to ascertain the best strategies for the treatment and prevention of breast cancer.

For many researchers, being involved in 1 landmark clinical trial is often enough to make for a storied and illustrious career. But being involved in more than 1 is something entirely different; over the course of his career, Norman Wolmark, MD, found himself in rarefied air.

For women prior to 1971, the standard surgery for breast cancer was radical mastectomy, promoted by the Johns Hopkins University surgeon, William Stewart Halsted, during the last decade of the 19th century. He believed that metastasis did not occur through the bloodstream. At the time, adequate local removal of the cancer (ie, radical mastectomy) was thought to cure the patient—any new instance of cancer that appeared was treated as a new process.

Radical mastectomy involves the complete removal of the breast, chest wall muscle, and underarm lymph nodes. This method left many women disfigured. The result is severe scarring and pain, making them hesitant to undergo the procedure. Other, less invasive, surgeries were also explored, but no randomized clinical trials had been initiated to find a definitive answer.

That changed when the National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated trial B-04, which sought to resolve the controversy over the surgical management of breast cancer. The NSABP is a clinical trials cooperative group that has been supported since its inception by the National Cancer Institute (NCI). Wolmark was a key investigator, along with former Giants of Cancer Care® recipient, Bernard Fisher, MD, the principal investigator. Wolmark says that Fisher “crystallized my thinking that underscored the fact that most medical decisions were driven by empiricism by the authoritarian tyranny of a small group of individuals who could influence the way a disease was treated for decades without any kind of scientific corroboration.”

Wolmark joined the group in 1973 and since then it has evolved "into the incubator for generating data-driven decisions for the treatment of breast cancer and oncology," he says. "This has been an exciting, active environment."

The findings from the study showed there was no significant difference in survival between women who underwent radical mastectomy and those treated with the less extensive total mastectomy in which the axillary nodes were not removed. This landmark study gave way to future breast-conserving procedures. Trial B-04 provided the rationale for B-06 in which 2163 women with invasive breast tumors that were 4 cm or less, with either negative or positive axillary lymph nodes (stage I and II breast cancer), were randomly assigned to 1 of 3 treatments: total mastectomy, lumpectomy, or lumpectomy followed by breast irradiation. B-06 results demonstrated that just removing the tumor and the underarm lymph nodes plus adding radiation therapy was just as effective as a mastectomy and was far less disfiguring.

"Trial B-04 challenged the sanctity of the radical mastectomy," Wolmark says. The subsequent trials "compared modified radical mastectomy with breast-preserving procedures, the results of which established breast-preserving surgeries as the standard of care in this setting," he adds.

Wolmark's research career at the NSABP also included trial designs that explored the role of adjuvant therapy in breast cancer.

"I've certainly witnessed the era of chemotherapy in the adjuvant setting," says Wolmark. In 1975, the NSABP published the first trial showing that L-phenylalanine mustard (L-PAM) administered for 2 years in women with histologically positive nodes prolonged disease-free survival, he said. In this trial, B-05, 380 women with node-positive breast cancer were randomly assigned to receive either L-PAM or placebo following primary breast cancer surgery. Results showed that postoperative adjuvant therapy could reduce the recurrence of the disease. Subsequent trials in patients with node-positive disease have studied combination and sequential chemotherapy. The foundation of those studies rests on B-05 and Wolmark's involvement.

> "[The NSABP] came perilously close to being dissolved," says Wolmark, once the group came under fire by Representative John Dingell, Jr, chair of the House of Representatives Committee for Energy and Commerce, for questionable data."

RARE, SCINTILLATING MOMENTS

Looking back over the course of his career, Wolmark doesn't point to a specific moment when reviewing data from these clinical trials led to an immediate breakthrough. The evidence and conclusions were cultivated and collected and reviewed, similar to the pieces of a puzzle that are laid out in front of you and just begging to be put together to make a whole.

But there have been a number of rare, scintillating moments that are embedded in his memory.

"In 2005, we analyzed the data from the combined trials

Going crabbing in Alaska.

B-31, from NSABP, and N9831, from the North Central Cancer Treatment Group. It was the use of Herceptin (trastuzumab) in women with HER2-positive breast cancer," Wolmark says.

Wolmark recalls that the data were presented at the American Society of Clinical Oncology meeting in Orlando, Florida, during a special education session because the analysis occurred after the deadline for a late-breaking abstract.

"As Edward H. Romand, MD, the lead investigator, presented the data, I turned around to look at the audience and a significant portion had tears in their eyes. We all stood back and admired the Kaplan-Meier curves. That's an illustration of the impact of the data when comparing the use of Herceptin in the treated group with the placebo group. This was a change in the standard of care and introduced the use of targeted agents as a new paradigm, not only for breast cancer, but for all oncology."

GREATEST CONTRIBUTION

Interestingly, Wolmark doesn't think his greatest contribution to the field involved the pristine evolution of science. "It was far more mundane," he says. "But I think it led to some lasting benefits, based on the subsequent clinical trials that were performed afterwards."

Wolmark was named the NSABP's new chairman in 1994. If he thought his first year was going to go smoothly, the congressional hearings in April of that year would dash any preconceived notions. That was the year that the NSABP came under fire by the subcommittee for the House of Representatives Committee for Energy and Commerce, which was chaired by then-Representative John Dingell, Jr.

One of the investigators in the network of study sites in Canada had falsified data in a trial. The NSABP had been slow to correct the public record, and it had continued to use data from the same site, with the negligent investigators as coauthors, in subsequent studies. This prompted an extensive congressional investigation of the NSABP, its leaders, and the NCI's oversight and corrective measures.

"All NSABP clinical trials at the time were halted during that period," says Wolmark. "It was a significant possibility that the group would be parceled off to other entities, including the prevention trials that were ongoing at the time."

He and the officers of the NSABP spent the better part of the year on Capital HIll, lobbying various members of

Congress to keep the NSABP an integral entity. “We came perilously close to being dissolved,” Wolmark says. Although there were oversights that had occurred at the Canadian site, it was also apparent from the analysis that the inclusion of data from the ineligible patients did not materially affect the conclusions of the study.

The efforts by Wolmark and his colleagues at NSABP eventually succeeded. “I think our interventions allowed the NSABP to continue doing the work that it’s known for.” If their efforts failed, “the whole cascade of subsequent trials, including the Herceptin trial, would not have occurred or, at least, the NSABP would not have been part of it, had I not spent the year on the hill,” he says.

UPBRINGING AND A WORD OF WARNING

Wolmark grew up in Montreal, Canada, the son of immigrant parents of modest backgrounds. He says they viewed Canada and the United States as providing a unique opportunity for everyone. “If you applied yourself, if you were diligent, if you had a little bit of intelligence, then you would succeed.” Doing something for your fellow man was instilled in him unequivocally and it is what guided his choice to pursue medicine, rather than biochemistry, when his interests turned to graduate learning at McGill University. “I received my acceptance letters from medical school and graduate school on the same day. But I realized that I could make a meaningful impact by pursuing medicine and it could be done with critical relevance.”

Despite being a father of 2 adult children and a grandfather to 5 children who keep him busy, Wolmark is still very involved with NSABP operations, from designing and overseeing trials to providing administrative oversight. He still has a clinical practice and performs surgeries—although not

Wolmark demonstrating that no one outgrows Legos (top) and family time (bottom).

Accepting his Giants of Cancer Care® award (top) and at work at the NSABP (bottom).

to the same extent as in the past. He recalls that when he finished his fellowship at Memorial Sloan Kettering Cancer Center in 1979, breast cancer was not yet an established specialty in the oncology field; it gradually evolved over time. "My residency experience interdigitated well because of the emphasis in breast cancer at the NSABP, and it influenced my clinical career," he says.

Ever the champion of evidence-based medicine, Wolmark is concerned about the resurgence of anecdotalism, noting that he is "always wary of the individual who is armed with a retrospective case series whose intention it is to influence the standard of care."

It is the antithesis of the NSABP.

"We're seeing smaller and smaller subsets and clinical trials that are not rigidly performed, and that's a dangerous thing," Wolmark continues. "We're also seeing the rise of discounting data from clinical trials, especially the rise in [preventive] bilateral mastectomies, despite the recommendations made by physicians who have reviewed the data."

He points to a recent study from Memorial Sloan Kettering Cancer Center that asked patients what influenced their decisions about their care. "Sadly, it wasn't the work of the NSABP, but what was read on social media. And that's another form of tyranny." ■

Nominate Today!

2018 GIANTS OF CANCER CARE®

The **Giants of Cancer Care®** program celebrates individuals who have achieved landmark successes within the field of oncology.

Help us identify oncology specialists whose dedication has helped save, prolong, or improve the lives of patients who have received a diagnosis of cancer.

PROGRAM OVERVIEW

- Nominations are open now through February 2018.
- Domestic and international nominations will be accepted. Self-nominations are permitted and encouraged.
- The **Giants of Cancer Care®** Advisory Board will vet all nominations to determine finalists in each category.
- A selection committee of 90+ oncologists will vote to determine the 2018 inductees.

Recognize Greatness. Recognize a Giant of Cancer Care.

2018

To nominate, please visit:

giantsofcancercare.com/nominate

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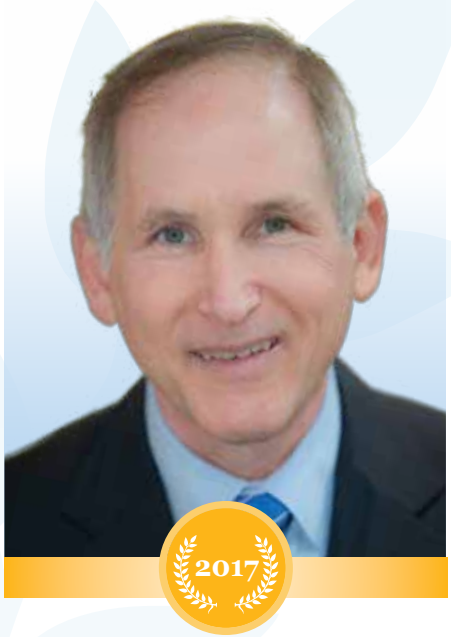


Charles S. Fuchs, MD, MPH

Richard Sackler and Jonathan Sackler
Professor of Medicine (Medical Oncology)

Director, Yale Cancer Center and
Physician-in-Chief, Smilow Cancer Hospital

For harnessing the power of big data to identify behaviors that increase and reduce the risk of incidence and recurrence of gastrointestinal cancer

The very notion of cancer-fighting food was long the exclusive provenance of the huckster and the quack. No rigorous study had ever tied better diet to better outcomes, and most experts doubted that strategic meal plans could affect a disease that typically overcomes million-dollar medications.

The research of Charles S. Fuchs, MD, MPH, has done much to overturn that conventional wisdom. Fuchs, who saw the power of big data before the advent of the term "big data," began using population studies more than 2 decades ago to demonstrate the vital roles that diet, exercise, and other very basic lifestyle choices play in both the prevention and treatment of gastrointestinal cancers. Indeed, Fuchs and his collaborators have demonstrated strong ties between cancer and an ever-growing list of items: vitamin D, aspirin, red meat, exercise, obesity, and more.

"I became interested, right at the very beginning of my professional life, in identifying risk factors for gastrointestinal cancers, and it occurred to me that I might spot them by analyzing data from a project that had been going on since long before I arrived on the scene—the Harvard cohort studies," says Fuchs, whose accomplishments extend far beyond data analysis.

His academic work, which has seen him lead major drug trials and perform just about every other form of cancer research, has produced more than 600 published papers. His administrative work, which saw him lead the gastrointestinal program at Dana-Farber Cancer Center for nearly a decade, inspired Yale University to name him director of its rapidly growing cancer center. Yet Fuchs remains most famous for the epidemiological work that started with those cohort studies.

"There were, and are, 2 huge cohorts, female nurses and male health professionals, with more than 200,000 combined

participants, all providing a huge amount of health-related personal information over decades of time. Such large populations were clearly going to develop a large number of gastrointestinal cancers over the years, and it was my hope that the numbers would be large enough and the patient information comprehensive enough to test hypotheses and identify risk factors with a high degree of certainty," says Fuchs, whose idea proved sound enough to furnish decades of new discoveries.

Fuchs was born in the Bronx and grew up just a few miles north, in New Rochelle, New York. His father was in the moving and storage business, and his mother was a homemaker.

He describes himself, in retrospect, as a good student—good enough to get into the University of Pennsylvania—but not exceptional. He developed an interest in medicine during his high school years, when he volunteered at a small local hospital that gave him a wide variety of tasks. The young Fuchs registered patients, wheeled people around, did simple lab work, assisted radiologists—whatever was needed on any given day. The experience gave him a broad overview of what different doctors did and his first inclination toward cancer care.

THE HARVARD HEALTH COHORTS

Fuchs committed to oncology during his years at Harvard Medical School and started to specialize in gastrointestinal cancers while doing his residency at Brigham and Women's Hospital and studying for a master's degree at the Harvard School of Public Health. The decision stemmed, in part, from the realization that the statistical skills he learned at the School of Public Health lent themselves to the analysis of such a common type of cancer and, in part, from the fact that it was the chosen specialty of Robert J. Mayer, MD, one of his mentors, who would later be named a 2015 Giants of Cancer Care® winner.

> "I became interested, right at the very beginning of my professional life, in identifying risk factors for gastrointestinal cancers, and it occurred to me that I might spot them by analyzing data from a project that had been going on since long before I arrived on the scene."

At that time, Mayer had already made a name for himself, not only as a great researcher but also as a great mentor, the sort who would give young colleagues the opportunity to do interesting and important work and offer the support they'd need to navigate the complexities of grant requests, research oversight committee, and the peer review process. Not that Fuchs needed all that much support.

"I vividly recall that we collaborated to write a review paper on gastric cancer for the *New England Journal of Medicine,* just when Charlie was starting out. He submitted his manuscript to me, and I got out my red pen, because he was at that age where I knew he'd need a huge amount of editing. Then I read through the whole thing without making a mark," Mayer says. "His ability to take a huge amount of information and present it all clearly and logically was amazing right

"My advice to anyone reading this who has an interest in doing research, is to pursue it."

from the very start. It shows in everything he does, but it is particularly important in epidemiological work."

The Harvard health cohorts are, for those who enjoy data analysis, an almost inexhaustible mine of medical insight. Because they collect detailed information about huge numbers of people decades before most of the participants develop any serious health problems, they are free from selection bias and thus a unique tool for identifying early risk factors for virtually any serious disease. Researchers can look for links between any metric or behavior the studies track and any common health outcome.

By testing hypothesis after hypothesis, Fuchs and his various collaborators have demonstrated previously unsuspected links between many lifestyle factors and cancer incidence. An analysis of 88,410 middle-aged nurses from 1980 to 1994, for example, found that those who ate beef, pork, or lamb daily were more than twice as likely to get non-Hodgkin lymphoma as those who ate such meats less than once a week. Another analysis associated working at least 3 nights a week for at least 15 years with an increased risk of colorectal cancer. A third study found a 30% reduction in colorectal cancer incidence among women who took more than 14 aspirin a week for more than a decade.

Fuchs and his collaborators kept coming back to the data and mining it for new insights. The associations they found provided the material for dozens of papers, and that early work established his reputation in more ways than one.

"It was apparent very early on that Charlie was a great collaborator," says Edward Giovannucci, MD, DSc, a professor of nutrition and epidemiology at the Harvard T.H. Chan School of Public Health (renamed in 2014). "He always does his share and gets it done on time, no matter how much else he has on his plate. I've been working with him for more than 20 years, and we've never had a conflict that wasn't resolved in minutes. That's very unusual in any academic collaboration that lasts more than a few months, let alone a few decades...People hear about that, and they want to work with him."

The Harvard health cohorts were actually large enough to weigh the costs and benefits of certain behaviors, at least when it came to very common medical problems. For example, Fuchs was the lead author of a 1995 paper that assessed the impact of drinking among Nurses' Health Study participants. The analysis, which appeared in the *New*

England Journal of Medicine, found that light to moderate drinking was associated with a lower relative risk of death than abstinence, while heavy drinking was associated with a higher risk of death. However, sub-analysis found that the benefits of drinking came mainly from reduced cardiovascular events, while the drawbacks came mainly from increased rates of cirrhosis and breast cancer. Therefore, the study concluded, women who otherwise faced a high risk of breast cancer and a low risk of cardiovascular disease faced a higher risk of death from any degree of drinking. It was a remarkable demonstration of how finely the data could be parsed, and it has been cited 763 times to date.

CANCER INCIDENCE, NOT CANCER PREVENTION

Of course, not every hypothesis panned out. Dietary fiber intake was not associated with 1996 colorectal cancer rates among 88,757 women who were healthy as of 1980, and fruit and vegetable consumption throughout the 1980s was not significantly associated with colon cancer rates as of 1996. But even negative findings such as these provided important enough information to garner several hundred citations apiece.

At first glance, the importance of such discoveries may seemingly lie in cancer prevention, but Fuchs doubts they will inspire the behavioral changes that will reduce incidence. "We already knew that obesity is dangerous," Fuchs says. "The discovery that it increases the risk of gastrointestinal cancers isn't going to make fitness nuts out of millions of Americans who ignored the risk of diabetes and cardiovascular events.

"The real value in the discovery that something unexpectedly increases cancer incidence is that you can then go to the laboratory, trace the pathway, and learn something new about the cancer. What's more, you can also see whether the same factor affects outcomes among people who already have the cancer."

Even the largest general cohorts never accumulate enough patients with gastrointestinal cancer to determine whether lifestyle factors affect outcomes after diagnosis, so Fuchs and his colleagues at Dana-Farber began a patient cohort in 1999. Immediately after surgeons removed all trace of cancer, the researchers enrolled patients and tracked the same information as the larger population cohorts.

Subsequent analysis found, contrary to the expectations of almost everyone, that seemingly minor lifestyle factors were associated with very significant changes in cancer recurrence and mortality. Mortality rates were 25% to 30% lower

Pictured with his young sons at the time, Fuchs says balancing family time with work life can be done.

among patients who took at least 3 adult aspirin every week than they were among similar patients who did not, 35% lower among patients who maintained healthy vitamin D levels, and 45% lower among patients who exercised regularly.

It is tempting to perform a bit of mental addition and conclude that patients who began a regimen of both exercise and supplements right after surgery could nearly eliminate the risk of cancer death, but Fuchs warns against such assumptions. Cohort studies find associations, not causes. It is possible that some underlying difference between aspirin users and nonusers—something besides the aspirin itself—affects outcomes. Even if you assume the studied behaviors are changing the outcomes, Fuchs says, the benefits would likely overlap rather than be fully additive.

If he's strategic about using his time, Fuchs believes he can be an effective researcher, clinician, and administrator.

"Still," he adds, "the number of associations and the strength of those associations argue that lifestyle choices made after the initial diagnosis will eventually prove to be major factors in patient outcomes. Making the right choices regarding diet and exercise still won't be easy for many patients, but a cancer diagnosis is a major motivator."

Research done mostly by others suggests that lifestyle may also play a large role in determining outcomes among patients with other tumor types, especially breast cancer, but any such link would be particularly important for patients with gastrointestinal cancers. Even though they collectively account for nearly a quarter of all cancer diagnoses, such tumors have seen fewer new treatments than many other tumor types.

Indeed, until 2014, when the FDA approved a novel angiogenesis inhibitor called ramucirumab (Cyramza) on the strength of a trial led by Fuchs, the only approved treatments for gastric cancer (the fifth most common of all cancers) were chemotherapies originally developed for other tumor types. (Even chemotherapy treatment for gastric cancer is relatively new: It wasn't until 2001, when targeted therapies were already transforming the treatment of many tumors, that the FDA first approved a chemotherapy for adjuvant use in patients with gastric cancer.)

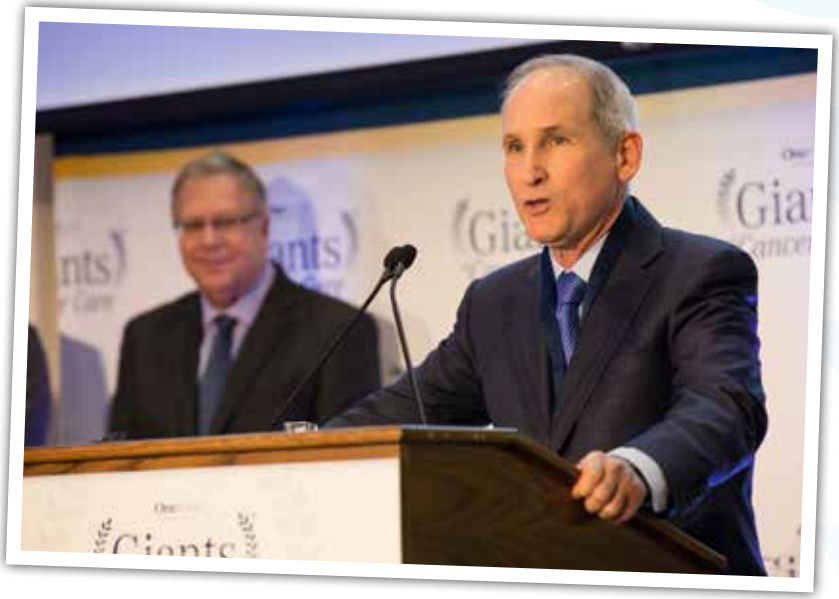
Fuchs hopes to improve the treatment of gastric cancer further still by adding the immunotherapy, pembrolizumab (Keytruda) to the mix. A small phase I study—undertaken after researchers found that many gastric cancers overexpress PD-L1—produced positive results, so Fuchs is moving forward with a large, single-armed, phase II study.

BALANCING THE PROFESSIONAL AND PERSONAL

Fuchs has balanced this research with a heavy administrative load for years. He was only the second specialist in Dana-Farber's gastrointestinal cancer division when he joined Mayer in the early '90s, but he worked to expand the division, first as Mayer's deputy and then (after Mayer's 2008 retirement) as division head. When Fuchs left for Yale earlier this year, Dana-Farber had 28 gastrointestinal specialists.

The move from head of a division to head of an entire cancer center will necessarily entail even more administrative work, but Fuchs still plans to make time not only for research but also for patient care. "I work long days, but I'm passionate about what I do, and I think I can be effective as a researcher, a clinician, and an administrator if I am strategic about how I use my time," he says, adding that significant achievement in medical research requires hard work—but not so much hard work that it precludes a normal life.

"My advice to anyone reading this who has an interest in doing research is to pursue it," Fuchs says. "It is hard to describe the satisfaction that comes with such work, and it does not require the sacrifice of normal life pleasures. I have been very happily married for more than 25 years. I have coached my kids in Little League and soccer. I go on vacation. It's very possible to do this work and have a life." ■



Dr Patrick I. Borgen (background), chair of the Advisory Board, looks on as Dr Charles Fuchs accepts his award.

Daniel P. Petrylak, MD

Yale University School of Medicine

An explorer's mentality leads to novel treatments in prostate and bladder cancer.

Although he held a longtime fascination with space exploration to the moon and Mars, Daniel P. Petrylak, MD, took a different path and broke new ground in another frontier: genitourinary oncology. A job in a lab while he was still in his teens launched a career aimed to improve treatments for patients with bladder and prostate cancers.

Petrylak, now 58, grew up in Queens—mostly in Whitestone—and is a self-professed New Yorker through and through. His parents wholeheartedly supported his and his brother's endeavors, stressing education most of all. "They sacrificed an awful lot, and I am forever indebted to what they did for us. Education, doing well, and exceeding was the most important thing [to them]," Petrylak says.

Although he was always interested in science and was particularly drawn to space science in the 1960s, Petrylak chose to apply his scientific mind to research in medicine. "We can better our lives, better ourselves with new discoveries and trying to use knowledge to help patients or to help society overall," he says.

INFLUENTIAL MENTORS

Petrylak was raised in a very science-heavy atmosphere. His scientific career began early. At just 16, he started working in a laboratory in New York under protozoologist Seymour Hutner, PhD. He was "a very interesting character," Petrylak says, and taught him much more than science; he covered literature and music in his mentorship, as well.

Hutner himself had an interesting mentor who also indirectly influenced Petrylak: James B. Sumner, PhD, the first to crystallize the jack-bean urease enzyme. In 1946, Sumner won the Nobel Prize in Chemistry for his work in crystallizing enzymes, proving that enzymes are proteins.

Under Hutner's guidance, Petrylak learned that any

research or knowledge you gain doesn't mean anything unless you can apply it to people. Internalizing this message, Petrylak decided to go to medical school, completing his bachelor of arts degree at Columbia College and his medical degree at Case Western Reserve University School of Medicine. He ultimately chose to specialize in oncology because of the research aspect to the field and its promise of new discoveries to help patients. "Years ago, oncology was almost like voodoo magic; there weren't great treatments and patients died," he explains. "So, what better field to explore, especially one in which you can apply your scientific knowledge, to try and improve treatments?"

After graduating from medical school, Petrylak embarked on a 3-year fellowship at Memorial Sloan Kettering Cancer Center (MSKCC) alongside Howard I. Scher, MD. At the time, Scher was focused on using biology to improve treatments, which taught Petrylak a lot about how to approach novel methods of treating patients. Then, in 1991, Petrylak moved to Columbia University as an assistant professor of medicine and had the good fortune to work with Alan Yagoda, MD.

Yagoda had trained several preeminent genitourinary oncologists, including Scher; Cora N. Sternberg, MD; and Dean F. Bajorin, MD. While at MSKCC in the 1980s, Yagoda, along with Scher and Sternberg, invented MVAC (methotrexate, vinblastine, Adriamycin, and cisplatin) chemotherapy for patients with bladder cancer. "It was an incredible experience working with [Yagoda]. He could generate numerous ideas; just sitting and talking with him was an unbelievable experience," Petrylak says.

For a week during his fellowship at MSKCC, Petrylak joined Yagoda for rounds. During this time, Yagoda further supported Petrylak's development, encouraging him to work on clinical trials, give lectures, and put his name out in the academic sphere so that people would become familiar with him. He often repeated this advice: "Work on prostate cancer; nobody's working on it."

> "If something doesn't seem to fit, or it doesn't seem to be working, keep on plugging, keep on going at it, because you just don't know what's going to happen. I've seen so many things that looked bleak and dim [but], in the end, turned out well."

Sadly, Yagoda died suddenly in 1995. "There isn't a day that goes by that I don't think about him," Petrylak says of the man who was a key inspirational force behind his ultimate career choice.

ACCOMPLISHMENTS WITH DOCETAXEL

Over the course of his career, Petrylak has been heavily involved in researching treatments for patients with bladder and prostate cancers. "[For prostate cancer], if you go back to the 1990s, there was nothing that worked for castration-resistant disease. We've seen a tremendous amount of progress," he says.

In 1996, while investigating taxanes' effects on prostate cancer cells in a laboratory setting, Petrylak discovered that docetaxel (Taxotere) combined with estramustine (Estracyt)

From left: Daniel P. Petrylak, MD; Peter G. Schulam, MD, PhD; and Peter A. Humphrey, MD, PhD, discuss a case.

demonstrated activity that he and his colleagues wanted to examine further. They designed a phase I trial with the combination, but when they approached the drugs' manufacturers, the response was, "We have good news and bad news." The good news was that the companies would happily supply their drugs; the bad news was they would not fund the trial.

So, naturally, the team came up with their own funding and ran their own trial. "I remember, very well, treating the first patient who didn't respond, and I said to myself, 'We put all this effort into this and look what happened here,' and then the next 5 or 6 patients responded," Petrylak recalls. At the next Southwest Oncology Group (SWOG) meeting, they presented their results and, with support from E. David Crawford, MD, moved forward with a phase III trial, SWOG 9916. The trial accrued patients and was one of the studies that led to docetaxel's approval for treating patients with castration-resistant prostate cancer (CRPC). To this day, docetaxel is a standard-of-care treatment for patients with CRPC in the first-line setting.

That trial taught Petrylak an important lesson that he carries as his philosophy: Never quit, and always remember to stay positive, because you never know what's around the corner. "If something doesn't seem to fit, or it doesn't seem to be working, keep on plugging, keep on going at it, because you just don't know what's going to happen," he says. "I've seen so many things that looked bleak and dim [but], in the end, turned out well."

Since then, Petrylak has led other secondary trials for combination treatments with docetaxel, including serving as the principal investigator on the SPARC trial that investigated satraplatin in patients with CRPC. "Unfortunately, that drug did not show a survival benefit, but I think if we did the trial now and selected patients who had DNA repair mutations, I think we'd see something," Petrylak says. This trial showed him how the field had evolved to look at more biologically targeted therapies against different markers.

NEW APPROACHES IN BLADDER CANCER

Reflecting on his field, Petrylak says that running trials for bladder cancer has greatly improved. "If you talked to someone about doing a bladder cancer trial with a pharmaceutical company 4 or 5 years ago, they would run in the other direction," he says. Now, many clinical trials are investigating treatments for bladder cancer because researchers have observed the effectiveness of novel treatments such as PD-1 and PD-L1 inhibitors.

According to Petrylak, 3 main areas hold the newest developments for treating bladder cancer: checkpoint inhibitors, potential interactions between antiangiogenesis and chemotherapy, and newer antibody–drug conjugates that are showing activity. He has been involved in the trials for atezolizumab (Tecentriq) and pembrolizumab (Keytruda) as treatments for bladder cancer. He presented data at 2017 ESMO Congress in December from the RANGE study, which is investigating ramucirumab (Cyramza) and docetaxel combined, compared with docetaxel alone, in patients who had prior therapy for metastatic bladder cancer.

Recently, he and his colleagues have been working with an anti–Nectin-4 antibody and an anti-SLITRK6 antibody, which are linked to chemotherapeutic agents, and are already seeing responses in patients who failed prior checkpoint therapy. He says integrating all these therapies will be a very interesting area, and he looks forward to working in it.

FUTURE RESEARCH

What's ahead for Petrylak? He hopes to continue to develop drugs. "That's what I have a passion for, that's what I really enjoy," he says. "We've come a long way in both [bladder and prostate] tumors, and there's a lot of room of improvement still."

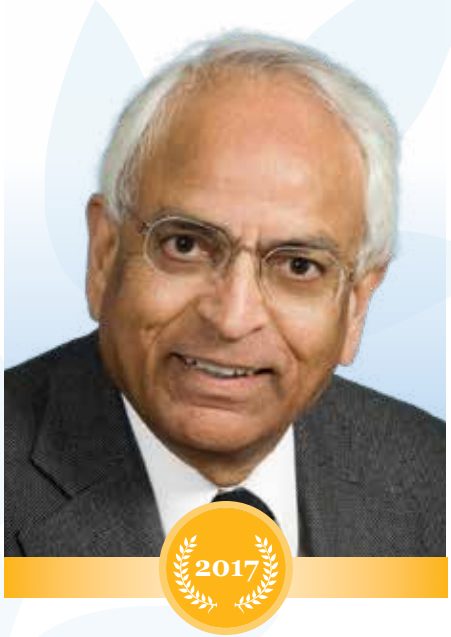
For prostate cancer, Petrylak sees research and treatment moving toward the era of personalized medicine, particularly with poly ADP-ribose polymerase inhibitors showing efficacy in patients with DNA repair mutations. There is also promise in identifying variants of the androgen receptor that may predict whether a patient will respond to the newer generation of hormonal agents. "I think both fields will start using a more personalized approach as we identify markers for each of those tumors," Petrylak says.

For bladder cancer, *FGFR3* is 1 target under investigation that interests Petrylak. However, he notes, researcher still have not figured out the whole cascade of markers that are involved in predicting response to immunotherapy, which is an exciting area of discovery. "I think all of these studies are crucial, especially now since we are cost conscious, and we don't want to treat patients unnecessarily. I think we have a lot of work to do, but I think the potential is bright," Petrylak says.

OFF THE CLOCK

Petrylak always keeps busy reviewing data, taking care of patients, setting up translational work, and forming alliances between basic scientists and scientists who may contribute to research that can be translated to the clinical setting. Although he spends most of his time involved in—and often leading—clinical trials, he also teaches formally and gives lectures for several organizations.

When not at work, Petrylak loves spending time with his wife, especially traveling. They also enjoy biking, tennis, and golf. In fact, his wife only recently took up golf and, according to Petrylak, she can already belt the ball nicely. "She has been absolutely supportive of my career, and I wouldn't be here now if I didn't have her support," he says. ■



Kanti R. Rai, MD

North Shore University Hospital-LIJ/
The Feinstein Institute for Medical Research

Her name was Laurie, she was 3 years old, and her love of life touched his heart.

"She was a bright, sprightly girl, walking with a hop, skip, and a jump," recalls Kanti R. Rai, MD. "I saw this young couple who had been told 3 hours earlier that their daughter might have leukemia, and they walked slumped over, steps behind her."

The year was 1958, and at the time, acute childhood leukemia was a death sentence. Rai, then chief resident in pediatrics at North Shore University Hospital in Manhasset, New York, was about to meet his first patient with the illness. Along with his attending hematologist, Arthur Sawitsky, MD, he examined Laurie and later learned that she had the fatal disease.

"When I heard from my teacher that this child would be dead in 6 months, I thought this teacher of mine was a horrible, heartless bastard," he says nearly 60 years later. "[In fact], he was none of that—he was very experienced and a kind human being, and he was telling me what the reality was."

It was a terrible era for pediatric cancer patients although leukemia research was just beginning in Boston under the leadership of Sidney Farber, MD, Rai notes). At that time, 90% of children diagnosed with acute childhood leukemia died within 6 to 18 months.

The news devastated Rai, who bonded with Laurie during her subsequent re-admissions until her death 7 months later. Noting his reaction, Sawitsky suggested Rai pursue a leukemia-themed fellowship after residency. "I thought that was very good," Rai says, "because I wanted to do something and learn about leukemia." And indeed he did.

He eventually developed the Rai staging system, which categorized the treatment and classification of chronic lymphocytic leukemia (CLL), helping to revolutionize how to best treat and help patients. Today, he is the director of the CLL Research and Treatment Program at Long Island Jewish Medical Center, a professor at the Karches Center

for Oncology Research at the Feinstein Institute for Medical Research, and a professor of medicine and molecular medicine at Hofstra Northwell School of Medicine, all based in Great Neck, New York. He has spent more than 50 years treating patients, training young physicians, and conducting research, and he has published his findings in more than 200 original papers and book chapters.

Above all, Rai says, he can't imagine doing anything other than what he has already done in medicine. "I have lived long enough, and I should be grateful for the opportunities I have had," he says. "I am truly a blessed person. I love what I do—it gives me a sense of purpose: doing something which is socially helpful and good."

FAMILY TIES

For Rai, 85, born and raised in Jodhpur, India, in the 1930s and '40s, the desire to help young children was ingrained at an early age. One of 8 children living in an area "where the standard of living was low," Rai says, he was raised by his father, an officer in the local government, and his mother, a homemaker devoted to her family. Love was plentiful even if money was not. "Jodhpur was a backward community, but in terms of values and standards, it was good," he says. "My siblings and I had all the give-and-take that is the usual universal experience, and my parents took care of everything. College, higher education—that was their mission and pride." His younger sister and his older sister's daughter also became doctors. "I was not the exception."

At about age 8, Rai spent a month one summer with his uncle, Vridhi Rai, a charismatic local doctor based in a village about 60 miles from Rai's hometown. One warm morning, Rai awoke and saw, on the street outside, "a line of camels with their drivers, who had been sent for my uncle, because somebody in those families had been sick and needed the doctor to come to their house." His uncle would head out early to see patients before attending his regular daily clinics.

> "[My uncle] took care of [local villagers] without any regard for how poor or how well-to-do they were. I saw children with malnutrition, infection—young children suffering—and he would care for them."

At his request, Rai accompanied his uncle on those house calls, waiting outside with the camels and drivers. "Word would go out in the house that the doctor's son was outside with the camel, and they would come and invite me inside the house," he recalls. "They treated me like royalty and would give me goodies. I was treated well."

The snacks aside, Rai was most impressed with his uncle's approach and focus. "I watched him deal with the people, not with artificial kindness or compassion, but genuine empathy," he says. "He took care of them without any regard for how poor or how well-to-do they were. I saw children with malnutrition, infection—young children suffering—and he would care for them."

Rai realized he wanted to help people in the same way. "I said [that] I would like to follow in my uncle's footsteps and provide service," he says. "And…if I [had] children, my children would be treated royally, too. It was a win-win for everyone!"

Rai, center, with his daughter Samantha, left, and granddaughter Ella, right.

Today, family continues to be a strong focus, and Rai readily cites his immediate family's support that helped sustain him throughout the decades. "I would not be anywhere if not for the trust and support and love of my dear wife Susan with whom I will celebrate 50 years of marriage in 2018," he says. They have 2 children: Samantha, who works as a family medicine physician with her husband, Jay Zaslow, MD, at the Open Door Family Medical Center in Mount Kisco, New York; and Josh, a software engineer for the educational software company, Quizlet, who lives in San Francisco, California, with his wife, Cici, a preschool teacher. The elder Rais also enjoy the company of their grandchildren, Ella and Mira.

THE PATH FROM INDIA TO NEW YORK

Rai attended high school and Jaswant College, both in Jodhpur, and ultimately went to Jaipur, 150 miles away from his hometown, to attend SMS Medical College. He graduated in 1955, but yearned to see more of the world.

"I wanted to travel, but I knew my parents could not afford to pay for it," he says. He learned about and was chosen for an overseas opportunity that offered internships and residencies in the United States for early-career physicians based in countries such as Pakistan, Sri Lanka, and India, because there weren't enough US-based candidates to fill the open seats.

"Where would you like to go?" the selection committee asked him. Rai had no idea, other than his interest in pediatrics. From a list of US hospitals, he chose Lincoln Hospital, based in the Bronx. "It was eeny, meeny, miny, mo," he says. "I knew I wanted to come to New York, because I'd seen pictures of neon lights in Times Square, and I knew the name Lincoln. I thought, 'How could I go wrong?'"

After his residency training, Rai became chief resident in pediatrics at North Shore University Hospital. It was there that he met Sawitsky, who would become one of his most revered mentors. "He was an outstanding doctor and very research-oriented, and he guided me and taught me hematology, taking me by the hand when this little girl came into my life," Rai says. "I want to absolutely recognize [that] if not for his guidance, mentorship, and teachings, I would be lost someplace—God knows where."

After doing a fellowship in hematology and nuclear medicine with Sawitsky at Long Island Jewish Hospital, Rai met and began working with Eugene Cronkite, MD, a scientist with the medical research center at Brookhaven National Laboratory in Upton, New York. Cronkite studied the rate

of proliferation of leukemia cells in people, comparing them with normal blood cell counts in bone marrow. He used the newly developed tracer technology with tritiated thymidine as a tool for measuring the rate of new cell birth. "It was the 1950s, and it was pioneering," Rai says. "It was hard work on my microscope, taking blood and bone marrow samples and spending hour after hour on each patient sample, working on them for months. At the time, it was heady work—we would work and talk and fight. It was an exciting period."

Rai notes that today, such work can be done reliably and quickly with the press of a button. "But do I have any sense of embarrassment or failure that today, it is child's play? No, at the time, this was the epitome of technological advancement."

A BREAKTHROUGH ON THE CUBICLE WALLS

Brookhaven was where Rai would eventually determine how to better treat patients with leukemia. Throughout Rai's life, his mentors advised him to grab opportunities as they arose, "to keep my eyes open and to take chances—see where it takes you," he says, citing Yogi Berra: "If you see a fork in the road, take it." Rai opened himself up to figuring things out.

That philosophy led to what has been called Rai's breakthrough and major contribution to the oncology world: the development of the Rai staging system. "[That] brought me fame, but I think it was the training and the opportunities [Sawitsky and Cronkite] provided that made it possible to see the light," Rai says.

At Brookhaven, Rai noticed that some patients with CLL, typically a disease of the elderly, would die within a few years of diagnosis, while others kept returning to the clinic for 15 to 20 years with the same diagnosis but no lingering health issues. "I asked Dr Cronkite, 'What is going on? Are we making a diagnosis error, that some people are doing so very differently?' He looked at me, put his hand on my shoulder, and said, 'That is for you to figure out.' That challenge sank into me."

Rai began to scrutinize the medical records of all the people in the clinic who had CLL and started charting the summaries of 65 to 70 people, along with their medical histories, on the walls of his cubicle using a pad of yellow lined paper.

"I stared at them, and nothing came through," he said. "Then I had the idea to put all the good prognosis people on one wall, then those dying or dead on the opposite wall, and everybody else on the middle wall. This was in the 1960s, so

Pictured from left: Dr Kanti Rai with research collaborator Dr Nicholas Chiorazzi, patient Abe Bernstein, and research collaborator Dr Jacqueline Claudia Barrientos.

there was no computer to use or any fancy computer fancy [software] that we have today. I still remember that people passing through my cubicle started to whisper, 'This Indian guy is crazy, always staring at the walls.'"

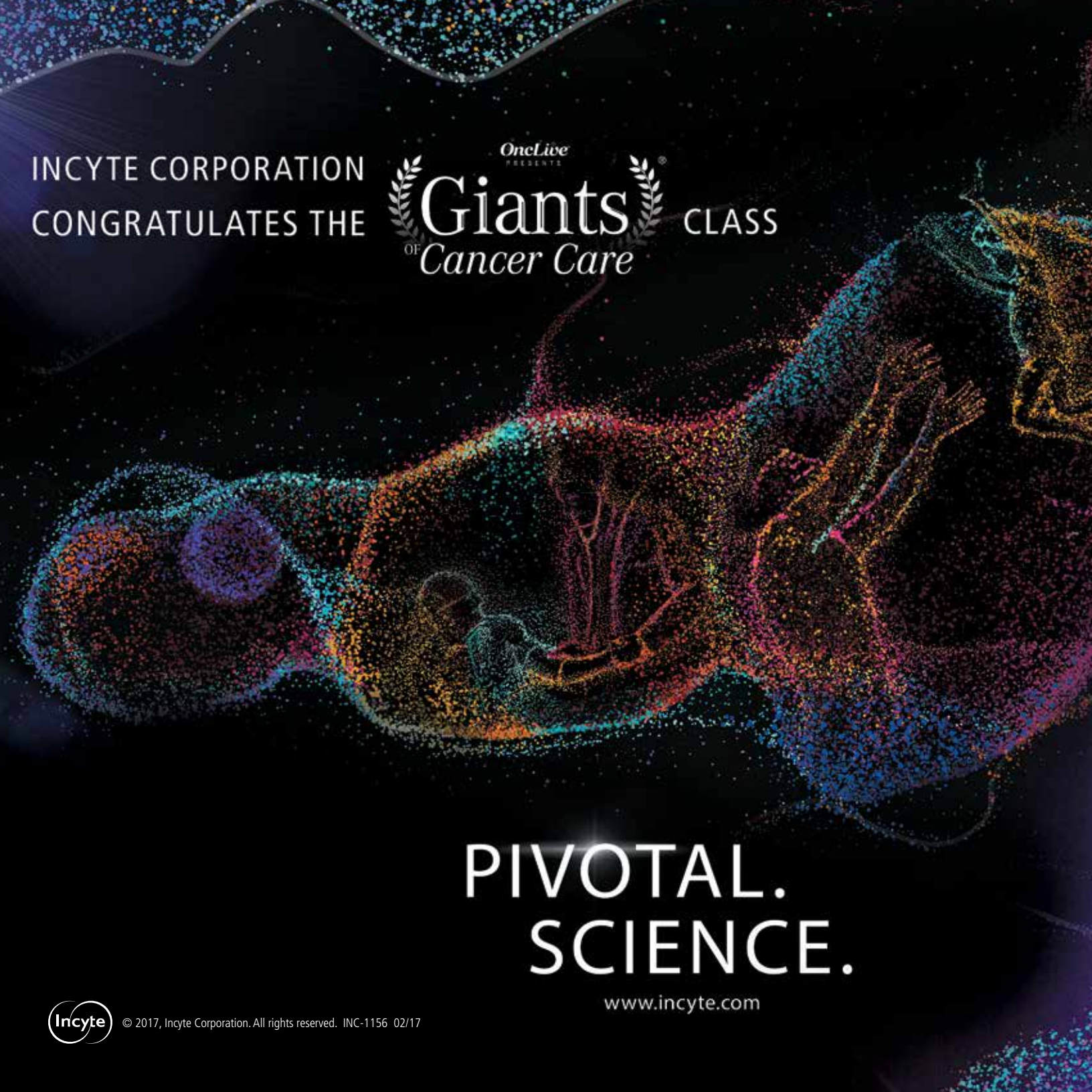
But over time, Rai worked it out. "All the people who died relatively quickly were different in that their hemoglobin red cells and/or platelets were low from the get-go," he says. "Those who had normal counts but the same disease were on the opposite wall, their bone marrow functioning was seriously compromised, and their outlook was poor. This was my aha moment."

His results took a few months to summarize and confirm, but when he shared his findings with his mentors, they were impressed: "Cronkite said, 'I think you've got something there, my boy.'" The journal *Blood* published his paper, "Clinical Staging of Chronic Lymphocytic Leukemia," coauthored by Sawitsky, Cronkite, and 3 other colleagues in 1975. More than 40 years later, his work is the basis for diagnosing and staging CLL in the United States.

"That made it possible for other people to become interested in how clinicians and researchers could get a handle on this disease," he says. "Before, it was an amorphous, boring disease. The staging made it possible to attack it in a sane, logical manner that was not possible before."

Rai is quick to share the recognition, even though it is his name that the staging system carries. "I am given a lot of credit today, but I saw [that] my idea was simple and got the ball rolling. The next generation of people, my active colleagues, deserve the credit for subsequent advances."

These potential innovations, such as the role immunology will play in future cancer treatment, are what excite Rai. "We have by no means reached a cure, but these immunological approaches are opening doors where we can eventually say that 'I would like to plan a strategy that might lead us to a cure,'" he says. "Before, we would say 'That could lead us to a better remission.' Now we are closer to eliminating residual disease. I would not have dreamed that was possible in my lifetime." ■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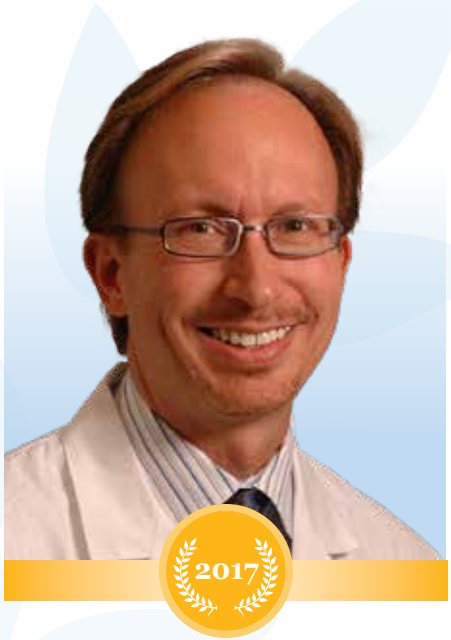


Thomas F. Gajewski, MD, PhD

University of Chicago Medicine

Never stop believing in the power of immunotherapy.

For many years, no one took immunotherapy seriously, but Thomas F. Gajewski, MD, PhD, persisted in his study of how the immune system interacts with cancer. Despite the naysayers, he searched for ways to harness the body's immune system to fight off cancer cells. His endless pursuit and study in the field of immuno-oncology paid off, and Gajewski is now hailed as a pioneer in the field of cancer immunotherapy, waving its banner even when no one else would.

That's why The CheckPoints, a band that includes co-founder Gajewski on guitar, tends to close out their set with the Journey classic "Don't Stop Believin'," says Patrick Hwu, MD, the other co-founder and a close friend and colleague of Gajewski. "It is kind of our anthem to show that we've persisted through all of these years and now everyone understands that immunotherapy is important."

Gajewski seems to have taken up the anthem as his own motto and never stops believing in the power of immunotherapy: "This is an exciting time for the field of cancer immunotherapy."

His drive to succeed is recognized by his colleagues and friends. "[Gajewski is] one of the smartest guys I know, hands down. He has very high standards, and he has really done some spectacular work in immunotherapy," Hwu says. "I appreciate that he makes us all better. He pushes us scientifically, and he pushes us musically."

Perhaps Gajewski is best known in the field of oncology for a discovery in his lab at the University of Chicago in 2015, when he showed that gut microbiota in mice have a role in responses to immunotherapy treatments. When *Bifidobacterium* was orally administered into the digestive tract of mice with melanoma tumors, it led to increased tumor control to the same extent seen with anti–PD-L1

therapies due to enhanced dendritic cell function and CD8-positive T-cell priming and accumulation in the tumor microenvironment. The combination nearly abolished tumor outgrowth.

This discovery required keeping a watchful eye on the mice used in the research. Gajewski and his colleagues were studying mice from 2 centers, and they noticed that mice from Jackson Laboratory tended to show a greater immune response than those from Taconic Biosciences. Yet when the mice were housed together, that difference was eliminated, which prompted the researchers to look into the types of bacteria in each mouse. *Bifidobacterium* stood out as having the greatest impact on outcomes.

Now Gajewski believes that discovering the connection between the microbiome and clinical outcomes will enable the development of microbiota-modulating interventions to improve outcomes in patients undergoing cancer treatments. "This finding provides a novel way to exploit that connection—to improve immunotherapy by selectively modulating intestinal bacteria," he says.

A longtime resident of Chicago, Illinois, Gajewski stayed in the city to study, from his undergraduate years all the way through his residency and fellowship. In 1989, he received his PhD and in 1991 his MD at the University of Chicago Pritzker School of Medicine, where he joined the faculty in 1997. He is currently a professor of medicine and pathology and runs a lab investigating antitumor immunity. Many brilliant minds, as well as research, have come out of Gajewski's lab. Hwu notes that Gajewski is a wonderful mentor and continues to train students and fellows at University of Chicago Medicine.

Gajewski is also well known for his study of RAS pathway signaling, which is involved in T-cell activation. He and his

> "Many community oncologists are waiting [to learn] what is the best combination partner with PD-1 so that they can...have an even greater likelihood of attaining clinical benefit from that first treatment straight out of the starting blocks."

Gajewski talks with a patient. Credit: University of Chicago Medicine.

PHTOTO CREDIT: UNIVERSITY OF CHICAGO MEDICINE

From left: Kyle Cron, Blake Flood, Leticia Corrales, Jason Williams, Stefani Spranger, Gajewski, and Brendan Horton during the Committee of Immunology Christmas Party Drink competition.

From left: Gajewski, Ayelet Sivan, Stefani Spranger, Jason Williams, Seng-Ryong Woo, Leticia Corrales, and Brendan Horton attending the Pops of Champagne Chicago Paper celebration.

team identified diacylglycerol kinase-alpha (DGK-alpha) as a key negative regulator of RAS activation and T-cell function in the anergic state. Regulation of RAS activation, he thinks, could be a potential target for immunopotentiation.

He and his colleagues also identified the role of the newly discovered stimulator of interferon genes (STING) complex, which triggers an immune response when it is activated. The STING pathway induces interferon-beta, which leads to the activation of specific T cells that then target the tumor cells. "Understanding the role of the STING pathway provides insights into how we can 'wake up' the immune response against tumors. This can be further boosted by checkpoint therapies," Gajewski says. New agents targeting STING could significantly augment anti-tumor immune responses and are currently in early-phase clinical testing.

Developing immunotherapies aimed at melanoma is of particular interest to Gajewski, and he has been involved in numerous clinical trials of experimental immuno-oncology agents for the treatment of patients with this disease. Based on preclinical data developed in his laboratory, a major focus is on combining IDO inhibitors with anti–PD-1/PD-1 therapies to augment the effector phase of anti-tumor immune responses. Studies of this combination are undergoing phase III clinical trial testing.

A study of metastatic melanoma tumors revealed an association between activation of the Wnt/beta-catenin signaling pathway and the absence of a T-cell gene expression signature in these patients. This signaling led to resistance to anti–PD-1/PD-L1 and anti–CTLA-4 therapies. Gajewski continues to explore elements of resistance to checkpoint inhibition, which is identifying oncogene pathways to target in concert with immunotherapeutic interventions. Inhibitors of Wnt/beta-catenin signaling also are in development.

Gajewski always tries to impart a sense of excitement about the progress being made in treating patients with this tumor type. "My job is to get both physicians and patients psyched up about what is just around the corner," he says. "Many community oncologists are waiting [to learn] what is the best combination partner with PD-1 so that they can treat their patients and have an even greater likelihood of attaining clinical benefit from that first treatment straight out of the starting blocks. I want them to get excited that we are working hard on problem, and I feel happy that we have discovered some of these components."

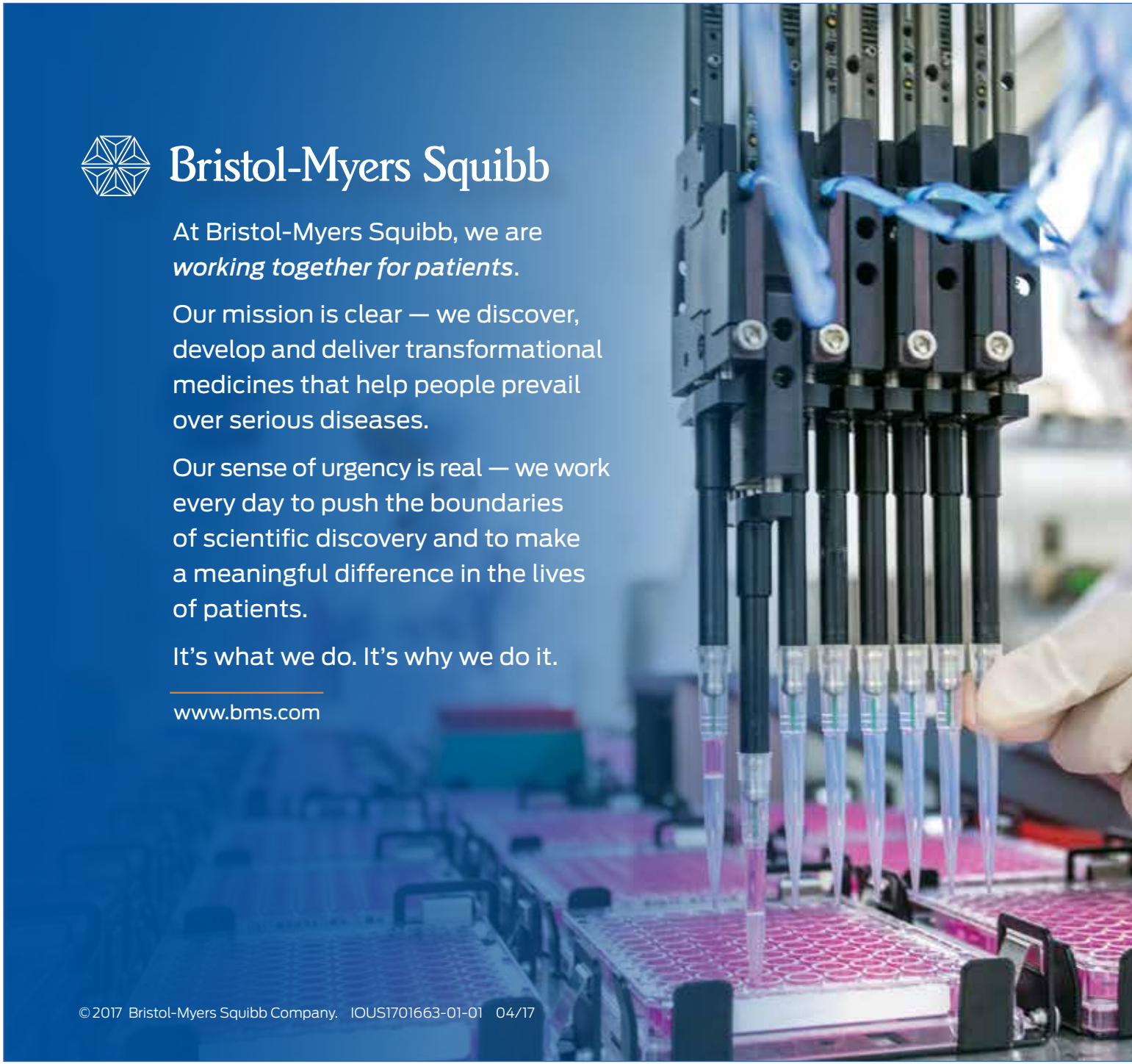
Beyond the lab, Gajewski maintains a steadfast loyalty to the field of immuno-oncology. He is a member of the Society for Immunotherapy of Cancer (SITC), the American Association of Immunologists, the American Association for Cancer Research, and the American Society of Clinical Oncology. He served as president of SITC from 2010 to 2012 and is active on planning committees for each of these societies. He is also an editor for the *Journal for Immunotherapy of Cancer,* the official journal of SITC; *Cancer Discovery*; and the *Journal of Experimental Medicine*.

In 2013, Gajewski and 5 other immunologists—including James P. Allison, PhD (another member of The CheckPoints); Padmanee Sharma, MD, PhD; Drew Pardoll, MD, PhD; Robert Schreiber, PhD; and Louis M. Weiner, MD—helped to co-found Jounce Therapeutics, which they hope will lead to the development of lifesaving immunotherapy treatments for patients with cancer.

Gajewski is also a member of the scientific advisory board of another therapeutics company, Evelo Biosciences, which focuses on bringing microbiome-based therapeutics for cancer into clinical practice.

This year has been an unprompted congratulatory one for Gajewski, who has received not only the Giants of Cancer Care® award but also an Outstanding Investigator Award from the National Institutes of Health. The 7 years of financial support offered by this award will enable him to continue the pursuit of his favorite long-term projects, including pooling past research, and perhaps lead to his next big discovery. ■

Gajewski and student Jason Williams.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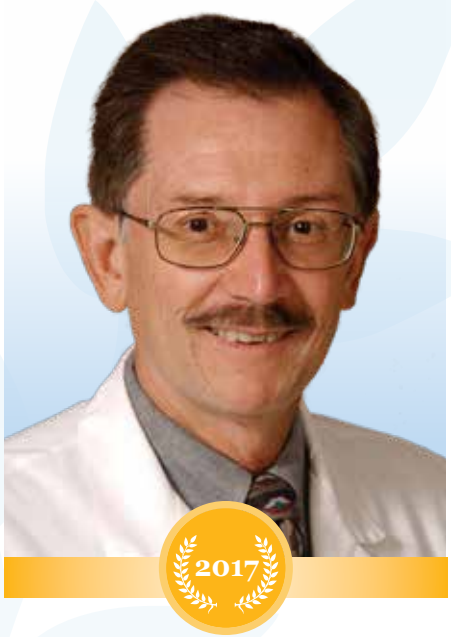

David Gandara, MD

University of California, Davis,
Comprehensive Cancer Center

"Live every day to the fullest. Take advantage of the time that you have."

Each morning, David Gandara, MD, wakes up energized to spend another day as an oncologist in lung cancer practice and research, a field in which advances have been more rapid than anything previously seen in oncology.

As the director of the Thoracic Oncology Program at the University of California, Davis (UC Davis) Comprehensive Cancer Center in Sacramento, he knows all too well about how quickly life can change when someone is presented with a diagnosis of lung cancer.

Lung cancer kills more than 155,000 people each year in the United States. But with dedicated experts, such as Gandara, the field of oncology is improving and new treatment options are being discovered.

Growing up in Tyler, Texas—a town 100 miles east of Dallas—Gandara knew from a young age that his dual calling was in medicine and in writing, and his current academic position at UC Davis marries those 2 skill sets. In his position, being able to communicate clearly is so important.

"I thought medicine would be a good way to be able to do that. I always envisioned myself being in academic medicine, where teaching is an integral part of what I do."

THE ROAD TO ONCOLOGY

Gandara started the journey by earning his undergraduate degree from The University of Texas at Austin. Then he went on to attend medical school at The University of Texas Medical Branch in Galveston, where he graduated with honors. At night, he worked as an emergency crossmatching technician for blood transfusions.

After medical school, Gandara headed west for his residency, which he completed at Madigan Army Medical Center in Tacoma, Washington. This is when he found his calling, zeroed in on the field of oncology, and began his training in

hematology-oncology in San Francisco at Letterman Army Medical Center.

"Every rotation in medical school that I went through, I enjoyed, and I thought, 'Well, I'm going to be an orthopedic surgeon or I'm going to be a psychiatrist,'" he recalls. But then he had "the opportunity to work with people in my residency who were oncologists, and I felt, 'Here's a big need and an area that is likely to really expand and take off within my career time,' which it has. I think it was a very good choice for me."

He adds, "I thought it was an unmet need and an area that would be of greater significance in the future."

Gandara has spent most of his career at UC Davis and, for 20 years, served as the associate director for clinical research. During that time, he also held a position as chairman of the Southwest Oncology Group (SWOG) Lung Cancer Committee, which he acknowledges gave him many opportunities to work with other leaders in the field, as well as people at the National Cancer Institute (NCI).

He doesn't credit one specific mentor for assisting in his development as an oncologist but rather the effort he made to take advantage of being associated with experts who were leaders in the field whom he met along the way.

"I have been fortunate enough to be surrounded by very bright, collaborative people who have worked with me and are responsible for many of my achievements," he says.

The biggest change in Gandara's career came after his appointment as chair of the SWOG Lung Cancer Committee. "It allowed me to express myself," he says. "I was relatively junior when that happened, and it allowed me to, over a period of 15 years, grow my own career and mentor a lot of other people and be associated with many important projects in lung cancer."

Gandara calls himself "a man for all seasons," as he doesn't do just 1 specific job. He spends his time teaching, conducting clinical research, designing clinical trials, doing administrative work, and seeing patients. "I take care of all the components of an academic career," Gandara says.

> "Never in the field of oncology have there been so many advances within a short period of time as there have been in lung cancer treatment over the last couple of years."

The focus of his research is on developmental therapeutics of new anticancer agents, preclinical modeling, and clinical research within the disease. His current work includes: phase I molecular and clinical pharmacology trials, early therapeutics trials with phase II emphasis, and discovery and identification of blood biomarkers for early detection of lung cancer.

In addition, Gandara is instrumental in teaching others in the field how to use multimodality therapy–how to integrate radiation with chemotherapy with surgery.

He is also one of the chief architects of the Lung-MAP clinical trial, a collaborative effort that uses multidrug, targeted screening to match patients, who have advanced stage squamous cell lung cancer, with studies of investigational new treatments.

The trial is open across the country at many cancer centers, community hospitals, academic medical centers, and physician cooperatives. Lung-MAP is the first large-scale

Top photo: After a day's work, Gandara says the first thing he does when he gets home is kiss his wife, Diane. **Bottom photo:** Gandara likes to spend his free time fishing because he calls it a great stress reliever. Here he is displaying a lake trout that he caught from his kayak.

precision medicine trial launched with support from the NCI.

"This is an entirely new way of looking at the development of cancer drugs," Gandara says. "This is no longer business as usual. This approach changes the paradigm."

And although he loves fulfilling all the demanding duties of an oncologist, he does enjoy his downtime. When he's not in the hospital, you can find him on the water, preferably in his kayak, catching fish.

"I like to fish. I think it's a great stress reliever," Gandara says. His latest victory: a big trout that he reeled in Fourth of July weekend while fishing from his kayak.

PERSONALIZING CARE

Around the office, Gandara sticks with the motto: Find the right treatment, for the right patient, at the right time.

His career ambition is to continue to find ways to personalize cancer care, so that "each patient is treated as an individual," he says.

STAND UP TO CANCER

One way in which he is working to further personalize lung cancer treatment is on a Stand Up to Cancer (SU2C) project that combines drug therapies with immunotherapy to improve patient outcomes. Gandara serves as principal investigator at UC Davis on the SU2C Dream Team project, which targets mutations in the *KRAS* gene, which are found in 20% to 25% of patients with lung cancer. Under Gandara's leadership, UC Davis is contributing preclinical modeling of new combined treatments using a patient-derived xenograft resource and in innovative clinical trials.

According to the project's website, "The team has devised a 3-pronged approach to create new treatments for patients with *KRAS*-mutant lung cancers. First, the researchers will

identify the most effective therapies for targeting *KRAS* and other related biological pathways. Second, they will develop approaches to exploit the immune system for the treatment of *KRAS*-mutant lung cancers. Third, they will integrate targeted therapies with immunotherapies as a novel combined approach to treatment of *KRAS*-mutant lung cancer."

Gandara went on to explain that the patients with lung cancer whom he treats on a regular basis are a unique group compared with those in other parts of the country.

"In northern California, the prevalence of smoking is much less, about 10% of the population," he says. "So my average patient with lung cancer is a woman, not a man. The average age is about 45 or 50, not 70. And about 40% of my patients have never smoked. These are not the typical faces of lung cancer that you read about. It's a very different sort of population."

Across the spectrum, there are many advances being made in cancer arena. In particular, lung cancer is seeing promise with immunotherapies and targeted therapies for specific mutations.

"Never in the field of oncology have there been so many advances within a short period of time as there have been in lung cancer treatment over the last couple of years," Gandara says. "Where that is headed is very unclear, and there are regulatory and political components to how these developments will play out that are beyond the control of investigators, so it has become much more complex to speculate on where things are headed in the future."

Gandara says that these treatment options will become more and more complex and that patients will start to play a greater role in determining what therapies they receive.

Another area in which Gandara says there is a crucial need, and one he feels he has played a role in implementing, is bringing together diverse groups of experts to work as a team, so-called team science.

David Gandara, MD, believes medicine was his calling. He focused on oncology because it was an area where he saw an unmet need.

"This is where the achievements of the team as a whole exceed that of any of the individuals, and that is my career," he says.

Although this paradigm has been present for many years, the idea went mainstream following former Vice President Joe Biden's plans for the Cancer Moonshot program. He suggested data sharing, which would allow patient information to be stored in 1 large database and help researchers work with one another to fight the deadly disease.

"More and more, in the last few years, this concept of team science has been recognized as incredibly important,

that when you put a lot of smart people together, you get more out of it than you would from any of the individuals by themselves," says Gandara.

A 'GIANT' LEAP

If he never took the path to become an oncologist, Gandara says he could have seen himself as a teacher or a writer.

"I think I have a knack for communicating. I specialized in developing some methods for facilitating communication between patients and their physicians," he says.

However, his passion is helping advance the field of oncology. His role as an oncologist, working to publish innovative research and clinical practice, has earned him the honor as a Giant of Cancer Care®, an award that he calls humbling.

"The prior recipients are all world-class oncologists and hematologists. To be included among them is a privilege," says Gandara.

To close, Gandara shared his favorite life quote: "Live every day to the fullest. Take advantage of the time that you have." ■

From left: Robert Goldsmith, vice president, Intellisphere Oncology Specialty Group, and Thomas J. Lynch, MD, executive vice president and chief scientific officer, Bristol-Myers Squibb, look on as David Gandara, MD, accepts his Giants of Cancer Care® award in the lung cancer category.

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Giants OF Cancer Care®

John M. Kirkwood, MD

UPMC Hillman Cancer Center
University of Pittsburgh

"The clinic is what keeps us honest. It's the place where our mission is both initiated and ultimately fulfilled."

For a time, John M. Kirkwood, MD, thought he might become a professional musician.

His mother, 2 sisters, and 2 brothers have worked as professional musicians, and he was as fascinated with music as with science. Kirkwood wanted to pursue both his passions in college, which is how a New York City kid wound up going to college in rural Ohio.

"I was intrigued by the possibility that a place would mix music and science and allow me to pursue the music that I thought might be an option to give serious consideration," he says. "It served me well because I could really get deeply into music and then decide the science was even more driving."

Kirkwood, 69, still pulls out the viola from time to time, although less often lately, as he's gotten busier. He used to play in 5 orchestras, and groups of musicians would join him at his wooded 40-acre property outside Pittsburgh to play the orchestral and baroque music he loves so much.

Someone heading past the property at the right time in the morning and evening might find him riding a strange contraption, a bicycle specially adapted to train the German shepherds his wife breeds and trains to compete in a sport called *Schutzhund*, a German word meaning "protection dog." The sport focuses on 3 areas: tracking, obedience, and protection work.

"That's how every day starts and every day ends," he says. "It keeps the lead out of your pants."

A GROOVE THAT USED TO BE A RUT

Kirkwood entered Oberlin College's Senior Scholar program before his junior year and left the school to study immunology with a pioneer in cancer immunotherapy who became one of his mentors, Lloyd J. Old, MD, at what was then the Sloan-Kettering Cancer Institute. Kirkwood never made it

back to Ohio, and the idea of a career in music took a back seat to his growing interest in oncology.

Instead, he stayed in New York and eventually matriculated at Yale School of Medicine, where he went to work in the laboratory of Richard K. Gershon, MD, professor of pathology, immunology, and biology and another giant in the field of immunotherapy.

Kirkwood received his medical degree from Yale in 1973 and founded the Yale Melanoma Unit alongside Aaron Lerner, MD, PhD, and Stephan Ariyan, MD, MBA, 5 years later. He led that unit until 1986, when the University of Pittsburgh Cancer Institute (UPCI) recruited him as professor and chief of the Division of Medical Oncology. He was named the school's vice chairman for clinical research 10 years later.

Today, Kirkwood is the Thomas and Sandra Usher Professor of Medicine, Dermatology, and Translational Science at the University of Pittsburgh School of Medicine and codirector of the UPMC Hillman Cancer Center, Melanoma and Skin Cancer Program. In the 44 years since he began his career, he has seen melanoma become a growing field of research.

"This is a groove now. It once was a rut," he says. "Melanoma, for many people, was a rut some wanted to get out of and people avoided."

Kirkwood played no small part in changing the field's reputation. He was the lead author on the pivotal ECOG EST 1684 trial published in 1996 that led to the approval of high-dose interferon alfa-2b for adjuvant treatment of deep primary (T4) or regionally metastatic (N1) melanoma.

ECOG EST 1684 was the first randomized, controlled trial of interferon alpha-2b to show a significant benefit for overall survival (OS) and relapse-free survival in patients with high-risk melanoma. Results from that study showed that interferon alpha-2b increased median disease-free survival from 1 to 1.7 years and OS from 2.8 to 3.8 years. Compared with observation, a median follow-up of 6.9 years, interferon alpha-2b treatment induced a 42% improvement in the percentage of patients who were continuously disease-free compared with observation (37% vs 26%).

> "The experience with serology... has finally been brought to bear on the tumor. In oncology, there's probably nothing more important than tenacity in attacking a problem to assure that if you just stick at it long enough, you will succeed."

Kirkwood also serves as the principal investigator of the National Cancer Institute's Specialized Program of Research Excellence in skin cancer at UPMC. The program's goal is to improve the understanding of molecular and immunologic mechanisms of cancer progression and to validate prognostic and predictive biomarkers for personalized treatment of advanced melanoma and cutaneous T-cell lymphoma (CTCL).

The program will evaluate (1) the prognostic and predictive value of the pro-inflammatory response and markers of immune suppression in relation to ipilimumab and interferon alpha adjuvant therapy (leveraging an ECOG-led adjuvant trial), (2) an engineered, 3-antigen dendritic cell vaccine

Training his dogs for Schutzhund ("protection dog"), a dog sport that was developed in Germany in the early 1900s as a breed suitability test for the German shepherd.

and interferon alpha boost in patients with metastatic melanoma, (3) a phase I study of anti–PD-1 antibody MK-3475 and peginterferon alfa-2b for advanced melanoma, and (4) a new personalized microneedle vaccination technology for patients with melanoma and CTCL.

He has also been chair of the ECOG-ACRIN Melanoma Group since 1989. That group summarized results from 70 trial arms covering thousands of patients in 2008 and reached a disheartening conclusion.

"We humbly had to admit that not one of the treatments we had brought forward in phase II trials really had significantly improved either the time to progression or the overall survival of our patients," he says. "The only immunotherapy approved for melanoma in the prior 25 years was interleukin-2 for metastatic melanoma, and that was approved not on phase III trials but on phase II trials [and] had response rates in the range of 15% to 20%. Maybe one-third of those were durable and high-quality responses, but that's all we really had.

"Interleukin-2 for metastatic disease and interferon alfa for adjuvant therapy were, really, until 2011, the only therapies that we really thought had any meaningful, durable impact on melanoma."

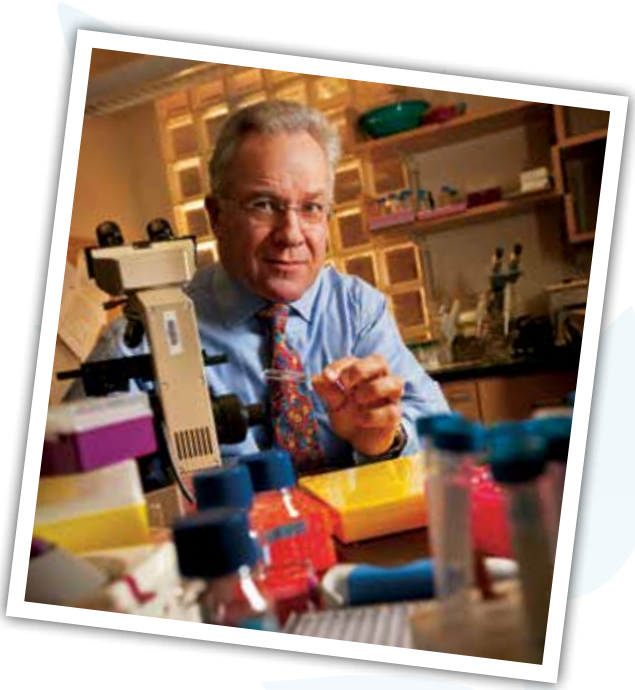
Kirkwood was part of the research team that investigated the next step in melanoma treatment, the cytotoxic T-lymphocyte antigen-4–blocking antibodies, ipilimumab (Yervoy) and tremelimumab. Ipilimumab won FDA approval for metastatic disease in 2011. The response rate wasn't spectacular (10.6%), but Kirkwood says it was the first FDA-approved treatment for metastatic melanoma shown to offer any survival benefit.

That approval was expanded in 2015 to include adjuvant therapy for patients with stage III melanoma to reduce the risk for relapse and again in July of this year to include treatment of unresectable or metastatic melanoma in pediatric patients 12 years and older.

Kirkwood is hoping to see another major shake-up in the field soon, perhaps as early as this fall. Speaking in late July, he said he was looking forward to results from studies evaluating nivolumab (Opdivo), pembrolizumab (Keytruda), vemurafenib (Zelboraf), and the combination of dabrafenib (Tafinlar) and trametinib (Mekinist), 3 of which were presented as positive new adjuvant trials at the European Society for Medical Oncology in September 2017. With these data there is hope that there may be several new options for adjuvant therapy of

melanoma available in the near future. After going from 1996 to 2015 with no new adjuvant treatments, oncologists treating melanoma may soon find themselves with an embarrassment of riches. It's the kind of moment Kirkwood has been waiting for since the 1960s.

"That would be truly stunning to have several adjuvant trials break positive and change the face of what we do," Kirkwood says. "The experience with serology in Lloyd Old's laboratory and with cellular immunology with Richard Gershon, and then with Harvey Cantor at Harvard in my fellowship days, which has finally been brought to bear on the tumor. In oncology, there's probably nothing more important than tenacity in attacking a problem to assure that if you just stick at it long enough, you will succeed. It's been gratifying for all of us, and it's a cast of thousands who've been involved in the assault on melanoma with immunology."



In the 44 years since Kirkwood began his career, he has seen melanoma become a growing field of research.

A PASSION FOR THE WORK

Kirkwood isn't sure what he'd be doing if he hadn't pursued medicine. Certainly, something would have captured his imagination by now; maybe he'd be a first-chair violist. Both his sons are engineers—one working on an oil platform in South Korea, the other at Stanford Research Institute—so it's likely he would have brought passion and intellectual rigor to another scientific discipline.

But for as much as he loves research, it's the practice of treating patients that truly motivates him. Kirkwood makes a point to work in the clinic at least twice, sometimes 3 days, every week.

"Clinic is what keeps us honest. It's the place where our mission is both initiated and ultimately fulfilled," he says. The patients I see every Monday, every Wednesday, and some Fridays are the motivation to do all the work." ■

Joseph V. Simone, MD

St. Jude Children's Research Hospital

When cancer struck its youngest victims, he offered hope, compassion, and courage to his patients and their families.

In the 1960s, programs for treating leukemia were few and far between—especially for children. The disease was just beginning to be understood, and rules and regulations for taking care of both adult and pediatric patients were underdeveloped and inefficient, as the first treatment for systemic cancers had been developed only a decade earlier.

A key player who emerged during those early years of pediatric cancer care was Joseph V. Simone, MD. Most notably, he chaired the Department of Hematology and served as associate director for clinical research at St. Jude Children's Research Hospital before becoming the director and CEO of the hospital from 1983 to 1992.

The Chicago native began his career in medicine as a resident at Presbyterian-St. Luke's Hospital. Initially studying internal medicine, Simone soon discovered his interest in hematologic diseases. That led him to the Pediatric Department at the University of Illinois, which had a big commitment to blood disorders and was conveniently located down the block.

After years of training in hematology and oncology, Simone left Chicago to take a job at the newly established St. Jude Children's Research Hospital in Memphis, Tennessee—a position suggested by a friend who had passed on the opportunity.

Simone was entering a challenging field. Until this point, almost all children with leukemia died of their disease. But by cultivating a communication model to reach the patients on their level, Simone began to see the difference in treating children versus treating adults.

The level of complexity of the treatment changes when speaking with a child rather than to an adult, so "we use words and concepts that the kids will understand. It's tricky, though, because you can scare them, the parents are scared—and sometimes I am scared. But I think [having] that group—parents, doctor, our superb nurses, and the patients

involved—is something [for which] we do not provide enough training for people," Simone admits.

Over the years, as St. Jude's prominence grew, so did Simone's reputation. After only a year, Simone had reorganized the clinic and laid the foundation for the reputation of efficient, personalized, patient-based care that St. Jude is revered for today.

Patients are what drove Simone to make St. Jude a home away from home. He was situated on the Mississippi River, and many of his patients lived in Arkansas and had to travel by bus or ask for a ride from neighbors just to get the treatment they needed. To alleviate this emotional and economic pressure, Simone and his colleagues developed a program where the hospital would pay for the families to stay in nearby hotels. This philosophy is demonstrated in the roots of St. Jude's current financial assistance policy for which it is highly praised. The hospital vows to never turn away a patient because of the inability to pay.

Notably, one of these patients who lived "across the river" in Arkansas was one of Simone's first cured patients. At 10 years old, the boy appeared to be cured—there was no sign of leukemia, but Simone and his colleagues were careful to warn the mother that this may not be forever. Simone continued to follow the patient's progress on a regular basis, and the boy continued to move along, developing as a normal child would—on to high school, college, and even marriage and children.

This case inspired Simone, pushing him to find cures for more children. "When you get one like that, you get very, very anxious to get more. That pushed us on," he says.

A MENTOR

When asked about the great strides made in the 1960s and 1970s for childhood leukemia, Simone credits his mentor, Donald Pinkel, MD. Pinkel was the first director of St. Jude and has been cited as one of the preeminent physicians in the fight against childhood cancers.

> "There is no question in my mind that my biggest impact in my career was developing treatments for childhood leukemia. Everything is dwarfed against that. I think that having become a pediatric oncologist was a godsend for me."

"He was there before the building was built—he was already putting in the structure for taking care of patients," Simone says of Pinkel. "He helped all of us youngsters learn how to conduct clinical trials so that we could find out what kind of treatment was better for that particular leukemia."

Simone's philosophies, medical and otherwise, have been formed by watching others. He cites working with seasoned physicians, listening to parents of children with cancer, and treating patients as his best lessons throughout his career.

One of the medical philosophies he followed came from Pinkel, which Simone said was best described as an attitude. Pinkel had a certain attitude regarding how physicians should handle and treat patients and their families, stating that both hope and truth are essential components of pediatric care.

Top and bottom: Simone examining his young charges.

Simone went on to serve as the associate director for clinical research. Together with his colleagues, Simone made great strides in the research field. Most notably, he developed the first curative combination treatment for select children with acute lymphoid leukemia, which led to the first patient with this disease successfully being taken off therapy.

Success did not come without its challenges, though. Reflecting on his work, Simone recalls finding curative treatments. He shared his findings during a national meeting and was met with resistance from the community. This, he says, was because the subject of leukemia was taboo in the community and suggesting that there was a cure for these patients was unheard of—but this reaction did not stop Simone and the team at St. Jude.

"We pushed on, and we got some terrific results over the next several years, and people started calling us, saying that they wanted to come to St. Jude to see how we did this," Simone says. "We had a whole trail of people from Germany, Poland, Japan—all over the world—who wanted to see how we could possibly get that result. That is really how it exploded."

One of the biggest challenges of a pediatric oncologist, Simone says, is working with the patients and their families to understand the illness and outcome. "You must adapt," he says. It is the doctor's responsibility to help the patient understand that he or she is trying to help them, not hurt them. Additionally, Simone says, a large part of treating a child is counseling the parents and cultivating the skill in which to do that effectively. He has seen this very challenge drive people away from the field, but it is this relationship that he feels is integral to truly treating a child with cancer.

In 1983, under Simone's leadership, the hospital was designated as the first and only National Cancer Institute cancer center dedicated entirely to children.

In 1984, St. Jude established what is now the world's largest long-term follow-up clinic geared specifically toward pediatric cancer survivors. Other successes during his directorship included researchers' finding the first 2 specific translocations known to cause pediatric acute lymphoblastic leukemia, and developing individualized chemotherapy regimens based on patient tolerance.

By the end of Simone's time at St. Jude, the survival rate for acute lymphoblastic leukemia had reached 73%, a rate that was once dismal. Currently the survival rate for children with acute lymphoblastic leukemia sits in the 90% range.

Simone's success in building St. Jude as a cancer center had institutions knocking at his door to help them do the same. After St. Jude, Simone was recruited to be the physician-in-chief of Memorial Sloan Kettering Cancer Center. From there his career path took him to the Huntsman Cancer Institute at the University of Utah, where he was the first senior clinical director, and then moved on to the Shands Cancer Center at the University of Florida. During these appointments, he also served as an external adviser for cancer centers such as Moffitt Cancer Center, USC Norris Comprehensive Cancer Center, Cleveland Clinic, and UC-San Diego Cancer Center.

Always humble, Simone reflects on his time building these cancer centers with a chuckle, stating, "I assume I did a good job because they paid me."

AWAY FROM THE CLINIC

Away from the clinic, Simone has also shaped practice within the larger oncology community. He led the development of the American Society of Clinical Oncology's Quality Oncology Practice Initiative, which is an oncologist-led, practice-based program. Additionally, he served on the editorial board for

According to Simone, it is the doctor's responsibility to help the patient understand that he or she is trying to help them, not hurt them.

Journal of Clinical Oncology from 1982 to 1983, before serving as an associate editor from 1984 to 2001.

Other notable positions he has held over his career were medical director and chair of the National Comprehensive Cancer Network, president of the Association of American Cancer Institutes, and vice chair of the Pediatric Oncology Group. He has also served on the board of directors for the American Society of Clinical Oncology.

Although mostly retired, Simone currently serves as the president of Simone Consulting, which provides services including strategic planning, program structure, quality assessment, recruitment, and physical facilities. He continues to write his own column, "Simone's OncOpinion," about his observations of the current oncology space, with advice for physicians in the field.

Simone has undoubtedly left a mark on the pediatric cancer world during his career. From his time as a resident at the University of Illinois and director of St. Jude Children's Research Hospital to his directorship of the Shands Cancer Center at the University of Florida, Simone has parlayed his expertise in the laboratory and the clinic into leading the charge on building up cancer centers around the United States.

With over 50 years in oncology, more than 140 publications spanning from 1965 to 2014, and countless professional society memberships, Simone has had a professional career that has filled his garage with awards.

A recipient of esteemed awards such as the American Association for Cancer Research's Richard and Hinda Rosenthal Foundation Award and the Distinguished Service Award for Scientific Achievement from the American Society of Clinical Oncology, Simone says nothing compares with interacting with the patients he has treated. To a man whom awards do not impress, being able to watch his former patients go on to high school, college, and marriage is worth more than any medal, trophy, or ribbon.

A day has not passed when Simone has regretted his decision to leave internal medicine to treat children with cancer. "There is no question in my mind that my biggest impact in my career was developing treatments for childhood leukemia. Everything is dwarfed against that," he says. "I think that having become a pediatric oncologist was a godsend for me."

Although he says that his entry to pediatric oncology was a "quirk," he knew that he could make the biggest impact on children dealt the unluckiest of hands. ■

Simone examining a child.

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Herman Suit, MD, MSc, PhD

Massachusetts General Hospital

With passion and persistence, Herman Suit, MD, MSc, PhD, spent his life changing the course of radiation oncology.

As he was growing up, Herman Suit, MD, MSc, PhD, took to heart his mother's advice: "If you really want something, ask for it politely and repeatedly." When he was recruited to Massachusetts General Hospital in 1970, he added that the requests not only be polite and repeated, but in writing. By employing that strategy throughout his career—combined with his carefully planned work and the support of numerous friends—he obtained virtually everything he requested along the way to changing the course of radiation oncology.

Born in Houston, Texas, in 1929, Suit frequented the honor roll as he accelerated through the public school system and went on to receive his bachelor of science from the University of Houston. There, he developed a deep interest in organic and biochemistry while taking a course given by Professor Eby Nell McElrath, whom he describes as the most impressive teacher he had—she made the subject truly stimulating to her students, Suit says. That led to Suit's career plan to be in a medical specialty that was heavily science based, preferably biochemistry. In 1948, at 19 years of age, he entered Baylor College of Medicine.

In that first year, Suit requested admission into the graduate program to receive an master of science degree in biochemistry as a second goal as a medical student. The chair of biochemistry was not impressed with Suit's résumé, which listed only freshman-level physics and math. Suit was informed that he would have to take a second year in math and physics at the University of Houston. During his second summer, he was to attend UT Austin and take atomic and nuclear physics. Near the end of one of his textbooks, he latched on to a small section that discussed the use of radiation to treat cancer patients with some impressive success.

"I read this and thought, 'Golly, that is fantastic!' I had

seen patients who had had their larynx removed in its entirety as their treatment for laryngeal cancer with loss of a critical function—ie, their voice. Apparently, comparable cure results could be achieved by use of radiation alone with clearly superior functional and cosmetic results," he says.

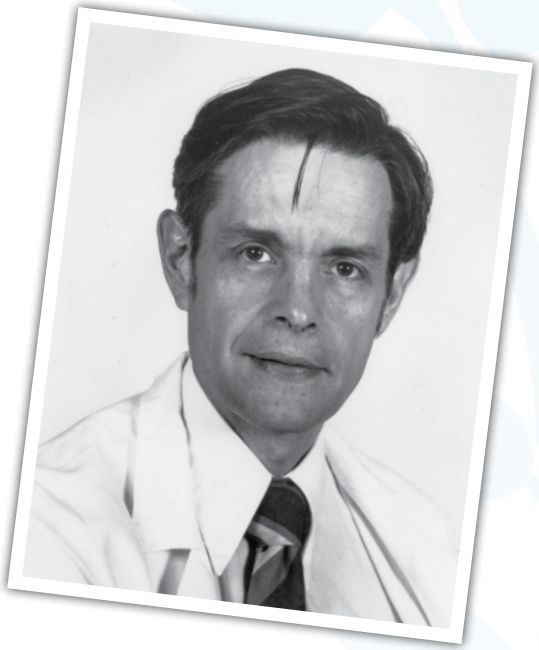
"So, I became intensely interested about this and rapidly learned more," Suit says. "I decided to change my goal to a physics-based medical field, vis-à-vis radiation oncology. I was puzzled in that radiation therapy had not been mentioned in any lecture that I had attended at Baylor."

In his fourth year at Baylor and confident of graduating with his medical and a master of science degrees, Suit faced another decision: where to study radiation oncology. Ever since childhood, he had believed the University of Oxford held one of the highest concentrations of intellect on the planet. The harsh reality, though, was that his family could not afford to send him to England. But a determined Suit applied for a funded position for graduate study, and—to his enormous surprise and pleasure—his request was granted. He was accepted.

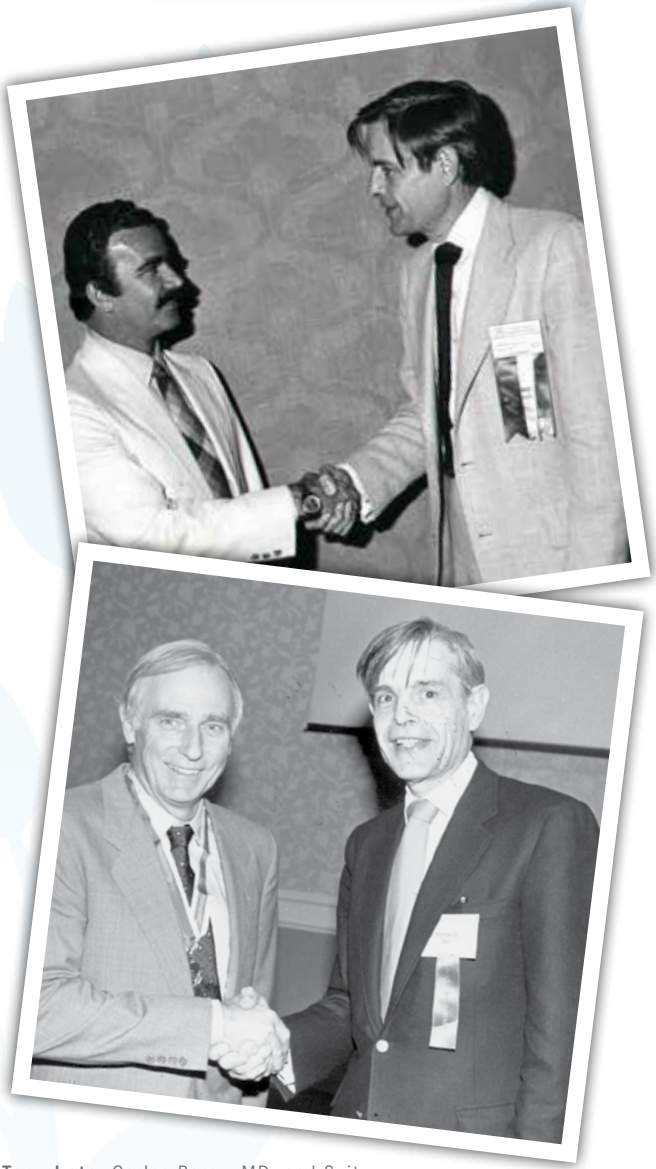
Meanwhile, Suit wrapped up his time at Baylor. Less than 2 months into his rotating internship, he was assigned to administer anesthesia alone to surgical cases, an area in which he'd received minimal instruction. That made Suit extremely nervous. "I had no real training in anesthesia and was scared to death to even try, but had no real option!" he recalls. "Things were much different back then."

One day early in his internship, while he was providing anesthesia for a thoracic surgical case, the operating room's head nurse told Suit to go to her office to read a letter that had been sent to him. Suit learned that he was being drafted to serve in the US armed forces and had to report for duty in 2 months—an extremely disappointing development, he says:

> "The chairman of the department would basically say, 'You don't believe me, and you don't believe anybody, when they say something if they do not have supporting data. Otherwise, it's merely their opinion.' "



A young Herman Suit latched onto the idea of treating certain cancers with radiation, and pursued it with impressive success.



Top photo: Carlos Perez, MD, and Suit.
Bottom photo: H. Rodney Withers, MD, DSc, PhD, and Suit.

"I just couldn't imagine what in the world to do, because I strongly wanted to do research at Oxford."

He followed his mother's early advice. "Well, my mother always told me, 'If you want something, son, you ask for it politely.' And so I got an appointment with the draft board," he says. "I went there, and they really had an unfriendly approach toward me. I was just asking for something over which they had absolute control," Suit says.

Suit stood before the board members to discuss a potential deferment, emphasizing that he wanted to learn about the biological effects of radiation and using it, instead of surgery, as a cancer treatment. He remembered to mention that he had a British fellowship that would cover all his room, board, and living costs. "At that point," Suit recalls, "the chair of that draft board looked at me with disbelief and shouted, 'Do you mean that the British are to pay all of the costs of graduate education of an American boy?' I answered politely, 'Yes,' and he slammed his hand on the desk and yelled, 'Deferment granted!'"

So, after completing his internship, followed by 6 months as a radiation oncology resident, Suit began his doctoral work at Oxford University on January 1, 1954. After several months in clinical residency, he focused on the study of the effects of ionizing radiation on iron metabolism in the blood-forming cells of bone marrow, in vivo and in vitro. He then spent a few months studying clinical radiation oncology before returning to the United States.

"That was one of the most intellectually stimulating times of my life," Suit says, describing his time at Oxford University. "The chairman of the department would basically say, 'You don't believe me, and you don't believe anybody, when they say something if they do not have supporting data. Otherwise, it's merely their opinion.' And opinion was

not a complimentary term," Suit says. "That was a highly challenging and exciting environment."

Suit anticipated that when he returned to the United States, he very likely would be drafted. Shortly before his departure, during a 3-day visit to the Royal Cancer Hospital in London, he met an American friend who asked, "Herman, why don't you apply for a deferment and go to a research center like the National Cancer Institute [NCI]?"

"Well, my eyes just lit up at that idea," Suit says. Once again, he didn't hesitate to ask for what he wanted. "I applied to join the US Public Health Service and to be assigned to the NCI," he says. "I lucked out, as there were not many applicants with interest in radiation biology. I enjoyed 2 years of research at the NCI."

Next, Suit was recruited by MD Anderson Cancer Center and stayed there 11 years, from 1959 to 1970. His clinical time was concentrated on patients who had cancer of the bone and connective tissue, assessing the efficacy of preoperative radiation treatment of patients with connective tissue sarcoma. This substantially reduced the need for large surgical margins for subclinical extensions because they could be eradicated by subradical radiation doses. This strategy substantially improved functional status and, in a number of instances, avoided amputation.

Finally, Suit found what might be called his professional home: Massachusetts General Hospital and Harvard Medical School. From 1970 to 2000, he served as chief of the Department of Radiation Oncology at the hospital and is now the Andres Soriano Professor of Radiation Oncology, Emeritus, at the medical school. Suit taught and mentored more than 100 residents and research fellows, many of whom went on to chair academic departments.

During those 30 years, Suit was a pioneer both in his research and in advancing Mass General in radiation oncology. In 1973, he initiated the first program to evaluate proton beam radiation therapy as a cancer cure using multiple dose fractions, based at the Harvard Cyclotron Laboratory in Cambridge, Massachusetts. Their physics/engineering team combined with the hospital's team of physicians and physicists from 1973 to 2001 to develop a proton therapy center in Boston. All of their work, including the land and part of the cost of the building and machines, was supported by Mass General, combined with generous, sustained funding by grants from the NCI. In 2000, the year before the center went into clinical operation, Suit stepped down as chief at age 71. He was replaced by another faculty member, Jay S. Loeffler, MD, who plans to start a second cyclotron early in 2018.

Suit with colleagues.

Suit counts the proton therapy program among his top professional achievements, because proton therapy

achieved spectacular results for many patients. Proton therapy centers now dot the globe and have treated more than 100,000 patients.

"When you see a patient 10 to 25 years after radiation treatment who is doing well with no cancer and near normal functional results, you can't have anything except a deep sense of your and the patient's good fortune," Suit says. "That's just natural. So that's one thing [in my career] that I would put up as highly important."

Suit continues to come in to work every morning, catching the 5:57 train to North Station. He has contributed 330 published papers and is writing a book, *The Biography of the Proton.* "Most of it is about the physics and nature of protons, the particle," Suit says.

When not working, Suit spends time with his wife, Joan, a Stanford University PhD graduate and retired Massachusetts Institute of Technology researcher in microbial genetics. She now volunteers at the Museum of Science, Boston, where she aims to increase the awareness and interest of the public, especially children, in science.

Suit is confident that the field of radiation oncology will continue to advance and improve in years to come. His prediction for the next 5 to 10 years: "I think we'll be able to genetically characterize the patient and their tumor so that there will be the ability to design management strategy for the individual patient." ■

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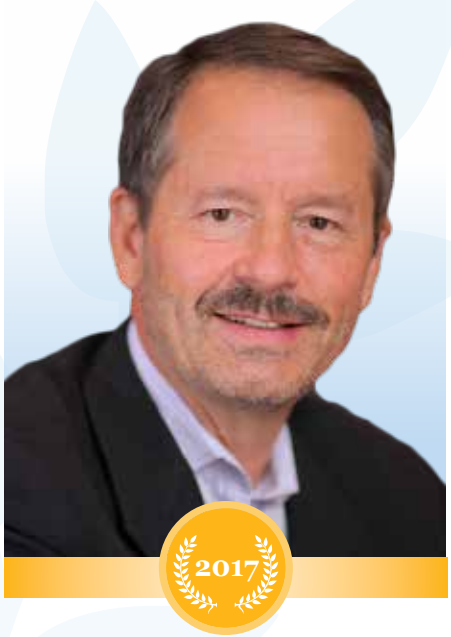

Lewis Cantley, PhD

Sandra and Edward Meyer
Cancer Center at Weill Cornell
Medical College

His discoveries on druggable genetic mutations led to a deeper understanding about tumor biology.

When Lewis Cantley emerged from Cornell University with a freshly minted PhD in biophysical chemistry, ready to begin his postdoctoral work at Harvard University, no one understood how insulin moved sugar from the blood and into individual cells. Given that properly metabolizing fuel is the single most important thing that cells do—no energy means no other activity—Cantley thought this a ripe area for study.

More than 3 decades of celebrated discoveries validate that intuition. Cantley and his research teams have uncovered much of what is currently known about the pathways that bring cells the fuel they need to function, grow, and multiply. It's hardly surprising, then, that they have also uncovered a dramatic amount of vital information about the workings of both type 2 diabetes (which occurs when insulin pathways break down and cells don't get enough fuel) and cancer (a disease that often involves cells taking too much fuel and growing too quickly).

Cantley's work led directly to the development of 1 novel FDA-approved drug, idelalisib (Zydelig), and numerous experimental compounds, such as Genentech's GDC-0077, that are working their way through preclinical and clinical trials. It also spurred interest in what may be the significant untapped cancer-fighting power of the diabetes medications, metformin and phenformin, along with that of simple vitamin C. There is, of course, no way to predict if any of them will prove to be safe and effective cancer treatments, but Cantley's work has revealed so much about tumor growth that many observers believe it's only a matter of when, not if, it pays off for patients.

"I knew that I wanted to become a scientist when I was 7 or 8 years old. I always loved figuring out why things work the way they do, and when I learned I could make a good living

doing that, I never really considered anything else," says Cantley, who is both the director of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medical College and the principal investigator at his own laboratory.

Cantley, 68, grew up in Big Chimney, West Virginia. His father worked for Union Carbide, starting as a machine operator but rising to the research laboratory despite his lack of a college education. His mother was a college graduate, although a somewhat unorthodox one, beginning her studies as a 29-year-old with 4 children ranging in age from 3 to 10. Still, she found the time to finish in 4 years and become a teacher.

Although Cantley was just 9 when his mother started college, he helped her study and quickly discovered that he could master her classwork. That was not, however, the only early evidence of his mental acuity. By the time Cantley reached middle school, he could dismantle and reassemble a car engine, and he had a college-level understanding of meteorology and ocean currents—a rare enthusiasm in landlocked states, but Cantley's father had developed an interest during his days in the Coast Guard and passed it on to his eldest son.

Cantley spent his undergraduate years at a small liberal arts school, West Virginia Wesleyan College. He chose it over STEM-oriented schools—those that focus on science, technology, engineering, and math—because he wanted to get a broad education before devoting himself to a single area of scientific study. Wesleyan not only offered classes in history, music, art, and philosophy, but it also required them. The school also forced him to develop a skill that would play an unexpectedly large role in his future success.

"Most of my undergraduate courses demanded a substantial amount of writing, and the professors held us to high standards. I spent 4 years working very hard to become a better writer, and it has benefited my scientific career enormously," Cantley says. "Science isn't just about discovering things. It's about being able to communicate your discoveries. Writing well gets you the grant money you need to do experiments. It helps get your papers into important journals. And it helps to get those papers read...It doesn't matter how bright or how productive you are, if you can't write, then there is a real limit in how high you can rise in the world of research."

> "I knew that I wanted to become a scientist when I was 7 or 8 years old. I always loved figuring out why things work the way they do, and when I learned I could make a good living doing that, I never really considered anything else."

After his time at Wesleyan and Cornell, Cantley spent a very productive decade elucidating many of the events that allow cells to signal their need for fuel and then allow growth factors, such as insulin, to get the proper amount of fuel into those cells. It was only afterward that he made his first cancer-related discovery: phosphatidylinositide 3-kinase, also known as PI3K.

The previously undiscovered enzyme co-purified with a

Above: Cantley in his office. **Below, from left:** Cantley and postdoctoral fellows, Cindy Hodakoski and Florian Karreth.

wide variety of oncoproteins that caused cancer in both chickens and mice. Initially, Cantley and his colleagues thought it was making a long-known lipid called phosphatidylinositol 4-phosphate (PI4P), but careful analysis showed that the lipid in question had slightly different properties from PI4P. The team then went on to show that PI3K was making a lipid that had never been observed before, PI3P. Both the enzyme and the lipid were, as further research would soon show, key components in the development of many tumor types.

If there is a secret to his success, Cantley believes it is an unwillingness to ignore "small" discrepancies. Indeed, he made the leap from postdoctoral student to assistant professor by noticing and explaining a seemingly trivial puzzle that researchers around the world had either overlooked or ignored for decades: the curious way that a particular brand of commercially produced adenosine triphosphate (ATP) behaved in the presence of sodium-potassium ATPase.

Because of his graduate work with other enzymes that hydrolyze ATP, Cantley expected the sodium-potassium ATPase to steadily hydrolyze the ATP, which he had bought from Sigma Chemical Company, for at least 30 minutes. But it didn't. The process stopped after only 5 minutes. Given that ATP from a different commercial source was hydrolyzed in a linear fashion for more than 30 minutes, Cantley concluded that there must be an impurity in the ATP produced by Sigma.

He set out to identify the impurity and ultimately discovered that it was vanadate, an oxidized metal produced when ATP is hydrolyzed. The amount of vanadate in the ATP was minute (1 part in 3000), but it was potent.

The discovery provided new insight about how sodium-potassium ATPase hydrolyzes ATP and, ultimately, led to the

use of vanadate to inhibit the function of many other enzymes that hydrolyze phosphate groups. On the basis of 2 highly cited papers describing this work, Cantley was appointed as an assistant professor at Harvard in 1978. Sigma quickly refined their purification procedure to produce vanadate-free ATP, which became one of their top-selling products.

Better still, the project didn't require Cantley to spend endless time in the lab, according to his younger brother Lloyd. "It is odd to say this about a world-famous researcher, but Lewis doesn't really like doing research, not in the sense of actually sitting in a lab and physically conducting experiments," says Lloyd Cantley, MD, a chaired professor of nephrology at Yale University who leads a research lab of his own. "He has always liked to make sense of data that research produces and write down the explanations.

"When Lewis made the vanadate discovery, he was still a postdoc, which is when most people are pretty happy to spend 14 hours a day in the lab. Lewis thought it such a poor use of his time that he paid me out of his own pocket to work in the lab during the summer between my junior and senior years in college. I did most of the physical experiments that summer. He considered the results, figured out what they meant, and directed me to do the next logical experiment."

The younger Cantley thinks this aversion to lab work has served his older brother well by shifting his attention away from data collection and toward data analysis—an analysis that comes from an unusual perspective. "Most people who do medical research are doctors, and they almost always start with the big picture and work down," Lloyd Cantley says. "Lewis is a physical biochemist. He starts from the individual molecules and works up. It gives him an unusually fundamental understanding of the body's workings, and it allows him to see things that others miss."

Another key to Cantley's success: an extreme ability to shut out the world and concentrate. His mother once took him to the doctor because it was so hard to get him to look up from a book or a project, she assumed something must be wrong with his hearing.

Since the initial discovery of PI3K, Cantley and his research teams have worked to understand how this enzyme is activated by insulin and other growth factors, as well as how the novel lipids produced by this enzyme tell cells to take up glucose and use it to make the DNA, RNA, lipids, and proteins needed for cell growth.

Mutations in genes of the PI3K pathway are now known to be among the most common events in cancers, and more than 25 PI3K inhibitors have entered clinical trials. Most of these drugs target the enzyme encoded by the *PIK3CA* gene, because this gene is mutated in about 40% of breast cancers and 50% of endometrial cancers. Unfortunately, it also encodes the PI3K that mediates insulin responses, making it a challenge to find doses that can kill tumors without causing dangerously high levels of serum glucose.

The first PI3K inhibitor to be approved, idelalisib, also produces high toxicity in some patients but for a different reason. Idelalisib does not target the *PIK3CA* gene product but, rather, targets a form of PI3K that is needed for the growth of B lymphocytes. Idelalisib was approved for treating chronic lymphocytic leukemia, a B-cell lymphoma. While effective in this disease, it also has some toxicity due to its effects on normal lymphocytes.

Despite those setbacks, a number of PI3K inhibitors that target different isoforms of PI3K are showing promising results in clinical trials as translational researchers learn more about how to avoid toxicities.

In addition to spurring new drug development, Cantley's

Not your typical world-class laboratory researcher, Cantley prefers data analysis to data collection.

research has provided new insight into how metformin and other commonly used drugs may provide a benefit for preventing or treating cancers.

Epidemiologic studies have long demonstrated that people who use metformin for diabetes suffer significantly less cancer than otherwise similar people who do not use the drug. In fact, the effect is so profound (up to a 40% reduction in cancer incidence and longer survival for those who develop a tumor) that metformin may well have saved more people from cancer than any cancer drug has. It has never been used to treat cancer, however, because no one knew how it combated the disease and, therefore, which patients were likely to respond. No one even knew how metformin reduced A1C levels and combated diabetes. That's not as unusual as it sounds; the workings of many long-approved drugs—even aspirin—are not fully understood.

Over the past few years, however, researchers in Cantley's laboratory have been figuring out what metformin does on the cellular level. Their work not only explains how metformin lowers A1C levels to fight diabetes but also provides a rational way to predict which tumors would likely respond to metformin treatment.

That same research has also led them to hypothesize that phenformin would prove an even more effective tool against cancer than metformin is—for the very same reason it is no longer used to treat diabetes: It acts in the whole body rather than confining its activity to the liver. Indeed, researchers at Cantley's laboratory, Memorial Sloan Kettering Cancer Center, and Massachusetts General Hospital have asked the FDA for permission to perform clinical trials with the drug in patients with melanoma.

Metformin and phenformin are not the only long-used substances that Cantley and his team are testing against cancer. Work from the laboratory has demonstrated that high levels of vitamin C (300 oranges' worth a day, mercifully delivered intravenously) selectively kills *KRAS* and *BRAF*-mutant colorectal cancer in animals. Trials in humans are already under way.

"I actually thought vitamin C was a long shot, but an instructor in the lab [Jihye Yun, PhD] thought that its ability to be oxidized by the reactive oxygen species produced by tumors and the ability of that oxidized form to sneak into the

cell might result in cell killing," says Cantley, who credits younger researchers for most of the groundbreaking work that comes out of his laboratory these days. "I just raise the money, throw out a few ideas, and ask questions to help them think through their work."

Such pronouncements illustrate another of Cantley's more unusual qualities. "He is genuinely humble, which is rare among the general population but vanishingly rare among world-famous scientists," says Laurie Glimcher, MD, who convinced Cantley to leave Harvard for Weill Cornell, where she was dean of medicine before she jumped to Harvard to become CEO of Dana-Farber Cancer Institute. "As a result, Lew is universally liked—which is pretty much unheard of in this business—and he gets the most out of his research teams, because he's totally open to ideas from everyone." ■

Donna Short, MA, executive vice president, Michael J. Hennessy Associates, Inc, presents Lewis Cantley, PhD, with his Giants of Cancer Care® award.

Hyman B. Muss, MD

University of North Carolina
Lineberger Cancer Center

Serving the needs of older patients with cancer.

The public's perception of a cancer patient is sometimes distorted by Hollywood, says Hyman Muss, MD, a lifetime oncologist and researcher who specializes in the treatment of older adults with breast cancer. The 1971 movie *Brian's Song*, for instance, told the true story of how Chicago Bears running back Brian Piccolo succumbed to cancer. The movie was hugely popular, and even its theme song, "The Hands of Time (Brian's Song)," became a hit. Many Americans became aware of the tragedy that cancer can represent. However, the film overlooked the fact that most patients with cancer are geriatric and have their own unique problems with this disease.

"When you watch a TV show in the United States about cancer, the patients are always young people or middle-aged people. In reality, the average age of a cancer diagnosis in this country is around 66 or 67, and the majority of people who die of cancer in the United States do so after age 65, so cancer is a disease of aging," says Muss, 74, who as a well-respected doctor, researcher, and mentor to many clinicians throughout his lifetime has significantly expanded the commitment to understanding and treating this patient population.

There is nothing particularly "sexy" about treating geriatric patients with cancer, but the truth is that geriatric oncology is where the action is, Muss says. There's a huge amount to be learned from this population of patients: They could have comorbidities, they may be frail, and they may be taking many medications for a variety of ailments, not all of which are related to cancer. These issues complicate the job of treating the geriatric population successfully but make the work interesting and challenging. Muss says he recognized early in his career that this was a wide-open field for discovery.

His first introduction to the field of geriatric medicine was as a faculty member at Wake Forest School of Medicine in North Carolina, where he was under the mentorship of William Hazzard, MD, chair of the Department of Internal Medicine at Wake Forest at the time and a founder of geriatrics in the United States. Hazzard is currently a professor of gerontology and geriatric medicine at the Sticht Center on Aging at Wake Forest. He encouraged Muss' interest in doing a project to look at outcomes in breast cancer among older women treated with chemotherapy. The result of that inquiry was a manuscript that so impressed the editors of *The Journal of the American Medical Association* that it was accepted without revision. "This shocked me," Muss says.

The effect of that publication was to give Muss a reputation in the medical community for knowing more about working with geriatric patients with cancer than he actually did, and people immediately began turning to him for guidance. He was willing to accept the responsibility of becoming a leader in this branch of oncology treatment, however, and he set to work to learn everything he could. "I really wasn't an expert at all in geriatrics. I knew very little about it, but I got calls. I got interested in the topic, and over the years, I transitioned into geriatric oncology with a focus on breast cancer," he says.

One of his activities in relation to this was his former cochairmanship of the Cancer in the Elderly Committee of the Alliance for Clinical Trials in Oncology, where he worked closely for 20 years with former committee cochairman Harvey Cohen, MD. In addition, Muss' collaboration with Arti Hurria, MD, led to development of the Cancer and Aging Group Geriatric Assessment, a brief list of questions that enabled clinicians to determine how well older patients can function independently. They demonstrated in the Cancer and Leukemia Group B Clinical Trials Cooperative Group Program that the questions could be used in a clinical trial. "We've included this shorter geriatric assessment into several clinical trials sponsored by the Alliance, a National Cancer Institute (NCI)-funded Cooperative Group, and we try to do this before we treat the patient and then use it as a baseline to see how they do. We're trying now, in individual trials, to do several assessments over time. We're working to get this out in the community in tablet form, and we're doing that with the NCI through the NCI Community Oncology Research Program to embed geriatric principals and assessments into clinical care. The hope is to develop models that can help determine more objectively who might do well in a clinical trial as well as the likelihood of severe toxicity," Muss explains.

> "He's taught me through example things that I could never have learned from a textbook. Just to have worked with him is a highlight of my career," says Arti Hurria, MD, director of the Center for Cancer and Aging at City of Hope.

Clinical trials are key for laying the groundwork for drug investigation and approval, but they generally recruit a younger set of patients, which means that the data that

Top photo: Fishing on the Madison River, Montana, 2016. **Bottom photo**: Loretta and Hyman Muss.

are gathered don't offer reliable guidance for treatment of older patients. "There's a shortage of knowledge there, and my career now is dedicated to looking at ways that we can develop trials, especially trials focusing on the newer biologic agents, to predict functional loss or toxicity with treatment," Muss says.

Currently at the University of North Carolina Lineberger Comprehensive Cancer Center, Muss serves as director of the Geriatric Oncology Program. More than just treating patients, Muss feels his duty is to broaden knowledge and training for oncologists who often don't know enough about how to manage the geriatric patients under their care. "Older people are frequently undertreated, with adverse consequences, and very few doctors have been trained to care for older people," he explains. "They don't think about the things that geriatricians see all the time—falls, dementia, polypharmacy, and the need for social support. They really are focused in on the tumor. People in their late 70s and older frequently come in with a lot of other issues that even the best oncologists are relatively unprepared for."

A seminal moment for Muss was a comparison trial of standard adjuvant chemotherapy versus capecitabine in women 65 years or older with breast cancer. The Cancer and Leukemia Group B/CTSU 49907 trial was unique in that it included only older women, and it demonstrated that the use of standard chemotherapy can improve survival in older women patients, contrary to the tendency among physicians to spare older women the discomforts of chemotherapy and undertreat them, which Muss believes is a disservice to this population.

"No one had done a similar study. We showed that older women benefited from standard treatment as opposed to oral chemotherapy. We also collected lots of data on function,

quality of life, and many other things that are important to older patients," he says.

It was not just being able to prove that older women could benefit from standard treatment that made this study significant for Muss. It was the successful cooperation among specialists from varied disciplines that demonstrated to him what could be accomplished by such an elaborate team effort. "I saw how important it was to build a team where we had social scientists and health service research expertise. We even looked at pharmacology and how people took their pills. By working with the right group of people who have similar interests but are knowledgeable in areas that I'm not, I saw how much we can learn about patients that, in turn, can be used to better inform doctors and patients about the consequences of treatment," Muss says.

Newer drugs—especially the class of biologics called immunotherapies—offer advantages for older patients in that their toxicities may be lower and the heavy damage that chemotherapies wreak on compromised systems can be avoided. Muss admits to feeling some excitement about the potential these agents represent, but again, he notes, not enough studies have been done to provide the data physicians need to judge how older patients are really going to be affected when they receive these treatments. "The data concerning how these approaches work in older people, as far as affecting their function and quality of life, are lacking, and that's an area where we need a lot more research."

Relatively few older patients have been included in studies of ipilimumab and pembrolizumab, he says. Older patients will suffer adverse effects that are common to younger patients, but others' toxicity may be different, and those need to be understood clearly. "I suspect there are not going to be dramatic differences in nausea and vomiting, for example,

Top photo: The family gathers for the holidays. **Bottom, from left to right:** Greg Kokinis, Sarah Muss, Hyman Muss, Jonathan Muss behind Loretta Muss, Candace Muss holding grandson, Jacob Muss, Daniel Muss behind Candace, and Lisa Muss.

but to take an older patient who is barely making it and add profound fatigue or muscle weakness, for example, is going to really change that patient's life, and we know very little about it," he explains.

Currently, Muss is working to understand not just the effects of treatment on older patients but also whether simple interventions, such as exercise, can stall the accelerated aging and other damage to the body that result from chemotherapy. He and his fellow researchers are monitoring patients' fitness routines and measuring their molecular markers of aging. "It's really a challenge that is lots of fun," he admits, "and during and after treatment, we try to get them into rehabilitation programs that can keep these older people as functional as possible with something that is scalable to their abilities: For example, walking 30 minutes 5 days a week is something that can be exported to a community much more easily than going to a gym and getting a trainer or going to a health center and participating in supervised programs. That's where a lot of our work is focused right now."

Muss receives high praise from a colleague who has worked with him in the field of geriatric oncology for almost 20 years: Hurria, director of the Center for Cancer and Aging at City of Hope in Duarte, California. Muss has led major research defining standards of care for how older adults with breast cancer are treated, she says. Hurria describes Muss as a humanitarian and a role model whose contributions to the research community have included fostering the careers of a multitude of clinicians.

"The fact that he chose to dedicate his career to geriatric oncology was a huge plus for our field because we need role models—people who are successful, people we need to emulate—and when you have giants of oncology go into a field that's relatively underrepresented and talk passionately about it, it's a game changer," Hurria says. "He's brought a lot of awareness to the field of geriatric oncology, and he has inspired a whole other generation of individuals to continue to work in this area."

Speaking from her own experience, Hurria says Muss' warmth, professionalism, and deep understanding of the field have made it easy and inspiring to work with him.

"He's the kind of person whom you seek out for feedback on your research, as he will always take it to a higher level. He is both brilliant and kind, always greeting his colleagues with a big hug. He wants to do anything to help you to do high-quality research that will ultimately help that next patient. It's just that pureness of motive. It's exceptional. He's taught me, through example, things that I could never have learned from a textbook. Just to have worked with him is a highlight of my career."

Muss grew up in a traditional brownstone in Brooklyn, New York. He attended Downstate Medical School in Brooklyn and graduated summa cum laude. He obtained his medical degree in 1968 and was drafted at the height of the Vietnam War. He had the opportunity to serve stateside but opted instead to do his part directly in the war effort. The 27-year-old doctor was assigned to an artillery unit with the rank of captain. Muss survived his 1-year tour of duty unscathed, and in 1972, he entered Brigham and Women's Hospital in Boston, Massachusetts, for hematology training and, later, the Dana-Farber Cancer Institute.

His other academic passion, besides medicine, was chemistry, but he has no regrets about the path he chose. He has had friends who became investment bankers, but he doesn't believe the money they earned has made their lives more fulfilling than his. "I've been very happy as an oncologist,"

he says. "Cancer is one of the key ailments of mankind. To be able to wake up in the morning and feel, 'I'm taking good care of my patients, I'm trying to do the best I can, and I'm involved in top-quality research both nationally and at a wonderful university'—that's tough to beat!"

While he is now in the same age population as those he looks after, he notes that his health is excellent and he has every intention of continuing in his profession. "I'm not looking forward to sitting with a bunch of old guys and talking about prostate problems, and I'm a lousy golfer," Muss says. His wife, Loretta, is a retired nurse but also continues to work, doing caregiver support and playing a major role in building patient advocacy at the North Carolina Cancer Hospital. The couple has a trio of grown children—a daughter and 2 sons—as well as a grandson and 2 more grandchildren on the way. ■

From left: Robert Goldsmith, vice president, Intellisphere Oncology Specialty Group and Patrick Borgen, MD, acknowledge Hyman B. Muss, MD, recipient of the Giants of Cancer Care® award in the supportive/palliative/geriatric care category.

John L. Cameron, MD

The Johns Hopkins University School of Medicine

"Good judgment comes from experience, and experience comes from bad judgment."

For John L. Cameron, MD, a few guiding principles have truly illuminated both the kind of medicine he practices and the lives he has helped extend.

"I have a few statements I'm fond of, and the first is, 'If you pick a profession you love, you never have to work a day in your life,'" he says. "Taking care of patients, helping them, performing surgeries, and dealing with their families—it's the best job there is."

His next favorite, he adds, addresses the ongoing learning process inherent in medicine. "'Good judgment comes from experience, and experience comes from bad judgment.' Even though you make mistakes, you learn from them and get a little smarter, so next time you do it, you can avoid them."

These are fitting phrases for Cameron, the Alfred Blalock Distinguished Service Professor in the Department of Surgery at The Johns Hopkins University School of Medicine and the world's foremost expert in the Whipple procedure, a surgery that treats 1 of the deadliest diseases in oncology: pancreatic cancer. He has completed more than 2000 Whipple operations, or pancreaticduodenectomies, more than anyone else in the world.

Named for Allen Oldfather Whipple, MD, who first wrote about it in 1935, the procedure treats pancreatic cancer by removing the head of the pancreas, a good part of the duodenum, some of the bile duct, the gallbladder, and nearby lymph nodes. Sometimes the whole pancreas, duodenum, and part of the stomach are taken out. It is a complicated process, taking up to 6 hours, and requires patients to recover in the hospital for 1 or 2 weeks. According to 1 journal article on the subject, the Whipple is considered "one of the most challenging surgical procedures, which requires the highest level of surgical expertise."

The Whipple isn't just a difficult operation; it has helped give some patients with pancreatic cancer hope at a time

when little else can. As a result of Cameron's work both performing the Whipple and teaching others to do it well, the procedure has helped extend the lives of some patients with pancreatic cancer. Today, the 5-year survival rate for patients who have had the operation is about 25%; for those who are treated before the cancer has spread to the lymph nodes, 5-year survival rates are closer to 40%. In the 1980s, when Cameron first began performing the operation, about 25% of all people who had a Whipple died. Today, the mortality rate is about 1.5%. Without the Whipple, pancreatic cancer is uniformly fatal.

A colleague quoted in a 2012 *Baltimore Sun* story about Cameron's 2000th procedure noted his influence on others. "A lot of surgeons do the operation well because [Cameron] trained them," said Julie A. Freischlag, MD, then the chair of Hopkins' Surgery Department and Cameron's successor in the position after almost 2 decades. "He's probably responsible for more like 10,000 surgeries."

A HOPKINS' LEGACY

Cameron chose to focus on the Whipple when, in 1984, he became chairman of the Department of Surgery and the director of the Section of Surgical Sciences at The Johns Hopkins University School of Medicine, where he had worked since attending medical school at The Johns Hopkins School of Medicine. He earned his medical degree in 1962, served his surgical residency from 1962 to 1970, and served as a clinical and research fellow for the next year. He also spent 2 years, from 1963 to 1965, doing a stint as a research surgeon for the US Army at the Walter Reed Army Institute of Research. Following a meteoric rise from assistant to associate to full professor in just 7 years ("It was, at that time, a record," Cameron says), as chair, Cameron recruited colleagues to join him in the Hopkins' Surgery Department in the mid-1980s. "I had to promise them they could do all the surgery in their fields that they wanted," he said.

> "Nobody wanted to operate on the pancreas, because if you did a Whipple, which was recommended for only 25% of all patients with pancreatic cancer, everyone died...I picked pancreatic cancer...because there were virtually no 5-year survivors."

That left him to focus on pancreatic cancer, which at the time had veryl little to offer patients in terms of treatment or long-term survival. "Nobody wanted to operate on the pancreas, because if you did a Whipple, which was recommended for only 25% of all patients with pancreatic cancer, everyone died," he recalls. "When I became chair, I picked pancreatic cancer to focus on because there were virtually no 5-year survivors."

Today, about 30% of patients with pancreatic cancer are candidates for surgery, based on the size, location, and metastatic status of the tumors. But once Cameron began doing Whipples, the success rate began to improve.

"People always ask me, 'How many Whipples do you have to do before you know how to do it?'" says Cameron. "I say, 'I don't know; I will let you know when I get there.' I used to

Doris and John Cameron, MD, surrounded by their children and grandchildren on Martha's Vineyard (top and bottom).

do 5 a week, but now I do 2 to 3 a week. It's a long operation and you have to resect a lot of organs." Cameron, now 80, still works full-time in the hospital, 7 days a week, operating on 2 to 3 of those days. About 350 Whipple operations are done at Hopkins each year, he says, with younger surgeons doing most of them.

In the 1980s and 1990s, he worked to refine the procedure, publishing multiple randomized studies following different techniques with his colleagues, he says. "That's the biggest contribution that has come from Hopkins," he adds. "The program I started in the mid-1980s focused on pancreatic cancer, and we now have more money devoted to basic research and clinical activities on pancreatic cancer than any other hospital in the world," he says. "We have $30 million in endowment and $40 million in direct funding supporting research in pancreatic cancer. We have one of the best training programs in the world. We have turned out probably 20 surgeons, mostly in pancreatic cancer, who have become leaders in surgery and the chairs of surgery departments around the country. They have all trained here at Johns Hopkins University, and most are pancreatic surgeons."

Cameron has left the department in good hands. "I'm probably only going to operate for another year or so," he says. "I have been goal oriented most of my life, but when you're 80 years old, you don't set many goals. I just continue doing what I do, being a surgeon. I'll still run the clinics and see patients and go to conferences and participate in clinical research."

He has also held many leadership roles throughout his life, including president of the American College of Surgeons, the Society for Surgery of the Alimentary Tract, the Southern Surgical Association, the Society of Clinical Surgery, the

Society of Surgical Chairs, the Halsted Society, and the American Surgical Association.

FAMILIAL INFLUENCES

Born and raised in the small city of Brighton, Michigan, Cameron moved at age 9 with his father, Duncan; his mother, Mary; and his siblings, Duncan and Sara Jane, to Detroit so his father, a general practitioner, could complete surgical training. "My father had grown up in modest circumstances and was the first person to graduate from college from his family. He worked his way through Wayne State University by being an oiler boy on Great Lake freighters," says Cameron, referring to bulk carrier ships that carried materials like limestone, ore, coal, grain, salt, and iron to and from industrial ports across the Great Lakes. "He would have wanted to go into academics."

Instead, the elder Cameron shaped his son's path. "I grew up in the generation where most of the time, you did what your dad did," says Cameron. "I went to a huge high school in Detroit, with 4000 kids, and I did well there. If you were smart and did well in high school, you went to the University of Michigan. My dad said, 'Why don't you apply to Harvard?' It was the only college I applied to, and I was accepted. I didn't know then how hard it was to get into."

On the train from Michigan to Massachusetts, Cameron lugged "a big foot locker I could hardly drag," he recalls. "I got to [Boston's] South Station and then took the subway to Harvard Square, and I dragged my foot locker to the dorm. There, I saw 16 other freshmen sitting around, reading the *New York Times*. I had never heard of the paper. It didn't have comics in it, and I couldn't figure out why they were interested in it."

For his classmates, students who had graduated from Phillips Exeter Academy and Andover prep schools, "Harvard

Cameron in his Johns Hopkins office in 1990.

was a natural step. But for a kid from Michigan, it was a big thing," Cameron says.

Going to Harvard proved to be a real life changer, he says.

"My first year, I was so afraid because all these sophisticated people from the East were there, so I did nothing but study," he recalls. But when he realized he could hold his own against the other students, both in class and out, "I demonstrated to myself that I could do just as well," he says. "So I eased up and enjoyed my final 3 years there."

He graduated from Harvard in 1958, then entered The

Johns Hopkins University School of Medicine, where he earned his medical degree in 1962 and where he has worked for virtually his entire career.

Along the way, Cameron met and worked with many people he considered great role models in medicine, including Hopkins Chiefs of Surgery Alfred Blalock, MD, and George Zuidema, MD, and his mentor and friend, the Hopkins' surgeon and oncology professor, R. Robinson Baker, MD.

FAMILY: HIS PROUDEST ACCOMPLISHMENT

Despite his long academic career at Hopkins and his success as the world's Whipple expert, Cameron says his greatest contribution has been his 4 children, Duncan, Heather, Shannon, and Andrew. His oldest son, Duncan MacTavish Cameron, holds a PhD in clinical psychology and practices in Texas. His eldest daughter, Heather Cameron Lowe, teaches fifth grade in Boston. His younger daughter, Shannon Cole Brown, holds a PhD in epidemiology and works at Johns Hopkins School of Public Health and Hygiene. And his youngest son, Andrew MacGregor Cameron, MD, is a Johns Hopkins surgeon, chief of the transplantation division, and does liver transplants.

"The Whipple operation and liver transplant are the 2 biggest operations someone can perform," Cameron says. "They are challenging, and they take someone who is about to die and makes them better," he says. If he weren't doing Whipples, Cameron says, "I think I would be like my son, doing liver transplants."

Doris, Cameron's wife, has been the rock of the family for more than 5 decades; this year, the couple celebrate 57 years of marriage. They met when a high school friend, Jane, set them up in Boston, when Cameron was at Harvard and Doris attended Wheelock College before becoming a teacher for third-graders with dyslexia. Years later, "Jane developed liver failure and hepatitis and was about to die," Cameron recalls. "Our son did a liver transplant on her, and she's living well now. And without her, there wouldn't have been a son to do that operation."

Cameron relishes the time he spends with his immediate and extended family. "We are fortunate that 2 of our 4 children live in Baltimore and work at Hopkins; they have 5 of our 7 grandchildren," he says. "We get together every Sunday evening and have Sunday dinner. One child is in Boston, and we get together in Martha's Vineyard 4 times a year for long weekends and the last 2 and a half weeks in August. The last child is in Texas, and we see him at least twice a year."

LOOKING AHEAD

Cameron envisions a time in the future when the Whipple operation will become minimally invasive, as "that's the direction surgery will go," he says. "Not all of them, but maybe 60% to 70% will be done that way in the next 10 years." He looks forward to seeing other treatments for pancreatic cancer evolve. "The biggest advances will be with chemotherapy and immunotherapy that will result in better outcomes," he says.

But his contributions to medicine have been substantial.

"When I got into the field, pancreatic cancer was one of the worst, if not *the worst*, cancer you could come down with," he says. Back then, "there were virtually no 5-year survivors." Today, with the advent of the Whipple and research efforts focused on neoadjuvant chemotherapy, immunotherapy, and radiotherapy, he says, "it's improving." ■

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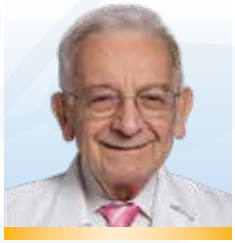

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