

OncLive[®]
PRESENTS

Giants[®]
OF *Cancer Care*

2015

C L A S S A L B U M

OncLive[®].com

INDIVIDUAL JOURNEYS, BUT UNITED BY A COMMON CAUSE

Although their individual journeys differ, what unites many in this class—the 3rd annual Giants of Cancer Care®—is their passion for research, for doing well by their patients, and for teaching future generations of Giants. It is a passion that fuels all aspects of their professional and personal lives and represents a commitment to the future of oncology. These Giants have inspired their trainees and fellow colleagues to look beyond the limitations of current treatments and to fully explore where potential new research leads.

These new Giants readily acknowledge the help of their colleagues and collaborators as advances in the field of oncology progress. Many of the Giants attribute a large share of their success not to their individual efforts but to the efforts of those who came before. It is this underlying graciousness and humility that is a testament to the greatness of character of each of these researchers and practitioners.

One of this year's Giants, Gabriel N. Hortobaygi, MD, explained that, "We all build on the observations and accomplishments of our predecessors. It's just that we had the opportunity and ability to synthesize the knowledge that existed at the time." Similarly, it's often the "fortuitous conversations" between peers and colleagues that can lead to a breakthrough, according to lung cancer award winner John Minna, MD. Or it's tackling a problem from a different angle. That's the realization Antoni Ribas, MD, had while working on how to make immunotherapy effective against cancer. His research helped identify the mechanism that tumor cells use

to avoid detection and destruction by the immune system. By developing agents that prevent tumor cells from using that defense, Ribas found ways to allow a patient's own immune system to do its job—and to do it well.

The connections in clinical research that these Giants have made often result in breakthroughs in cancer care that are both great and small. They result in patients benefiting from some shared kernel of knowledge that may not reach fruition today, or tomorrow, but almost certainly will further down the line.

In many of these profiles, we highlight the obstacles that each Giant has overcome. These challenges take many different forms—whether Giants had to flee their native countries to avoid conflict and persecution or if they had to shine a spotlight on the barriers that underserved populations face as they seek adequate cancer care. The challenges may have been personal or societal; nevertheless, these Giants were able to triumph.

Take a few minutes to read about these remarkable men and women who have dedicated their lives to overcoming cancer and bringing compassionate care to the patients and their families that it affects. These outstanding researchers and practitioners may have had different individual journeys, but they are all focused on a common cause.

MIKE HENNESSY
CHAIRMAN/CEO
MJH ASSOCIATES, LLC

TABLE OF CONTENTS

03 NOTE FROM THE CEO

06 2015 GIANTS OF CANCER CARE® ADVISORY BOARD

07 LETTER FROM THE ADVISORY BOARD CHAIR

10 BREAST CANCER

Gabriel N. Hortobagyi, MD

The University of Texas MD Anderson Cancer Center

16 COMMUNITY OUTREACH/EDUCATION

Harold P. Freeman, MD

Founder, Harold P. Freeman Patient Navigation Institute

22 GASTROINTESTINAL CANCER

Robert J. Mayer, MD

Dana-Farber Cancer Institute

28 GENITOURINARY CANCER

Maha H. Hussain, MB, ChB

University of Michigan Comprehensive Cancer Center

34 GYNECOLOGIC MALIGNANCIES

Robert C. Bast Jr, MD

The University of Texas MD Anderson Cancer Center

40 IMMUNO-ONCOLOGY

Carl H. June, MD

Perelman School of Medicine at the University of Pennsylvania

44 LUNG CANCER

John Minna, MD

The University of Texas Southwestern Medical Center

50 LYMPHOID NEOPLASMS

Emil J. Freireich, MD, DSc

The University of Texas MD Anderson Cancer Center

58 MELANOMA

Antoni Ribas, MD

UCLA School of Medicine/Jonsson Comprehensive Cancer Center

64 MYELOID NEOPLASMS

Clara D. Bloomfield, MD

The Ohio State University Comprehensive Cancer Center

70 SCIENTIFIC ADVANCES

Robert A. Weinberg, PhD

Massachusetts Institute of Technology/Whitehead Institute

74 SUPPORTIVE/PALLIATIVE CARE

Charles L. Loprinzi, MD

Mayo Clinic

80 2014 INDUCTEES

81 2013 INDUCTEES

83 INDEX

2015 Giants of Cancer Care® Selection Committee

C H A I R

Hope S. Rugo, MD

Director, Breast Oncology and Clinical Trials Education
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
San Francisco, CA

Johanna Bendell, MD

Sarah Cannon Research Institute/
Tennessee Oncology
Nashville, TN

Patrick I. Borgen, MD

Maimonides Hospital
Brooklyn, NY

Julie Brahmer, MD

Johns Hopkins Sidney Kimmel
Comprehensive Cancer Center
Baltimore, MD

Raoul Concepcion, MD

Urology Associates, PC
Nashville, TN

Massimo Cristofanilli, MD, FACP

Robert H. Lurie Comprehensive Cancer Center
Northwestern University
Chicago, IL

Myron S. Czuczman, MD

Roswell Park Cancer Institute
Buffalo, NY

Alessandra Ferrajoli, MD

The University of Texas MD Anderson Cancer Center
Houston, TX

David Gandara, MD

UC Davis Comprehensive Cancer Center
Sacramento, CA

Lori Goldstein, MD

Fox Chase Cancer Center
Philadelphia, PA

Leonard G. Gomella, MD

Kimmel Cancer Center Thomas
Jefferson University
Philadelphia, PA

Andre Goy, MD, MS

John Theurer Cancer Center at
Hackensack University Medical Center
Hackensack, NJ

Roy S. Herbst, MD, PhD

Yale Cancer Center
New Haven, CT

Corey Langer, MD, FACP

University of Pennsylvania
Perelman Center for Advanced
Medicine
Philadelphia, PA

Jason Luke, MD

University of Chicago
Chicago, IL

Eleftherios (Terry) P. Mamounas, MD

University of Florida Health Cancer Center
Orlando, FL

Maurie Markman, MD

Cancer Treatment Centers of America
Philadelphia, PA

Susan O'Brien, MD

UC Irvine Medical Center
Chao Family Comprehensive Cancer Center
Orange, CA

William K. Oh, MD

Mount Sinai Medical Center
New York, NY

Joyce O'Shaughnessy, MD

Baylor Charles A. Sammons Cancer Center
Texas Oncology/The US Oncology Network
Dallas, TX

Daniel Petrylak, MD

Yale University Cancer Center
New Haven, CT

A. Oliver Sartor, MD

Tulane Cancer Center
New Orleans, LA

Debu Tripathy, MD

The University of Texas MD Anderson Cancer Center
Houston, TX

Alan P. Venook, MD

UCSF Helen Diller Family
Comprehensive Cancer Center
San Francisco, CA

Heather Wakelee, MD

Stanford University Medical Center
Stanford, CA

Jeffrey Weber, MD, PhD

NYU Langone Medical Center
Laura and Isaac Perlmutter Cancer Center
New York, NY

Howard L. (Jack) West, MD

Swedish Cancer Institute
Seattle, WA

Nicholas J. Vogelzang, MD

US Oncology Research,
Comprehensive Cancer Centers NV
Las Vegas, NV



A WIDE DIVERSITY HIGHLIGHTS GIANTS OF CANCER CARE® AWARDS



HOPE S. RUGO, MD

DIRECTOR, BREAST ONCOLOGY

AND CLINICAL TRIALS

EDUCATION

UNIVERSITY OF CALIFORNIA,

SAN FRANCISCO

HELEN DILLER FAMILY

COMPREHENSIVE CANCER CENTER

SAN FRANCISCO, CA

This marks the third year that we honor the recipients of the **Giants of Cancer Care®** awards. They are physicians and scientists with expertise spanning a broad range of disciplines, representing some of the most important areas in cancer today. These individuals are well-recognized leaders in oncology, and we are proud to acknowledge them for their importance to us as providers and, most important, to our patients.

As chair of the Selection Committee, I am proud to commend the diligent and thorough work the members of the committee have undertaken to choose the members of the 2015 class of Giants of Cancer Care. The selection committee chose the 12 finalists from among more than 60 individuals, themselves taken from an initial collection of 200 nominees chosen from across a dozen categories.

Our selection committee has expanded since it was first convened in 2013, and its members now represent many disciplines in oncology care. As a committee, we have worked together to refine the selection, the voting, and the vetting processes for potential candidates, as well as the categories that we vote on each year. In addition, we have made changes for next year that will improve the program even more. These changes will ensure the future success of this initiative.

During the awards ceremony held in Chicago, Illinois, we honored the best and brightest physicians and scientists in the field of cancer care and research. One Giant has championed the plight of underserved populations who face many challenges in trying to obtain quality cancer care. Another Giant was a key contributor in discovering the role of the Philadelphia chromosome in patients with acute lymphoblastic leukemia. Yet another Giant recognized the individual struggle of undergoing cancer treatment by encouraging expression of that experience through creative works of art. Recognizing their collective work and the professional and personal challenges that many of these Giants have overcome to achieve what they have is the selection committee's honor and privilege.

As long as there are innovative advancements in the field of oncology, we will continue to honor the greatness of these physicians and scientists who have devoted their lives to understanding cancer and providing compassionate care to their patients. Please join me as we kick off the nominations campaign for the 2016 class of the Giants of Cancer Care at the *33rd Annual Chemotherapy Foundation Symposium: Innovative Therapy for Tomorrow* in New York City.



BREAST CANCER

Gabriel N. Hortobagyi, MD

THE UNIVERSITY OF TEXAS
MD ANDERSON CANCER CENTER

Promoted the use of chemotherapy prior to surgery

As a boy growing up in 1940s Budapest, Hungary, Gabriel N. Hortobagyi, MD, devoured as many books as he could—receiving them as gifts and tearing into biographies about physicians and scientists and learning about how science changed the world. He was prompted by his mother, Edith Nyisztor, who had wanted to become a doctor herself but never did since “it was not socially appropriate for women to go into the profession in the 1910s, 1920s, and 1930s.” Her influence was strong, though: “By the time I was in middle school, I knew I would go into the sciences and be a physician,” he said. “I never looked back.”

But social unrest in Hungary created some roadblocks. In 1949, the secret police (backed by the Soviet Union which had invaded Hungary) forced families like Hortobagyi’s into concentration camps in southeast Hungary. He was 3 years old at the time. They lived there until 1953, when the Soviet leader, Joseph Stalin, died.

“We were given amnesty that year, on the condition that we could never return to Budapest,” said Hortobagyi. “My parents could not get a job in any supervisory positions, and neither my sisters nor I were allowed to finish our education. Had I stayed in Hungary, I would have been a driver or a street sweeper.”

Instead, his family moved to Vienna, Austria, where Hortobagyi, at age 10 didn’t know

enough German to attend school, so he remained in a refugee camp. By 1957, his family emigrated to Bogota, Colombia, where he was able to continue elementary, then middle and high school, at the private school Colegio Helvetia, from 1957 through 1963, graduating in 1963. He then attended the Universidad Nacional de Colombia, a public medical school in Bogota that offers admission to 120 students, out of more than 6000 applicants.

His family's foresight to move to where the opportunities are is just one example of a thread that's been woven throughout Hortobagyi's life and career as one of the world's foremost breast cancer researchers and clinicians: to go where it's possible to make great things happen. Doing so was just an early step in his life: "I was able to surpass what could have been a completely different path in life to help countless breast cancer patients, train hundreds of clinicians in the field, and create lifesaving drug regimens that have helped transform the field of oncology from a hopeless one to one bursting with potential and lifesaving treatments," he said.

After finishing medical school, he accepted an internal medicine clinical residency at St. Luke's Hospital, Case Western Reserve University in Cleveland, Ohio. Why the move from Colombia to Cleveland? The program paid its residents a third more than any other residency program Hortobagyi had considered. The city also boasted a large Hungarian population at the time, giving him "a certain sense of comfort," he said.

CURIOUS ABOUT CANCER

The Case Western residency was the launching pad for Hortobagyi's earliest interest in oncology. In the 1960s and early 1970s, "there was no such thing as oncology, and I had not given a single thought to cancer," he said. When physicians went on rounds, cancer patients "were mostly looked at as 'here are the people on

death row; it's just a question of time before they die and there is nothing we can do about them.' If there were patients with cancer on rounds, we would skip to the rooms to someone curable. You didn't want to tell someone, 'You're just going to die of your disease.' If you're not trained for that, it's very difficult."

But in 1972, his second residency year, Hortobagyi received a flyer about a cancer conference at the Ohio State University in Columbus, Ohio; intrigued, he went. "It was a life changer," said Hortobagyi. After the "boring talks about how lung and colon cancer kills everybody, Emil J. Freireich, MD, DSc, (a University of Texas MD Anderson Cancer Center researcher and fellow 2015 Giants of Cancer Care recipient) gave this electrical dynamic speech. He said, 'We are curing acute leukemia of childhood, and Hodgkin's, and we are well on our way to fighting cancer. We are going to lick this disease.'"

Hortobagyi was transformed.

"This presentation woke me up and knocked the socks off my feet," he said. "I realized this was the next frontier." Upon returning to Cleveland, he wrote a letter to Freireich, asking if there were any openings in MD Anderson's training programs. There were—and Freireich instructed Hortobagyi to come down south.

It seemed to be an unusual move, and one he wasn't entirely prepared for, in at least one sense: "I packed all my belongings in my trunk—I had a '71 Dodge Challenger that didn't have air conditioning," he said. "I was going to die in Texas without air conditioning." And his colleagues wondered about his motivation, too. "My training companions in Cleveland asked, 'Why on earth are you going to Texas? You can't shoot. You don't speak proper English.' I didn't know, but I cannot tell you the sense of excitement I had—that we are going to take care of this and we are going to cure cancer."

Before he left Cleveland, though, he oversaw some direct care

for 2 patients with widespread metastatic breast cancer that had also spread extensively to the bone. “There was no way to support them, and they didn’t have good pain medications—it was horrible,” Hortobagyi recalled. But he remembered reading an abstract from a few years before that discussed a cocktail of 5 chemotherapy drugs that offered a 90% remission rate. “I was very excited for that, but my boss said, ‘Don’t get excited; leave them alone.’” But I wrote a chemotherapy prescription for them, and the assistants shrugged, and gave the patients the chemotherapy. I was almost expelled from my program for it, for being “in contempt of court.” But my saving grace was that both women responded to the treatment and walked out of the hospital. That pretty much sealed my passion for treating breast cancer.”

FURTHERING THE CANCER FIGHT

Once at MD Anderson Cancer Center, Hortobagyi took in all he could about breast cancer and knew he had found his passion. “It’s a fascinating disease,” he said. “Some people will die in 6 months and others [will] live the rest of their lives. Some respond to hormones and there’s an endocrine part of it. There were a lot of issues in the development of oncology, with cytotoxic agents and immunotherapy. It brought together a number of disciplines. I

never really gave a second thought to brain tumors or cancers of the left big toe. It was so obvious that I was fascinated by breast cancer.”

He moved up through the academic ranks, from instructor to professor and eventually, became the director of the entire breast cancer research program. Throughout that time, he helped pioneer various drug treatments for breast and other cancers. They included giving patients chemotherapy before surgery to remove tumors, rather than afterwards; chemotherapy before surgery has since become the standard of care for many different types of cancer. He also helped develop the practice of adding bisphosphonates to treatment regimens to care for bone metastases. And he also introduced numerous cancer drugs, including tamoxifen, Taxol, Taxotere, cisplatin, and a number of other hormones now used regularly for cancer treatment. But he noted that such accomplishments are based on what others have done before him. “It’s hard to think of science in terms of ‘you invented something,’” he said. “We all build on the observations and accomplishments of our predecessors. It’s just that we had the opportunity and ability to synthesize the knowledge that existed at the time.”

His colleagues, however, are more likely to sing his praises. “To my point of view, he is one of the greatest oncologists in the world





NDATION
D'ASTUCE PARLANT
avec
et la ne plus faire que le cancer

XVe anniversaire de la Charte de Paris contre le cancer
Château de Versailles
2 février 2015

and THE best specialist of breast cancer,” said David Khayat, MD, PhD, the head of the Medical Oncology Department at Pitié-Salpêtrière Hospital and an oncology professor at Pierre and Marie Curie University, both in Paris, France. “His contribution to this field is tremendous: from primary chemo (neoadjuvant) to the role of platinum in breast cancer. He contributed to the development of a huge number of new drugs in this indication, including the taxanes, vinorelbin, anthracyclines, bevacizumab, pertuzumab.”

Such accomplishments are a testament to Hortobagyi’s life philosophy of perseverance: If at first you don’t succeed, try, try again. “One of the most important things for progress and for success is to fail,” he said. “If you have not failed, you haven’t tried. And if you haven’t failed, you are not thinking outside the box. Failure is an important part of life and progress and makes life exciting.”



SHARING KNOWLEDGE

Hortobagyi’s days are packed with intention and activity. After arriving in the office between 6:30 or 7 AM, he drinks his third cup of coffee of the day, organizes his thoughts, and decides what his 3 priorities of the day will be. While some days are filled with meetings and/or projects, he sees about 25 patients each week during a 1-day clinic on Thursdays. “When I’m there, I focus entirely on that,” he said. Patient care is a particular interest, noted colleague Cliff Hudis, MD, chief of the breast service and the institutional vice president of governmental relations at Memorial Sloan-Kettering Cancer Center in New York, New York. “It is clear he is devoted to the well being of patients and the patient experience is always front and center for him,” he said. “He’s extraordinarily warm and caring. He gets a tremendous pleasure out of sitting with patients, talking, and interacting with them.”

Such empathy and care extends to Hortobagyi’s trainees, too. By his own estimation, he has taught more than 500 oncologists over the years, including a few dozen who “now populate the department that I think is one of the top breast cancer centers in the world, with translational research and superb care for patients,” he said. Such influence extends across the United States and around the world.

“Because of his leadership at MD Anderson Cancer Center and internationally, he is as responsible as anybody for a large cadre of doctors who work in breast cancer and other cancers,” said Hudis. “He is a model, clinically, for hundreds of people. He has had a reach that extends far beyond the walls of his office or institution. He is one of the most recognizable names in cancer medicine around the globe.”

While he has mentored many, Hortobagyi himself cites several mentors who have taught him in different ways over his life. “I used to think of mentorship as a giant who takes you under his or

her wings, but it turns out there are many forms of mentorship,” he said. “Lots of people influence your career in many ways. Some are peers who unknowingly influence your career or profession, and some are ahead of you and some are younger.”

He cites MD Anderson Cancer Center colleagues such as former president John Mendelsohn, MD, and head and neck oncology physician and professor Waun Ki Hong, MD, FACP, his close friend for decades, as his own mentors.

“They have introduced me to many people, and have opened my eyes to different ways of dealing with different people, and being strategic about how to conduct business,” he said. But even patients can teach physicians. Hortobagyi cited one woman, a breast cancer patient he saw 20 years ago, who would come to see him regularly from Germany. She would ask for his clinical recommendations, but then go against them entirely, “doing exactly what she pleased.” For a decade, this continued, and Hortobagyi grew frustrated. Finally, he asked her why she would waste her time, and his, likely at great expense as she traveled to see him from Germany, to seek his insights. “You obviously don’t care about my opinion,” he said.

But to his surprise, she said he had her all wrong, she greatly respected his opinion, but that she ultimately made her own decisions about her life. “It made me understand that I can serve people in many different ways,” he said. “It is not about me telling people what to do. And she eventually did quite well in spite of not following my clinical advice,” he said.

He also counts his wife, Agnes, 62, a former fashion buyer, radio personality, and a one-time officer for the Harris County (Texas) Medical Alliance, as one of his biggest mentors, as well. They met on a blind date while in Toronto, Canada, at a conference in 1976, Hortobagyi asked her to marry him on their second date, and 6 months later, they were. “She has been a real

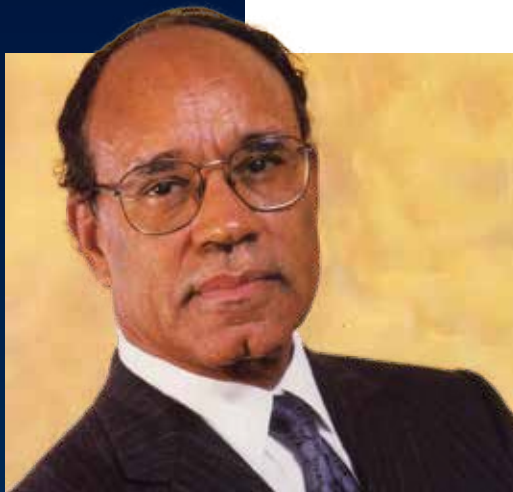
partner,” he said. Together, they have 3 daughters, Zsuzsanna, 37, a rheumatologist at Johns Hopkins University, Baltimore, Maryland; Krisztina, 35, a human resources executive for Ranger Offshore, an oil company in Houston; and Monica, 32, a journalist in Washington, DC. His family has helped play a pivotal role in his success.

“I have been privileged to have a very stable home and emotional life, with full and dedicated support from my family, especially my wife,” he said. “I wonder how people who don’t have that have accomplished what they have—it must be incredibly difficult.”

With such accomplishments supported by a strong family, Hortobagyi is thoughtful about what the future of cancer research holds. “We are accelerating the pace at which we understand the biology of breast cancer and developing treatments based on that,” he said. “For much of my career, we have been using a sledgehammer to treat a fly. Now, we are at a level of a high quality development of science that is individualized and personal. Treatments will become more effective and less toxic to patients, with a lesser effect on their quality of life. And that is just marvelous.”

He’s honored to be a part of it all, as well—always continuing to seek out opportunities to help make progress happen.

“It is an incredible privilege to spend your career doing what you want to do,” he said. “I would gladly do what I do for free, but I get paid for it. My life has been an incredible privilege, especially for the foresight of my parents—to take me out of where I was. I have great friends, great family. Without all that, I would be collecting garbage or sweeping streets and being bitter about my life.” ■



COMMUNITY OUTREACH/EDUCATION

Harold P. Freeman, MD

FOUNDER, HAROLD P. FREEMAN
PATIENT NAVIGATION INSTITUTE

The architect of patient navigation

When Harold P. Freeman, MD, began visiting American cities more than 25 years ago to learn about the effects of race and poverty on cancer outcomes, few people were talking about disparities in access and care.

By the end of his seven-city tour, Freeman, who was then president of the American Cancer Society, not only had enough testimonies from patients with cancer and their families to form a groundbreaking portrait of the challenges that poor people face in obtaining care, he also had a sharper vision of the patient navigation concept that he would pioneer.

Throughout a long and storied career in medicine, Freeman has met 5 US presidents, including 3 whose cancer panels he chaired, worked alongside celebrities such as LeBron James and Kareem Abdul-Jabbar, and was so well known that then-candidate Barack Obama remembered the first time he met Freeman better than Freeman remembered meeting him. His efforts have been recognized with a Lasker Award for public service, the American Cancer Society's Medal of Honor, a special award from the American Society of Clinical Oncology, and a host of other honors. In June, Freeman won a 2015 Giants of Cancer Care Award in the Community Outreach category.

Through it all, Freeman has been motivated by the needs of the patients that he met in his daily practice, starting in Harlem in the late 1960s, and has not stopped focusing at-

OncLive
PRESENTS
Giants
OF *Cancer Care*
INDUCTEE
2015

tention on his core mission of improving access to care for people regardless of economic status.

“You shouldn’t die, because you are poor, from cancer or anything else,” he said. “Patient navigation is one of those elements that, in my view, tends to temper the point that we have great systems, wonderful specialists, powerful cancer centers, and we say we can give the best care in the world—but they don’t say what they should say, which is, ‘If you can pay for it.’”

PATIENT NAVIGATION TAKES HOLD

At the age of 82, Freeman spends most of his time teaching and promoting his signature idea of patient navigation—systems through which trained nonprofessionals and oncology care providers help patients with cancer to obtain the care they need in timely fashion throughout their journey. The Harold P. Freeman Patient Navigation Institute in New York City trains nurses and other healthcare providers and community members in how best to guide patients through the continuum of cancer care, from outreach efforts to the finding of abnormalities to timely diagnosis and treatment. Individuals who complete the 2-day training program receive a certificate in patient navigation.

Although Freeman developed the concept for patients with cancer, the institute has expanded the model to include managing individuals with other chronic conditions, such as diabetes, heart disease, infectious diseases, and mental health conditions. In essence, patient navigation is about helping patients overcome barriers to care, whether they are complex barriers involving fear, knowledge, and a lack of insurance coverage or easier-to-solve obstacles, like getting to appointments.

“Whatever the barrier is, it’s the navigator’s job to solve it, so the patient can move in a timely way from the point of finding to diagnosis and treatment,” Freeman said. Beyond that premise,

navigators are trained to “virtually integrate” the fragmented healthcare system for each of their patients, he said.

Under Freeman’s concept, the level of professional training that a navigator needs depends on the stage at which he or she would be helping patients; oncology nurse navigators, for instance, would step in to assist patients in understanding the implications of their diagnosis and the recommended treatment plan. Freeman initially developed his navigation ideas to help people without economic resources gain access to care. A 2005 federal law established demonstration programs in medically underserved communities help foster his concepts.

Since then, elements of patient navigation have been embraced by cancer centers throughout the country. The American College of Surgeons has made a patient navigation process part of its accreditation standards for hospital cancer programs.

Freeman believes that patient navigation system is particularly helpful in guiding patients through the highly specialized health care system. “We don’t have a system that is necessarily friendly to the movement of the individual through a complex journey, including things that have to happen in the community early on, such as the outreach element, and then the clinical element getting from finding to treatment and followed by supportive care back in the community,” said Freeman. “We’re concentrating on specializing.”

However, funding to help healthcare providers with the cost of patient navigation is insufficient, Freeman notes. Although the Affordable Care Act, signed into law in March 2010, extended funding for one federal initiative, it did not make navigation a billable service.

“I think there is a lot of evidence that patient navigation helps patients. The next set of questions is, at what cost? I believe the evidence is coming in more and more than not only is it a good



OncoLive
PRESENTS

Giants
OF
Cancer Care

thing related to patient outcome, because you'd have one-on-one attention to a person moving through a complex system, but it appears that evidence is coming that it is saving resources and saving money," Freeman said.

For healthcare providers, the benefits of having trained navigators may include increased patient retention, diagnostic, and treatment resolution rates, as well as improved organizational efficiencies—such as boosting the rates of patients who actually show up for their appointments—thus preventing lost revenues and ultimately increasing revenue. Interestingly, Freeman notes, the positive benefits of patient navigation have been scientifically proven after the program was initiated in response to the needs of patients in a community, reversing the standard sequence in which evidence is required before ideas are studied.

"The practice preceded the evidence and to me that's kind of an intriguing change of the usual course of things," said Freeman. "If patient navigation came out of a neighborhood and a community and then was later evaluated and proven, for the most part, to be a sound concept, I kind of wonder whether there may be a lot of other things that are going on and being practiced around parts of the country or the world that never get a chance to be evaluated and valued."

ACTING ON WHAT HE SAW

When Freeman reflects upon the trajectory of his life, he often thinks of it in terms of Einstein's

theories about the nature of existence as part of a space–time continuum.

"What you see depends on where you stand," Freeman explains. "That is a good way to look at my life because I stood in a world that made me see things differently. I came up in a world of people having problems—segregation, racism, and there was poverty.

"Then I got a chance to be educated and then I have a chance to reflect back on, not just my little part of the world where poor black people in a particular community were having problems, but also sought to understand the universal meaning of these circumstances," said Freeman. As an important recognition of his contributions, Dr. Freeman was named a Lasker laureate for "enlightening scientists and the public about the relationship between race, poverty, and cancer."

Freeman's beliefs were framed by a sense of pride and responsibility stemming from his family history. His great-great-grandfather was a plantation slave in North Carolina who bought his freedom in 1838 with \$3000 saved from carpentry work done on the side. He called himself 'Freeman' when he became free. His great-granduncle, Robert Freeman, the son of a slave, graduated from Harvard Dental School in 1869, becoming the nation's first black dentist and also the grandfather of Robert Weaver, the nation's first black cabinet member. Like Freeman, his grandfather was a physician.

"I'm looking at an ancestor who came out of slavery and raised a family, where his son became a dentist and who owned a home in Washington,

DC, by 1845, seven years after coming out of slavery,” Freeman said, explaining where he gets his inspiration. “If he did that, I’m challenged to do a lot more. So that’s a good thing for me to think about.”

Freeman was 13 when his own father—who put himself through law school by working extra shifts at night—died of testicular cancer. His mother, who was a schoolteacher, struggled financially to raise her 3 sons.

Schools were still segregated when Freeman was growing up, but he was able to attend the Paul Laurence Dunbar High School, an aca-

demically elite institution for black students. He also earned a scholarship to The Catholic University the tennis and basketball teams. Freeman later qualified to play in US national tennis championships for 3 years in the 1950s Freeman was inducted into its Athletes Hall of Fame at Catholic University.

After obtaining his medical degree from Howard University in Washington, DC, he went to New York to train in cancer surgery at the renowned Memorial Sloan Kettering Cancer Center (MSKCC) and to work in the predominantly poor and black community of Harlem, where he believed he could make a difference.

STARTLING DISPARITIES IN CARE

In 1967, Freeman became an attending cancer surgeon at Harlem Hospital, ready to put his skills and education to work. Yet he found that patients, particularly women with breast cancer, were arriving in his clinic with disease too far advanced for effective treatment, including “some women who came in at a stage in which cancer had replaced the breast,” Freeman recalled.

“That was a turning point for me—women coming in that late,” he said. “So I began to look at who these people were and what were their circumstances. And it turned out that these women were all poor and all black. So I began to look at the meaning of poverty and race.”

Realizing that a lack of access to early detection, including mammograms was part of the problem, Freeman set up free breast cancer screening clinics in Harlem, first pushing the rules to offer the service on Saturdays at Harlem Hospital and later obtaining funding for off-site breast cancer screening. However, although support for such community-based screening programs increased in New York state, Freeman knew that impoverished patients faced many more barriers to care.

Through his work in New York City, Freeman saw those needs



firsthand. He served as director of surgery at Harlem Hospital from 1974 to 1999, when he also was a professor of clinical surgery at Columbia University College of Physicians and Surgeons. He was becoming a leading authority on the interrelationships between race, poverty, and cancer at a time when such matters were not commonly discussed. In the late 1970s, he became a member of the American Cancer Society's (ACS's) board of directors; he then led the society's initiative on cancer among the nation's poor. In 1988, he was named the ACS's national president.

Freeman also has served as chairman of the President's Cancer Panel, on which he worked under presidents George H. W. Bush, Bill Clinton, and George W. Bush. He is also the founding director of the National Cancer Institute's Center to Reduce Cancer Health Disparities.

A LITTLE BIT OF LUCK

Amid such a record of achievement, Freeman acknowledges a sense of tremendous accomplishment—but does not attribute the credit solely to his own efforts. “Things don’t happen always by how hard you work,” he said. “You also have to be lucky.

“Some of this is based on working hard and having the right idea,” Freeman added. “Some of it is related to what happened to allow you to do what you do. I did some hard work, but I got promoted to places of authority that allowed me to say to a broader audience what my thoughts were.”

Freeman credits 2 people in his life for helping him reach those heights. The late Arthur I. Holleb, MD, a surgical oncologist at MSKCC hailed for his efforts to promote Pap smear screening for women, encouraged Freeman to pursue his career at that institution. Holleb later helped Freeman become a board member and president of the ACS. Then there's Freeman's mother, Lucille Thomas Freeman, who encouraged him not only to obtain an education and play tennis, but also raised him as a devout Catholic.

“I wouldn't say I am very religious at this point” but the influences of his faith are ingrained in him, said Freeman. “When I was young, my mother would say you have to drink milk. It wasn't always a quart of milk, but I had to drink a lot of milk every day. At a certain point when I became 13 or 14, I would tell my mother I don't want to drink milk that much anymore. She was OK with that—she said the calcium is in your bones.

“I think you can stop drinking milk at the age of 14 and still have strong bones,” he continued. “I think that's true of religion and other things that happen—that's the way I think about it. How you are raised becomes so critical in what you become with respect to being fair, being concerned about people who don't have resources, coming out of a segregated life, and finding your way to believe that you should care about everybody who is disadvantaged.”

These are the values that have influenced Freeman's life and that have made a compelling difference in his work. ■



GASTROINTESTINAL CANCER

Robert J. Mayer, MD

DANA-FARBER CANCER INSTITUTE

*Improved treatment approaches to colon and rectal cancer,
and to pancreatic cancer*

Oncology and hematology arguably attracts more research funding, more media attention, and more talented minds than any other medical specialty—but that wasn't always the case. When Robert J. Mayer, MD, graduated from Harvard Medical School in 1969, the profession was just emerging from its infancy. Its training programs were still a work-in-progress, and it struggled to attract top researchers.

Thousands of people deserve some of the credit for changing that reality, but Mayer deserves a particularly significant share. He has, like all Giants of Cancer Care, published important papers. Indeed, Mayer's research has helped create standards of care for leukemias and gastrointestinal cancers. Perhaps more importantly, though, Mayer has spent much of his career working to improve and expand the entire field of oncology and hematology. He was a key architect of one of the first postgraduate training programs in cancer, a tireless worker for the development of professional groups such as the American Society of Clinical Oncology (ASCO), a catalyst for the increased specialization among cancer doctors, and a mentor to hundreds of young physicians from institutions all around the world. He was, in other words, a driving force in the professionalization of an entire specialty.

"Bob has a commitment, not only to cancer patients and cancer research, but to the

field of oncology itself. He is just one of life's natural mentors, and he has mentored individuals at his own and at other institutions," said Alan Venook, MD, the Madden Family Distinguished Professor of Medical Oncology and Translational Research at the University of California, San Francisco.

"I first met him when a flight cancellation stranded us both at Frankfurt Airport on the way back from a conference where I'd done a small presentation. He was already well known and I was just a very junior researcher. He introduced himself and we spent the day looking for a way home while we talked about my research and my interests. Within a week of returning to San Francisco, he had appointed me to a committee. He basically mentored me from across the country. He gave me the opportunity to do truly meaningful work far faster than I could have done otherwise, and he has done the same for a number of accomplished researchers."

A COMMITMENT TO MENTORING

Mayer's commitment to mentoring may stem from the difference between his years as a college undergraduate and his years as a medical student. During the former, Mayer developed a deep and lasting relationship with a faculty advisor who helped him make the most of his time inside and outside the classroom. During the latter, Mayer's advisor left a few months into his first year, and the school did not replace him.

Mayer overcame that challenge, of course, but he had always been unusually bright and energetic. Born to Jewish immigrants who fled Nazi Germany for Long Island in the late 1930s, Mayer decided at an early age to follow in his father's footsteps and become a doctor. He graduated first in his high school class and went on to be a standout undergraduate at Williams College before moving on to Harvard Medical School and a residency at



Mount Sinai Hospital in New York. He then took a fellowship at the National Cancer Institute (NCI), both because it was then the world's leading center of cancer research and because the job fulfilled military obligations that might otherwise have sent him to Vietnam.

Mayer says he learned more about medicine in a few years at the NCI than he did in all his prior medical training. He was soon, however, on his way back to Boston, when Emil Frei, MD, offered him a job at a new cancer center that Harvard was building. It was only a 1-year fellowship, but Mayer so enjoyed working at



NOVARTIS

MERCK



Giants
Cancer Care

OncLive

OncLive

NOVARTIS

Giants
Cancer Care



MERCK

OncLive



OncLive
PRESENTS

Giants
OF
Cancer Care

the what would come to be known as the Dana-Farber Cancer Institute that he has stayed for an extra 40 years (and counting).

“The NCI was a wonderful place to treat patients and do research, but it had no ties to any medical school and it trained no residents, so it was really missing most of the teaching component that had been integral to academic medicine for more than a century. What’s more, virtually none of the academic centers with medical schools and residency plans had programs focused on oncology and that’s what Dr. Frei wanted to create at Harvard and Farber. I believed it was vitally important to teach doctors far more about cancer than they were learning, so I very much wanted to be a part of that effort.”

A GROWING FIELD

It is hard to imagine now how quickly the field of cancer medicine has grown over the past several decades. Another of this year’s Giants, Emil Freireich, recalls that as late as the 1940s, the entire medical school curriculum on systemic cancer could be boiled down to a couple sentences: there is no treatment. Just keep your patients comfortable. In addition, less than 20 years elapsed between Sidney Farber’s discovery of the first antifolate treatment and the first treatment that could cure some cases of acute lymphoblastic leukemia (ALL). Less than 30 years elapsed between Farber’s break-

through experiment and the development of a broad spectrum of treatments for many more malignancies.

By the time Mayer returned to Boston in 1974, millions of patients who would have quickly died from their disease in years past were demanding newly developed forms of effective cancer treatment, but virtually no doctors were trained to provide them. What’s more, the Nixon Administration was pouring billions of dollars into cancer research (back when \$1 billion was worth more than 5 times as much as it is today), yet there were hardly any researchers who had enough experience in cancer biology to use the money wisely.

Mayer launched a medical oncology fellowship program in 1975 that brought advanced cancer training not only to Dana-Farber, but also to Brigham and Women’s Hospital and Massachusetts General Hospital. He also helped design the first oncology and hematology curriculum at Harvard Medical School and define the hematology and oncology rotations for residents at all of Harvard’s hospitals.

BIRTH OF ASCO

As he was doing this, Mayer was also active in supporting ASCO, the professional organization of cancer specialties. He has, in the past 40 years, held every conceivable position at ASCO. He has recruited members, shaped its system for adopting standards of care, designed educa-



tional programs for members, and has raised millions of dollars. He has even headed the entire organization. In 1974, when Mayer attended his first ASCO meeting, there were only 250 members in attendance. They could all go out for a drink together in a single large bar. Today, ASCO has more than 35,000 members, and colleagues say Mayer deserves as much credit as anyone, both for the organization's growth and for its success in disseminating best practices.

Colleagues also say that Mayer deserves praise for his skills as a clinician.

"Any discussion of career achievements tends to get focused, with some justification, on things that affect large numbers

of people: breakthroughs made, protégés trained, organizations built. They often don't mention whether a great doctor was actually a great doctor, but any piece on Bob should mention that he is truly great at treating individual patients, as good as any clinician I have seen," said George Canellos, MD, who ran Dana-Farber's Division of Medical Oncology from 1975 to 1995.

"My mother-in-law had a serious blood disorder. She went to see another doctor, who was probably better than average, but he still wasn't equipped to make a plan for managing such a complex disorder and to communicate the plan to her. She was depressed. She was confused.

She was giving up hope. I told her to go see Bob, and the next time I saw her, she seemed like a new woman. She understood her situation and the plan for treating it. She was even optimistic. I asked her what had happened during her visit with Bob and she said, 'It was like being in a downpour and having someone open an umbrella over my head.' That's the best description I've ever heard of a great clinician, and that is exactly the sort of impact Bob has on a lot of patients."

Mayer's commitment to education, clinical care, learned societies and other interests, which range from being the dean for admissions at Harvard Medical School to serving as a trustee for the Boston Symphony, have not prevented him from doing significant research. To the contrary, he has spent the past 45 years

publishing papers that at first ranged from basic research to trial results in both leukemia and gastrointestinal cancer and then—after Mayer decided that an increasing knowledge base demanded greater specialization—focused exclusively on gastrointestinal cancers. There are many who believe that Mayer’s very public decision to specialize convinced many other academic physicians to do likewise and, as a result, brought increased research and treatment expertise to every tumor type.

THE HIDAC REGIMEN

The best known of Mayer’s papers tend to be those that report on trials of new drugs and new treatment protocols. In 1994, for example, he led a group that demonstrated the efficacy of the high-dose cytarabine (HiDAC) regimen for some patients with acute myeloid leukemia (AML); that treatment is still used today in many patients who have AML. In the years since then, Mayer has conducted trials that have determined optimal postsurgical treatment for patients with cancers of the colon and rectum. He also led a recent research effort that demonstrated the effectiveness of a novel drug—TAS-102—in the treatment of refractory colorectal cancer.

Looking forward, Mayer sees a wide range of interesting research topics. He is (like nearly everyone else in the cancer world) excited about the incredible results seen with drugs that modulate the immune system, and he is interested in developing better ways to determine, in advance, which patients will respond. Indeed, much of his focus these days is on learning useful



ways to differentiate gastrointestinal cancers and finding which treatments work with specific tumor subtypes. That said, such research efforts will not crowd out his other activities.

“There are times when I think that I have spread myself too thin over the course of my career, that I might have accomplished more if I had concentrated my efforts on just a couple of fundamental activities. Most of the time, however, I feel that the variety has kept me from burning out and that each thing I do makes me better at the others. Working with patients makes me a better researcher. Doing research and editing journals keeps me up-to-date with what students need to know and how I should treat patients,” Mayer said. “There are certainly benefits that come with specialization, but there are also benefits that come with living a well-balanced life.” ■



GENITOURINARY CANCER

Maha H. Hussain, MB, ChB

UNIVERSITY OF MICHIGAN
COMPREHENSIVE CANCER CENTER

Translates scientific discoveries into clinical advances

Life hasn't always gone as planned for Maha Hussain, MB, ChB, FACP, FASCO. When she graduated from Baghdad University College of Medicine in June of 1980, Hussain thought she had everything figured out. She would complete her residency at the main teaching hospital in Baghdad and then join her new husband, also a doctor, who was heading to England for a few years to finish their training. After specialization, the 2 would start their careers in Iraq. Hussain had her heart set on becoming a hematologist. But the start of the Iraq-Iran war changed everything.

"We began hearing about the troops amassing on the borders between Iraq and Iran. Literally, within 3 days, I had to decide if I was going to join my husband and leave Iraq for England," said Hussain. "This was the era of Saddam Hussein and all the political unrest and brutality of the regime. It was a lot of pressure to decide what to do, but we could sense that a war was coming."

Hussain made the difficult decision to leave her home in Aug. 1980, escaping just five weeks before the war began. The couple planned to return and rebuild their lives in Baghdad once it was safe again. That day never came.

FINDING HER INSPIRATION

Today, Hussain is the Cis Maisel Professor of Oncology and a professor of medicine

and urology at the University of Michigan. After first joining the university in 2002, she now she serves as the associate director for clinical research and co-leader of the Prostate Cancer/GU Oncology Program at the University of Michigan Comprehensive Cancer Center. She has made significant contributions to the field of genitourinary (GU) cancer, particularly prostate and bladder cancers, where her work has led to changing the standards of care for patients with metastatic prostate cancer.

“I am first and foremost a physician,” said Hussain. “I’ve also been fortunate to be able to participate and lead clinical trials, translating the ideas that I’ve come up with both at the national and international levels,” said Hussain. “We have been able to affect the field in terms of managing advanced prostate cancer and really push the envelope with regard to developing new treatments. I am proud of that.”

Getting to where she is today did not come without its challenges. A few years after leaving Baghdad for England, Hussain and her husband made another international move, this time to the United States. One of Hussain’s uncles, who was also a doctor, lived in Michigan, so the couple settled there in 1983. At the time, there were not many other people of Middle Eastern descent in Michigan.

“It was not very easy to establish another new life in another foreign country,” said Hussain. “However, very soon after arriving, we ended up loving Michigan and the United States, the people, and the style of living. You could make friends easily and integrate. Although the language and the society culture are different, people are the same everywhere.”

After completing her training at Wayne State

University, Hussain took a job as a staff physician in the Hematology and Oncology Department of the VA Medical Center in Detroit, where she stayed for 10 years. Working with veterans was an experience that had a significant impact on her life, both personally and professionally, said Hussain.

When she first started at the VA, Hussain wasn’t sure how her patients, many of whom served in the military in the Middle East, would respond to a female Iraqi physician.

“My last name, Hussain, sounds the same as Saddam Hussein,” said Hussain. “You can get singled out immediately as a foreign person with a funny name and a name that is not really favorable because of its similarity with an evil person’s name.” But her patients’ reaction to her ethnicity surprised her.

“Not only were these men supportive of me as their doctor and allowed me to take care of them, but they showed genuine concern about my family who were still in Iraq,” she said. “People wrote me letters, telling me not to worry, reassuring me that



they had my family in their thoughts and they were praying for my family. It wasn't just patient to doctor, it was human being to human being and that was amazing." That strong connection with her patients who were military veterans, many who were fighting losing battles with GU malignancies, motivated Hussain to refocus her career goals.

"At the time I started, there weren't that many research opportunities or treatment opportunities within GU malignancies," said Hussain. "I became really fascinated by the biology of prostate cancer and how little we had to offer patients with metastatic disease."

At the time, prostate-specific antigen testing was just beginning to become more commonplace, said Hussain. Many of her patients presented with advanced cancer and had limited treatment options. Hussain made it her goal to discover novel treatments that offered hope to these patients.

"I started my career in the laboratory asking questions about micrometastases in the setting of prostate cancer," she said. "I published on the subject early in my career. As I got more involved with patients, I became more interested in clinical research. Ultimately, my goal was and is to help patients."

Her contributions as a clinical researcher and leader led in part to the 2004 FDA approval of docetaxel, the first drug to

demonstrate a significant survival advantage for men with advanced resistant prostate cancer. She has also led studies that defined the role of intermittent androgen deprivation and, more recently, was part of the team that demonstrated docetaxel's significant survival impact in patients with hormone-sensitive metastatic prostate cancer. Hussain, in collaboration with colleagues across the country, has also facilitated national research through various leadership positions, including as co-chair of the Prostate Cancer Subcommittee of the Southwest Oncology Group (SWOG) GU committee. She has served as a member for several years on the Integration Panel of the US Army Medical Research and Materiel Command Prostate Cancer Research Program and as its 2013 Chair, and as a member of the National Cancer Institute's prostate cancer task force, among other scientific leadership roles.

In her current role at the University of Michigan, Hussain launched first-of-their-kind novel clinical trials investigating therapeutic targeting of molecular alterations in prostate cancer. On top of her research contributions, she also teaches, mentors, and continues to see patients, primarily those with prostate and/or bladder cancers.

In addition to her patients, Hussain said she has been inspired by a number of col-





NOVARTIS



Giants
Cancer Care

OncoLive

On



NOVARTIS

NOVARTIS



Giants
Cancer Care



OncoLive
PRESENTS

Giants
Cancer Care

OncoLive



leagues, including those she met during her fellowship and tenure at Wayne State University, in SWOG, and in her current position at the University of Michigan.

“I have been quite fortunate because we have a tremendous team here in the clinical area, the translational area, and in basic science,” said Hussain. “The fascinating part about the University of Michigan is that we have tremendous strength in many schools. The depth is really amazing.”

WORKING IN A “MAN’S WORLD”

Being a female GU specialist has also presented some unique challenges of its own. When Hussain first started working with prostate cancer and other GU patients, she could count on one hand the number of other women in her industry.

“There was a perception that maybe women can’t deal with male-type malignancies,” she said. “It can be challenging trying to manage male-related disease with all of the issues involved with it—impotency, incontinence, etc—issues some patients

could be uncomfortable talking about with a female doctor.”

Despite this, Hussain said she was welcomed with open arms by both the patients and her male colleagues.

“My interactions over the decades have been wonderful,” she said. “I do not feel, by any means, that because I am a woman that my patients did not value my expertise and care or that my colleagues valued me any less.”

Today there is a growing number of women entering the GU field.

“What I tell other women is the most important thing is that you love what you do and that you are

passionate about it,” said Hussain. “You have to be attracted to the field itself. The fact that you’re a woman or a man, it doesn’t really matter. What people are looking for is the human side and the intellectual side of the person who can contribute to science and patient care.”

EVOLUTION OF PROSTATE CANCER TREATMENT

The treatment of prostate cancer has come a long way since Hussain began her career. In the 1980s and 1990s she recalled telling patients with metastatic disease that they would not likely live more than 2 years.

“When I was a resident, we had patients being admitted through the emergency room that were diagnosed there with what appeared to be metastatic prostate cancer,” she said. “The cancer would respond to hormone treatment, but at the time, the main hormone treatment was actually surgical castration, and the minute the cancer became resistant to hormone treatment, patients had, on average, only 9 months left to live.”

Today patients with new metastatic disease are likely to live an average of 4 years, and when the cancer becomes resistant to hormone treatment, there are multiple options available to them. Despite advances, however, over 27,000 men per year still die from prostate cancer, said Hussain, so much more work needs to be done. Survivorship and quality-of-life issues also need more attention, as men are living longer with the disease. The understanding of prostate cancer has become more advanced in recent years, said Hussain.

“We are really starting to understand the complexity of prostate cancer and why it is that some cancers are resistant to certain treatments,” she said. “The investment in research and the partnership with patients in clinical trials makes it possible to change prostate cancer into a chronic disease with the hope of a cure. I think that can be a reality in the near future, hopefully before I retire.”

Future goals for Hussain outside of work include continuing her hobbies of reading, gardening, photography, cooking, and

traveling and spending time with her husband, her 2 grown children, family, and friends. She is still in touch with family and friends in Iraq, Europe, and the United States and has even reconnected with her medical school class of 1980 via Facebook, despite never being able to return because of safety issues.

Hussain hopes to someday return to Iraq and contribute in whatever way she can. She has an immense respect for the people that work and live there despite its challenges, but said that after over 30 years of living here, the United States is home.

“Some of the choices that I’ve made were difficult, but I think leaving Baghdad when I did and coming to the United States were the best decisions I’ve made,” she said. “I have been so fortunate here to have the opportunity to work with talented teams locally and nationally with the ultimate goal of making a real impact on our patients’ lives. I think there must have been a higher power watching over me.” ■



GYNECOLOGIC MALIGNANCIES

Robert C. Bast Jr, MD

THE UNIVERSITY OF TEXAS
MD ANDERSON CANCER CENTER

Developed antibody that led to ovarian cancer biomarker

Discovering the first useful blood biomarker for ovarian cancer involved an element of serendipity as well as a lot of hard work, said Robert Bast, MD, a master of translational research who continues to break new ground in the battle against cancer more than 35 years after the now famous CA125 assay for ovarian cancer was developed. “The one hundred and twenty five really refers to the number of promising hybridomas that we screened to find a murine monoclonal antibody that would bind selectively to human ovarian cancer cells.”

At Harvard Medical School, Bast and Robert Knapp, MD, developed the first monoclonal antibodies against ovarian cancer in an attempt to provide more effective treatment for the disease. “The 125th clone looked promising for therapy until we found that the cancer cells actually shed the antigen to which the antibody bound,” Bast recalled. “That was a problem, because if you are going to inject antibodies intravenously or even intra-abdominally, shed antigen might neutralize the antibodies before they could bind to cancer cells. With Bob Knapp, we attempted to make lemonade out of lemons, reasoning that if you could use the antibody to measure shed antigen, then that might provide a biomarker to monitor response of ovarian cancer to therapy.”

The two men were onto something. There were no useful biomarkers for ovarian cancer at the time. They found that rising levels of CA125 can indicate growth of ovarian can-

cer during treatment and falling levels can signal a response to therapy. Rising CA125 could also detect disease recurrence several months prior to detection by symptoms or physical exam. “With the CA125 test, you could measure total tumor burden body-wide, even where there were numerous small cancer nodules too small to image. That improved monitoring, so an oncologist could tell whether the cancer was responding or not responding to chemotherapy. In this regard, CA125 resembles other biomarkers that have been developed over the last 60 years, like PSA in prostate cancer, CEA in colorectal cancer, HCG in *choriocarcinoma*, and AFP in testicular cancer. Those are markers that go up or go down with tumor burden, and CA125 is very similar,” said Bast, who is now vice president for translational research at the University of Texas MD Anderson Cancer Center in Houston, Texas.

Over the years, CA125 has been applied to fill other unmet needs in ovarian cancer care. Surgical management of ovarian cancer has been distinctive in that gynecologic oncologists have believed that removing most, but not all, of the cancer surgically can improve the efficacy of chemotherapy. In recent years, it has become apparent that ovarian cancer is not so different and that patients do best when you can remove all of the visible cancer. Achieving this goal requires special surgical training. Even in 2015, only half of ovarian cancer patients are referred to a gynecologic oncologist with the needed skills to remove all of the cancer. There are now 2 Food and Drug Administration-approved CA125-based blood tests that can assure referral of >90% of patients to a surgeon with the right skills, provided one of the tests is actually utilized. Through monitoring and triage, CA125 has contributed to the care of hundreds of thousands of women with ovarian cancer worldwide.

Perhaps the most important application for CA125 would be earlier detection of ovarian cancer when it is still limited to the ovaries



or pelvic organs and can be cured in 70% to 90% of cases. Using a Bayesian approach developed by Steven Skates, PhD, of Massachusetts General Hospital, Boston, Bast has collaborated with Karen H. Lu, MD, chair of the University of Texas MD Anderson’s department of Gynecologic Oncology and Reproductive Medicine, to evaluate a better system for determining whether a rise in CA125 is enough to worry about. Postmenopausal women at average risk for developing ovarian cancer come back yearly for a CA125 test and each woman establishes her own baseline, ‘personalizing’ screening. “If the CA125 has gone up significantly based on the Bayesian algorithm, women are referred to ultrasound, and if the ultrasound is abnormal, then to surgery. If the CA125 remains the same, then

they come back in a year; but if it is somewhere in-between, they return in 3 months. Most encouraging is if you use CA125 in this manner, only 1% of women will undergo ultrasound each year and you ignore a lot of the benign disease that you would detect on imaging that would result in unnecessary surgery to be certain that the lesion is benign. Consequently, the specificity is much, much higher, so you do only 3 operations for each case of ovarian cancer detected instead of 30,” Bast said. Among 4500 women screened over the last 15 years, 18 surgeries have been performed and 10 invasive ovarian cancers have been detected, and 7 in early stage. A much larger study of 200,000 women has been conducted in parallel in the United Kingdom (UKCTOCS) that is adequately powered to show a survival advantage. Results will be announced in December and could lead to the first effective screening test for ovarian cancer.

Bast, 71, was described as exceptionally dedicated by Knapp. “Bast as an individual was an unbelievably hard worker,” said Knapp, recalling those days in the 1970s when he and Bast worked together on the monoclonal antibody effort. “He was a driver. He drove himself. He drove the technicians. Time-wise he would be there until he felt a particular part of the project was completed. I don’t think he knew if it was 12 o’clock or it was 9 o’clock. He was amazing. He just worked.”

In recent years, Bast has continued his work in ovarian cancer by seeking ways to improve the performance of the chemotherapeutic drug paclitaxel (Taxol). While paclitaxel is given routinely to all women with newly diagnosed ovarian cancer, less than half respond to the agent. Bast’s group found that the enzyme SIK2 (salt-induced kinase 2) not only is critical to the process of cell division, but also when its presence is reduced, cells become more sensitive to paclitaxel. Bast gives much of the credit for this discovery to postdoctoral fellow Ahmed Ashour Ahmed, MD,

PhD, who is now a professor at the University of Oxford. Currently, Bast’s group is working with Oncolexis, a biotech company, to develop a small molecule SIK2 inhibitor, which can stall tumor growth and enhance paclitaxel sensitivity. “If preclinical data continue to look promising, we hope to move the SIK2 inhibitor to clinical trials,” Bast said.

In addition, Bast and his fellow researchers at the University of Texas MD Anderson Cancer Center have explored ways to eliminate dormant cancer cells and have developed the first inducible model for dormancy in ovarian cancer driven by re-expression of the gene *ARHI* (*DIRAS3*), which is downregulated in 60% of ovarian cancers. Re-expression of *ARHI* not only establishes dormancy, but also induces autophagy, a process by which cells consume their own organelles to generate energy that could sustain nutritionally challenged dormant ovarian cancer cells in small scars on the peritoneal surface. Comparison of primary and positive second look surgical specimens—examined at later stages of the disease—suggests that ovarian cancer cells in less than 20% of primary cases, but in more than 80% of second look specimens from the same patients, express *ARHI* and are undergoing autophagy. Thus, anti-autophagic therapy might eliminate dormant, drug resistant cancer cells that remain after primary surgery and chemotherapy.

Bast is very enthusiastic about this current era in cancer research, which he says is moving rapidly and appears to be on the brink of significant advances in cancer patient care. In early detection, for example, spiral computed tomography holds great promise for improving outcomes in lung cancer. Blood biomarkers may help to identify ex-smokers who would benefit most from screening, as well as to determine optimal intervals for follow-up when indeterminate nodules are detected in the lung, he said. “For prevention, predictive risk models could facilitate cost-effective research and practice, but their development and validation



is a longer-term challenge. For personalized therapy, predictive biomarkers will be required to identify combinations of targeted therapy that are likely to be effective in particular patients.”

BETTER TARGETING WILL LOWER COSTS OF CARE

However, bringing down the societal cost of drugs will be diffi-

cult, but must be done, he says. The extraordinary price of many new targeted therapies is not sustainable and excludes many patients unable to pay. Companies attempt to justify prices by pointing to the many candidate drugs that do not prove successful. “One of the challenges we face is to be more efficient in developing effective targeted drugs. Of 20 new oncologic agents

that are moved into clinical trials from pharma, 19 will fail, and it is not because the FDA is being particularly strict. Drugs are being approved that only extend progression-free survival by a few months. Our preclinical models are simply not adequately predictive of efficacy in patients. Much more attention needs to be devoted to developing and validating highly predictive preclinical models and choosing targets wisely, as well as to discovering biomarkers with high negative predictive value, comparable to estrogen and progesterone receptors in predicting lack of response to hormonal therapy in breast cancer. If we could predict with high accuracy who would not respond to costly therapy, we could cut costs by more than half in most cases, spare patients from toxicity, and provide them with the agents that are more likely to help. Academe should take a more active role in developing such biomarkers,” Bast said.

He laments, however, the impact on young investigators of the current, poor state of funding for biomedical research, and says

that this is discouraging physicians from becoming researchers. “It never occurred to me that I could not support my family and send my daughter to college and still be a scientist and a physician. I think these days young physicians are really wondering whether there is a future in biomedical research,” he said. Recent efforts by Congress to restore cuts in National Institutes of Health funding are extremely important.

At the University of Texas MD Anderson Cancer Center, Bast coordinates programs to develop the careers of physician-scientists in laboratory-based research and clinician-investigators in hypothesis-driven clinical trials. He is also involved in graduate and post-doctoral programs to ensure that doctoral students get more exposure to human biology and to clinical research so that their usefulness in translational research can be maximized. “When I was going through medical school at Harvard, there was a strong commitment to provide doctoral candidates access to medical knowledge, and they spent the first 2 years taking

medical school classes so that they knew anatomy and physiology and microbiology and pharmacology—all of the things that physicians learn. Over the last 40 years that has completely changed, due in large part to the fact that there is so much fundamental science to master. Most PhD curricula include very little medicine,” Bast said.

At the Graduate School of Biomedical Sciences, co-sponsored by the University of Texas MD Anderson Cancer Center and the University of Texas Health, courses are being established for graduate students in human biology and



Traveling is one of Bast's major passions when he is not wearing a lab coat. Here he visits Yosemite in 2012 with his daughter, Elizabeth, son-in-law Steve Kretzman, and grandson Silas.

pathophysiology, clinically relevant cancer biology, translational cancer research, clinical trial design and execution, cancer immunotherapy, and clinical oncology. Opportunities are provided for graduate students and postdoctoral fellows to shadow surgeons, radiation therapists, medical oncologists, pathologists, and imagers, often caring for patients with the type of cancer that the trainees are studying in the laboratory.

Bast says a realization of the urgent need for solutions is partly behind his dedication to the craft of oncology practice and research. “I care for patients every week. It is not a huge number, probably only a couple of hundred in total, but I think that caring for cancer patients really keeps you focused, and shows that our progress can never be fast enough from a patient’s perspective. It reminds you every week why you are doing what you are doing, and also I really enjoy caring for patients and practicing oncology.”

In preparing a recent grant application, Bast calculated that he has mentored at least 190 undergraduates, graduate and medical students, clinical and postdoctoral fellows and established faculty members over the years, many of whom were truly exceptional.

He feels that he has also been particularly fortunate to work with other members of the faculty at Harvard University, Duke University and the University of Texas MD Anderson Cancer Center. It is to these individuals that he gives much of the credit for the advances in medicine with which he has been involved. “I think that it is impossible to accomplish a lot without working collaboratively with great people around you. You also have to give young people space to develop and to work on their own projects, and that has been a principle of mine—to try to encourage people to develop their own careers and to try to find people who are highly motivated, if not driven, to do something about cancer and to help them accomplish that goal, however I can,” he said.

His most enduring contribution to medical science, however, may be the development of the CA125 blood test. Knapp gives him all of the credit. Without Bast, he says, there would be no CA125. “He was the one who did it all.” ■



IMMUNO-ONCOLOGY

Carl H. June, MD

PERELMAN SCHOOL OF MEDICINE AT
THE UNIVERSITY OF PENNSYLVANIA

Pioneer in the development of gene transfer therapies

As with software upgrades, Carl H. June, MD, sees his work in cancer research as a job with ever-evolving updates.

June, 62, won an OncLive Giants of Cancer Care Award® for his work with chimeric antigen receptor (CAR) therapy in patients with different forms of leukemia and lymphoma. Such research, which uses the patient's own white blood cells to help destroy tumors, is "an ultimate form of personalized medicine," said June, speaking with OncLive in a video interview when presented with his award this summer. "It's kind of like computer systems, where we're just seeing the launch of Windows 10," he said. "What we have right now is CAR 1.0, and [the research will] get better and better with next generations. I'm very excited about that prospect—it will be both more potent and safer with what's going to come."

CAR therapy has been studied in adults with chronic lymphocytic leukemia (CLL) and adults and children with relapsed/refractory acute lymphoblastic leukemia (ALL). It was heralded as a breakthrough therapy designation from the FDA for ALL in 2014 for the investigational therapy CTL019.

CTL019

It begins with the patient's own immune system, June said. CTL019 is being developed

OncLive
PRESENTS
Giants
OF *Cancer Care*
INDUCTEE
2015

through an agreement between the University of Pennsylvania and the pharmaceutical company Novartis. White blood cells are taken from the patient's body, engineered over a 5-to-10-day process to become "leukemia-specific killers, and then they are given back through a simple blood transfusion process to the patient," June said. The cells, known as serial-killer T cells, work by annihilating cancerous tumors.

"We found that each of these gene-modified CAR cells that we transfused into the patient can be responsible for killing more than a 1000 tumor cells," he said. "There's no precedent for that—where the cells are both a living drug and they divide in the body, so the body becomes, actually, a bioreactor."

The technique differs from other cancer treatments because of gene modification. "It's gene transfer technology that makes the cells chimeric, so they have the properties of other cells, but they are not found naturally in the body," said June. It's a case of synthetic biology, of making the immune system better than it was before the transfusion.

Another remarkable element is how treated CAR T cells in the body are on patrol to attack cancer cells. "These cells are living drugs. We still detect CAR T cells in patients infused 5 years ago. They're hunter cells, and that's the power of the immune system. It can have a memory—in this case of the cancer cells—and it can prevent the tumor from coming back," June said.

This past July, the first patient treated with CAR T cells celebrated a half-decade of remission. "He just passed the 5-year mark and remains free of leukemia, which was his initial form of cancer," June said. "He's enjoying his retirement."

AN IMPROVEMENT OVER BONE MARROW TRANSPLANTS

CAR T-cell therapy is also notable for how it prolongs life, particularly when compared with bone marrow transplants—the

traditional treatment for these types of cancer, June said. "When I began training on bone marrow transplantation in the early 1980s, we had what was called the rule of 10. For each decade of life, you had a 10% chance of dying. So if you were 30, you had a 30% chance of dying after a bone marrow transplantation. What we have today is already much less than it was in those early days. With time, bone marrow transplantation has gotten much safer and the same thing will happen with CAR T cells," he said. Of about 180 patients who have been treated with CAR T-cell therapy, fewer than 5 have died from adverse effects.

Also, CAR T-cell therapy can help patients at earlier stages of cancer development, which is when they have virtually no risk of cytokine-release syndrome, an infection-like response that can cause high fevers, low blood pressure, and pulmonary edema. Being able to administer therapy earlier to patients also allows for more treatments to take place in settings other than specialized oncology units.

"In very late-stage leukemias, about one-third of the patients need to be cared for in intensive care environments found in cancer centers, but we found as you move to do this earlier on in patients—where they don't have such advanced disease and high levels of cancer—that it could be done in a community-hospital setting as an outpatient therapy," he said.

Ultimately, such treatment could change the course of cancer treatment. "Right now, when patients get leukemia, the first line of therapy is chemotherapy and/or radiation therapy," he said. "What we would like to use is a targeted immune therapy and replace the need for chemotherapy."

June's work has also helped to develop targeted therapies for chronic myeloid leukemia, which received FDA approvals between 2001 and 2012 for numerous drugs, including imatinib, dasatinib, nilotinib, ponatinib, bosutinib, and omacetaxine.

CAR T-cell therapy is also being examined for use in treating other types of cancers, with ongoing trials studying patients with lymphoma and myeloma, another form of bone marrow cancer and considered the most common kind of bone marrow cancer in the United States. “And then the big question in the field is solid cancers and what will the role of this kind of immunotherapy be,” June said. “Trials will begin in lung cancer and every solid cancer you can think of, by various groups, over the next year or so.”

A LIFETIME OF ACCOLADES

June, the Richard W. Vague Professor in Immunotherapy in the Department of Pathology and Laboratory Medicine at the Perelman School of Medicine at the University of Pennsylvania and director of translational research in the Abramson Cancer Center, is no stranger to success. In April 2015, the American Association for Cancer Research (AACR) and the Cancer Research Institute awarded him the Lloyd J. Old Award in Cancer Immunology for his work.

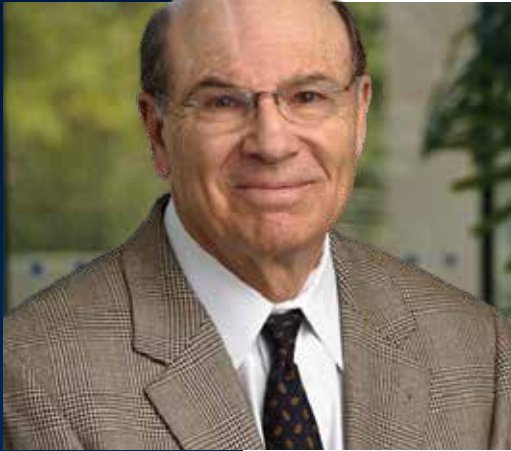
According to an AACR news release, June is an active AACR member and a senior editor of *Cancer Immunology Research*. He has won many awards for his work, such as the Taubman Prize for Excellence in Translational Medical Science, the Karl Landsteiner Memorial Award from the American Association of Blood Banks, the Steinman Award for Human Immunology Research from the American Association of Immunologists, the Richard V. Smalley Award from the Society of Immunotherapy of Cancer, the Paul Ehrlich and Ludwig Darmstaedter Prize (shared with a 2014 Giants of Cancer Care inductee, James Allison, PhD), the Legion of Merit from the US Navy, and election to the Institute of Medicine and the American Academy of Arts and Sciences. These honors date back to 1978 when June won the Michael E. DeBakey Scholar award as the most outstanding medical student at Baylor

College of Medicine. Before that, June earned a bachelor of science degree in biology from the US Naval Academy.

Prior to joining the Perelman School of Medicine faculty in 1999, June was based at the Naval Medical Research Institute in Silver Spring, Maryland, from 1990 to 1993. There, he founded the Immune Cell Biology Program and oversaw the Department of Immunology.

Sharing the knowledge and educating others about such scientific advances in the field of oncology is crucial, said June.

“It’s important for scientists to talk, so that the public can learn about these new kinds of therapies,” he said. “Most physicians have very little understanding about how the immune system really works, especially in the field of oncology where, until just recently, there was no immunotherapy. Education is really important so there’s not a barrier to this going forward and [it is] being used in a way that patients receive the most benefit.” ■



LUNG CANCER

John Minna, MD

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER

Translating molecular and radiotherapy discoveries in lung cancer

For many physicians, regardless of specialty, the decision to pursue a medical career is made in childhood. For John Minna, MD, whose father had the largest family practice in San Diego and whose mother was the nurse that ran the office, his career path was cemented by the 500 house calls he went on with his dad when he was a kid growing up. His career choice was a foregone conclusion.

The only question that remained was if he'd pursue academic medicine—something his father wanted for him—or if he'd become a practicing surgeon in his hometown—something his father's friends (themselves surgeons) wanted him to do—because his father referred his patients to so many of them.

During the course of his studies at Stanford University School of Medicine, Minna found himself in the clinical and research laboratories of Henry Kaplan, MD; Saul Rosenberg, MD; and Leonard Herzenberg, PhD. They took Minna under their collective, and rather expansive, wings.

Kaplan was a pioneering radiologist and radiobiologist. Together with Edward Gintzon, they invented the first medical linear accelerator in the Western hemisphere. Rosenberg was a pioneer in lymphoma research. Herzenberg, in the Department of Genetics, was best known for developing and collaborating with his wife on the fluorescence-activated cell-sorter (FACS). Like a coin sorter that separates a jumble of change

into neat stacks of quarters, nickels, dimes, and pennies, the FACS sorts cells according to fluorescent tags attached to their surfaces and keeps the cells viable during the process.

These were Minna's mentors, and their effect on his medical career set the stage for his future endeavors in lung cancer.

BEYOND MEDICAL SCHOOL

After graduating from medical school, Minna entered the intern and residency program at Massachusetts General Hospital (MGH), where he learned aspects of clinical medicine and made friendships that inspired all of his future clinical work.

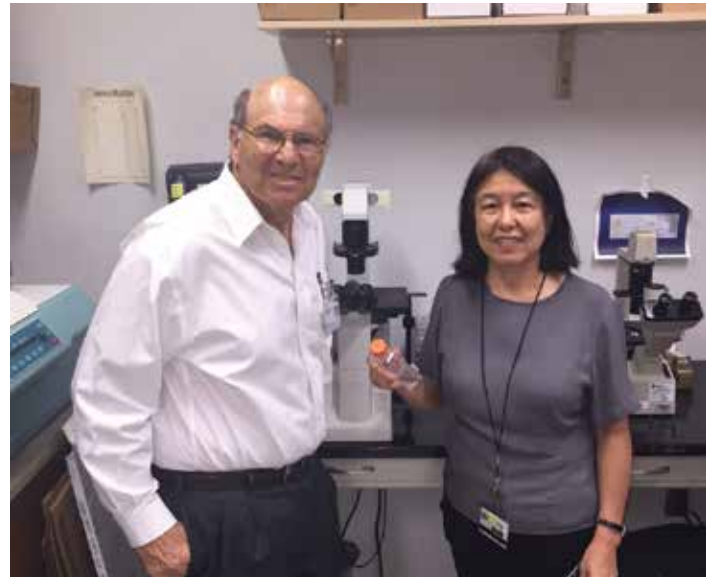
"It was amazing—the other interns and residents I was with. They turned out to be many of the future leaders of clinical medicine in the United States," Minna said.

Following his time at MGH, he went on to the National Institutes of Health (NIH), as part of the United States Public Health Service, and joined the laboratory of Marshall Warren Nirenberg, PhD, the Nobel Prize-winning biochemist who had just cracked the genetic code. Coincidentally, also working in the same laboratory were other young post-doctoral fellows who would go on to become famous scientists and Nobel Prize winners, Alfred Gilman, MD, PhD, and Joseph Goldstein, MD.

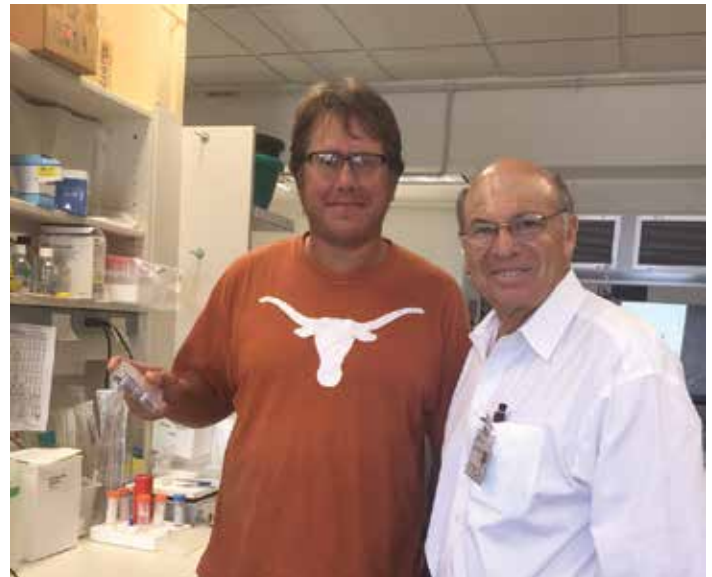
Minna remembers that "besides being a very generous and caring mentor, Marshall taught me how to frame a research question and to be totally fearless in attacking a problem. Just because no one else had done it, didn't mean that you couldn't. He also encouraged and helped me to set up my own laboratory, and gave me my independence, which were wonderful gifts."

LUCKY BREAK

While he was conducting research in Nirenberg's department, Minna also discussed his interest in cancer, developed during his tenure



Boning Gao, PhD, assistant professor of pharmacology, and Kenneth Huffman, PhD, research scientist, work with John Minna, MD, in The Minna Lab, part of the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research and the W.A. "Tex" & Deborah Moncrief Jr. Center for Cancer Genetics.





D. Minna, M.D.
Director, Hamon Center
Therapeutic Oncology
Research



at Stanford Medical School, with Vincent DeVita, MD, a 2013 Giants of Cancer Care award winner for his work ground-breaking work in lymphoma, and his need to get more training.

“And then came a totally lucky break for me: Vince offered me a job almost on the spot—running the NCI [National Cancer Institutes] Veterans Administration Medical Oncology Branch. Of course, I jumped at the chance, but I knew I needed a lot of help.”

DeVita suggested that Minna approach Paul Bunn, MD, a 2014 Giants of Cancer Care winner in lung cancer, and Dan Ihde, MD, who were just finishing their oncology fellowships. These 2, along with Martin Cohen, MD; Mary Matthews, MD; and Desmond Carney, MD, taught Minna how to conduct clinical research. It was this group that focused primarily on lung cancer research.

Another major person in the equation was Eli Glatstein, MD, who had just come from Stanford University. He and Minna were both disciples of Henry Kaplan, and they formed a strong bond in clinical trials research at the NCI.

“Can you believe how lucky I was?” said Minna. “Here I am, in a brand new job with huge clinical research responsibilities, and I have Paul Bunn, Dan Ihde, Martin Cohen, Mary Matthews, and Eli Glatstein, not only on my team, but teaching me every step of the way.”

GENETIC STUDIES OF LUNG CANCER

The laboratory research portion of Minna’s work, which had been focused on genetics in general, now switched to genetic studies of lung cancer specifically.

“Again, I realized there was no way I could do this alone, especially with all of the clinical responsibilities that came with the position. Fortunately, I had a great collaborator and pathologist, Adi Gazdar, MD, who was already part of the NCI and famous for his work on tumor viruses.”

Minna approached Gazdar to “roll the dice and tackle something entirely new” to set up a genetic studies lung cancer branch at NCI.

“The 2 of us have worked on the lung cancer problem side-by-side for the past 40-plus years.” But back then, “there were no tumor lines. There were, at most, 1 or 2 lines in the whole world.”

When lung cancer patients started walking into the medical center, Minna said, “Let’s take all of these patients, get them biopsied, and we’ll start tumor lines.” And this was the work he set out to do with Gazdar, which has lasted to this day.

The idea was initially met with skepticism back then, but today, “we have whole genome sequences of lung cancer.” During his years at the naval medical center, from 1975 through 1981, these tumor lines became the basis for most of the pre-clinical research that has gone on in the field of

lung cancer. The tumor lines are now used frequently by thousands of investigators around the world.

It might have been a case of being in the right place at the right time, but “those lines had some of the first EGFR mutations that were known. The 10 or so lines that we collected turned out to be the pivotal resources that were used to prove that sensitivity to EGFR could be used in preclinical models to lead to targeted therapies.”

Epidermal growth factor receptor (EGFR) is a transmembrane protein with cytoplasmic kinase activity that transduces important growth factor-signaling from the extracellular milieu to the cell. Given that more than 60% of non-small cell lung carcinomas express EGFR, it has become an important therapeutic target for the treatment of lung cancer tumors. Minna and his fellow researchers did not squirrel away the lung cancer tumor lines, though. Their objective was always to make the lines accessible to every researcher around the world in order to facilitate col-

laboration, corroboration, and sharing of resources.

“There was a very free give-and-take exchange that occurred. It wasn’t just me that set the tone for that. We always understood that the real enemy was not each other, but the disease.” Couple this with a desire to nurture research ideas

through teaching younger researchers or fellows and you have a potent combination of objectives.

These dual objectives, to freely share resources and to teach, are the most important things Minna believes that he has accomplished in his storied career. “I’ve been involved in the training of all these people who have gone into lung cancer translational research.” His list of collaborators, students, and fellows is a veritable “Who’s who?” in lung cancer research, many of whom consider Minna a mentor and a friend.

That extensive collaboration proved beneficial, especially when working with lung cancer tumor lines, which proved very hard to grow, said Minna. It is a difficult proposition to undertake. “It turns out that lung cancer cells would often float. The cells would be discarded when the media they were growing in was changed.”

Minna was familiar with the work of Gordon Sato, PhD, a cell biologist who first attained prominence for his discovery that polypeptide factors required for the culture of mammalian cells outside the body are also important regulators of differentiated cell functions.

“Sato had the idea that you could take and grow cells in completely defined media and add in growth factors. This was better than using serum. We started doing that with lung cancer, and it turned out that you could inhibit the growth of tumors early on. The cells do much better if they were grown in defined media that had 4 or 5 specific hormones and chemicals added to them. I had heard and discussed this idea with Gordon, so the first time an opportunity presented itself, we took some patient specimens out and put them in defined media. We tried several different combinations and all of sudden we saw things grow that we hadn’t seen before.”

FORTUITOUS CONVERSATIONS

One benefit of being regarded among your peers as someone who



shares discoveries and advances without regard for career advancement is that it can result in fortuitous conversations that can move research forward. Minna recalled the use of the Southern blot, a method implemented in molecular biology for detection of a specific DNA sequence in samples from lung cancer tumor lines and noted the amplification of the *MYC* gene. Further research resulted in the discovery of other *MYC* gene family members: *N-MYC* and *L-MYC*.

As these discoveries were made, Minna received a phone call from J. Michael Bishop, MD. Bishop is best known for his Nobel-winning work on retroviral oncogenes. Working with Harold E. Varmus, MD, in the 1980s, Bishop discovered the first human oncogene, *c-Src*. Bishop had been studying childhood lymphoblastoma and neuronal-like neuroblastoma, in particular, a gene that appeared to be amplified. Before Bishop could say anything further, Minna asked, “Any chance this is related to *MYC*?”

Minna said the silence on the other end of the phone was deafening. Bishop asked him, “How did you know that?”

“I’m looking at this blot in lung cancer, and there’s an amplified gene that exhibits those very same characteristics,” said Minna.

Looking back on the conversation, Minna said, “It was one of those things where suddenly you knew it had to be true. That kind of discovery results from the sharing of information and data, and that led to the eventual identification of that gene.”

The ramifications of that discovery are still evident to this day through Minna’s work with a team of scientists from the University of Texas Southwestern Medical Center, the University of Texas MD Anderson Comprehensive Cancer Center, and the Baylor University College of Medicine. Their objective is to discover all of the acquired vulnerabilities in lung cancer and their associated predictive molecular signatures to provide a new functional classification of lung cancer and rationale therapeutics for all new patients with lung cancer.

PAST IS PROLOGUE

Minna believes the next frontier worth exploring is the emerging role of molecular markers, which has been his focus since he joined the University of Texas Southwestern Medical Center in Dallas in 1991 as professor of medicine and pharmacology. He is currently the director of the Hamon Center for Therapeutic Oncology Research, The Moncrief Center for Cancer Genetics, and co-director of the Experimental Therapeutics Program for the recently NCI-designated Harold C. Simmons Comprehensive Cancer Center, at the University of Texas Southwestern Medical Center. It is the only NCI-designated comprehensive cancer center in north Texas.

“We now see that there are certain molecular markers that predict which cells are going to respond or not respond to therapy. If we can understand how this works in the preclinical stage, we can bring it through to subsequent therapeutic development.”

After nearly 50 years in research, you’re bound to be able to draw upon your past experience. This is where Minna finds himself today. In his current research, he and his collaborators are testing their chemical library of drugs, including 250,000 natural products. They are testing these substances against lung cancer tumor lines and lung epithelial cells to determine which ones only affect the tumor cells, much like his earlier research with EGFR inhibitors. His team’s efforts have resulted in “about 300 new agents that look to be absolutely specific for lung cancer, but don’t affect normal lung epithelial cells and also only kill subsets of lung cancer.”

Minna is optimistic about the future. “It’s clear that we now have a whole new case of treatments that could have a therapeutic window with high specificity. If we can figure out how well these new, potential treatments do, that’s how I want to be remembered, and that’s how I’m going to ride off into the sunset.” ■



LYMPHOID NEOPLASMS

Emil J. Freireich, MD, DSc

THE UNIVERSITY OF TEXAS
MD ANDERSON CANCER CENTER

*Refined multidrug chemotherapy regimens that
form the backbone of treatment today*

Emil J. Freireich, MD, DSc, was the originator of combination chemotherapy, the primary architect of the first cure for a systemic cancer, a major contributor to the cures for half a dozen other systemic cancers, and, quite possibly, the man who did the most to transform MD Anderson from a minor facility in the east Texas swampland to the world's leading cancer center.

He is also a man who has been fired 8 times during the course of his career—a fact that astonishes both total strangers and his closest friends. Strangers are naturally amazed that a man who ranks among the greatest medical researchers of the past century has ever been fired. Friends, on the other hand, tend to be amazed that the 88-year-old has not been fired more often.

Many scientists fancy themselves daring truth seekers who follow the evidence wherever it leads, damn the consequences, damn the bureaucracy, and damn the feelings of those who are too timid or too stupid to embrace the truth. Freireich actually is such a man, and his unrelenting commitment to all-out war against cancer has led to a life of both incredible achievement and unending conflict, not only with the disease that he swore to defeat, but also with a large number of his ostensible allies in the war against it.

“They say I’m retiring this year, but that’s a lie. They fired me again. I will keep working anyway, assuming they will not actually have security throw me out. I will not

stop until I die. I do not want to relax. There is nothing else,” said Freireich, who still lives with his wife in the home they bought after a single day of house hunting 50 years ago for the simple reason that he’s been busy with more important things for the past half-century. “I want to cure cancer, and I’m willing to suffer whatever abuse I need suffer to test as many ideas as possible. I could even endure all those 20-somethings in Washington telling me I know nothing about cancer, but for the fact that they control all the grant money.”

Actually, Freireich would welcome the insults of 20-somethings, if they were mocking an old man’s conservatism. Science, he believes, progresses when the daring ideas of each new generation unseat the ossified convictions of its elders. What terrifies him is that an overly conservative system has so neutered younger scientists that they are more timid than researchers who supplement their salaries with Social Security.

Things were very different in 1955, when a 27-year-old Freireich took a job with the National Cancer Institute (NCI) to escape the draft and, on the strength of a hematology residency, ended up in charge of the pediatric leukemia ward, free to give the kids nearly any treatment he found promising. The resources at the brand-new facility were unbelievably good. Staff outnumbered patients. Labs stocked every conceivable new technology. Researchers got whatever funding they needed.

The biggest advantages, however, may have been a couple of intangibles. Freireich took his job less than a decade after the invention of the modern medical trial, and he was among the first people to apply the technique to cancer. He also had the good fortune to serve a generation of people forged by World War II, people who thought it normal to take great risks in pursuit of great ends. When his boss assigned him his job he said, “I’ve got a good idea for you. Cure leukemia.” In addition, he meant it.

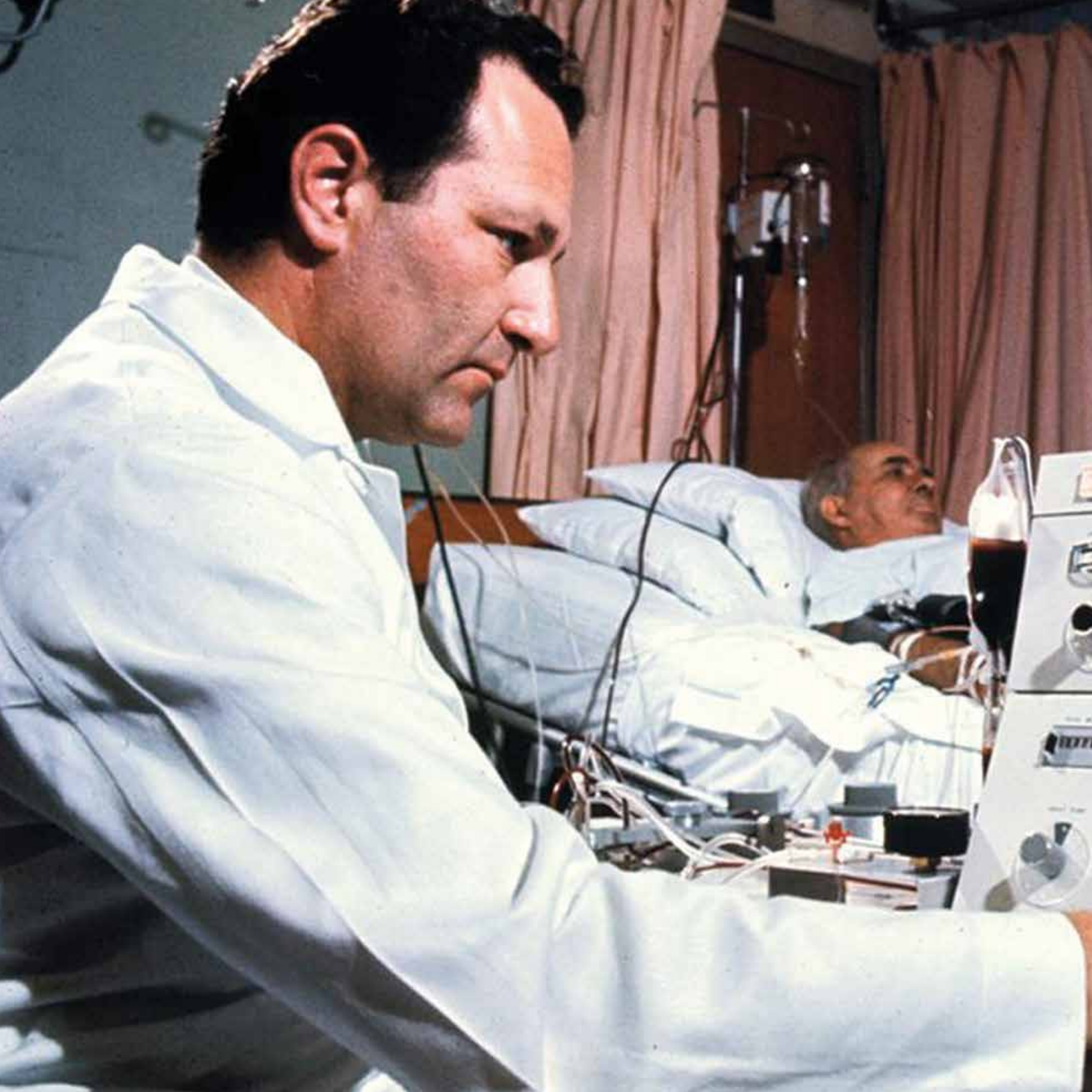
Still, it would have been hard for a visitor in the pediatric leukemia ward circa 1955 to imagine that such advantages would have enabled Freireich to save any of his young patients. Only a few years had passed since Sydney Farber had devised the first treatments that had any effect on systemic cancers, and the newest treatments available to Freireich only managed to let the kids suffer an extra couple of months before they died.

The ward looked like a butcher shop. Kids bled from their eyes, ears, mouths, noses and the skin around their nails. Nurses repeatedly changed each patient’s bloody sheets, and they spent their idle minutes scrubbing blood off the walls. Idle minutes were scarce, however, even in a half-empty ward, because the staff spent so much time racing from emergency to emergency, trying to keep internal bleeds from killing patients.

Freireich decided that the only way to buy himself enough time to address his patients’ leukemia was to get the bleeding under control, so he began to study their blood. What he saw looked normal, except for a near total absence of platelets. He therefore took his own platelet-rich blood, mixed it into patient blood, and found that the platelets made it behave normally.

Others had made similar observations long before Freireich, but Freireich was the first to isolate the clot-inducing lipid inside platelets (now known as platelet factor 3) and, more importantly, the first to figure out why it was impossible to reproduce the results of the blood-mixing experiment by giving leukemia patients banked blood from healthy donors. Platelets in donor blood, his simple observations revealed, disintegrated in about 48 hours regardless of whether the blood was refrigerated or stored at room temperature.

Freireich hypothesized that transfusions of fresh blood would prevent his patients from bleeding to death, so he got 30 volunteers to provide a full transfusion for a single patient. The fresh





blood stopped what would have been a fatal bleed and enabled Freireich's 4-year-old patient to form clots normally for a couple days. The bleeding then returned, but fresh transfusions kept stopping it, so Freireich inferred that fresh blood would help all his patients, and he demanded it from the blood bank. The blood bank refused on grounds that success with a single patient was not enough to overturn conventional wisdom about the efficacy of blood storage and justify the enormous effort required to provide fresh blood. Freireich denounced this logic in terms that made a lifetime enemy of the man who ran the blood bank, a man who demanded a randomized trial of fresh blood before he would supply it and then, when the results demonstrated that fresh blood virtually eliminated bleeding problems, accused Freireich of rigging outcomes and tried to prevent the resulting paper from being published. Fortunately, Freireich's boss backed him and the paper's publication in *The New England Journal of Medicine* proved a breakthrough, not only in the treatment of leukemia but in the treatment of many diseases that cause dangerous bleeding.

Freireich and a colleague then experimented to see just how many platelets, given how frequently, would keep patients safe from bleeding, while Freireich and another colleague built a system for sending a unit of drawn blood directly to a centrifuge, which, in turn, spun out the platelet-rich plasma, returned the rest of the

blood to the donor, and pushed the plasma into a bag that held a unit of normal blood, taken at the same time from the same donor. Freireich and a third colleague then paid homeless men to participate in a trial that demonstrated that healthy donors could safely give 2 units of double-platelet blood per week. This output, by a very happy coincidence, was exactly enough to sustain a bleed-prone patient for a week. Essentially, Freireich figured out that a single person could safely donate enough blood to keep a loved one clotting normally forever, and he built a system that made the whole process easy. Subsequent research has made some improvements, but the basic system remains in use today and it has saved untold millions of lives.

Once Freireich had the bleeding under control, he turned to the next most pressing problem, which still was not leukemia itself. It was infection, which had been killing nearly every patient who didn't bleed to death. Careful examination quickly determined that the blood of leukemia patients had virtually no neutrophils, and careful experimentation quickly demonstrated that people needed a certain concentration of these neutrophils to fight off infections normally. The relationship between neutrophils and infections was, in almost every respect, a perfect parallel with the relationship between platelets and bleeding, but the transfusions that stopped the bleeding provided far too few neutrophils to provide any real defense against

infection. The only way to protect patients against infection was to regularly give them the number of neutrophils contained in all the blood of a healthy donor.

It was, Freireich quickly realized, impossibly arduous to get enough neutrophils for a large number of patients by drawing donor blood pint-by-pint and putting each pint into a centrifuge. He needed an imaginary device that could separate a continuous flow of donor blood and send the neutrophils into a bag while it sent the rest of the blood back into the donor. Just as he was imagining this device—which would have to work fast enough to separate an entire body's worth of blood in a reasonably short time—an IBM engineer, whose son was being treated at NCI, knocked on his door and asked if he could do anything useful to help with cancer research. Freireich gave the person a list of the seven properties he thought a continuous blood separator would need and hoped for the best.

The engineer, whose name was George Judson, convinced IBM not only to give him a paid sabbatical so he could design the device, but also to donate parts, so he could actually build it. He set up shop at NCI and spent the next few months assembling prototypes out of spare parts while Freireich tested them with expired blood from the blood bank. When they thought they had a device that worked pretty well, Freireich went to his boss and asked to test the absurd-looking and unprecedented contraption on human subjects. Somehow, he got the green light. The pumps worked poorly and the seals leaked because the device was a hand-rigged collection of second-hand parts, but the thing worked well enough to serve as proof-of-concept. Freireich and Judson had clearly achieved a breakthrough.

The NCI paid IBM to make a professional version of the same basic design and the resulting product dominated the market for continuous blood separators for more than 5 decades. It was

another world-changing advance that saved millions of lives and gave researchers a powerful new tool that has benefited every corner of hematology. The blood separator was certainly a lifesaver for leukemia patients, particularly after Freireich figured out a way to stimulate the production of extra white blood cells in healthy patients. That allowed each donor to provide enough neutrophils to protect a cancer patient without leaving themselves dangerously exposed to infection.

“These days, getting permission to undertake any individual step in the platelet or neutrophil projects would take longer than the entire actual duration of either project back then. Worse, there is no way you could get permission to undertake many of those steps today, not unless you wasted the better part of a decade with intermediate steps. A young researcher who suggested using that jury-rigged blood separator on a live human today would probably be fired on the spot, and anyone who thinks this reflects well on modern safety procedures is a fool who doesn't understand how to weigh potential risks and benefits,” Freireich said.

“It isn't like no one sounded the alarms back then. There were plenty of people who denounced the experiments we did. But we had the guts to tell them they were fools, and we had the incredible luck to have a boss named Gordon Zubrod, who understood what people working all-out can accomplish. He put his career on the line time and time again to help us keep moving quickly on something of real importance.”

When Freireich first came to NCI, methotrexate, corticosteroids, and 6-mercaptopurine (6-MP) were the only drugs known to have some therapeutic effect in patients with acute lymphoblastic leukemia (ALL), which is the most common form of the disease in children. The first drug, methotrexate, often produced remissions of 2 or 3 months, but the cancer always returned to claim its victims. The other 2 drugs just slowed the cancer's pro-

gression slightly.

Each of the 3 drugs was always used as a monotherapy until Freireich read how medications that only ameliorated tuberculosis temporarily when used sequentially could cure the disease when used together. Freireich advocated a combination cancer treatment that added 2/3 the normal dose of methotrexate to 2/3 the normal dose of 6-MP. A few weeks later, Freireich was running trials with several colleagues and finding that remissions became more common and more durable. Freireich later added a full dose of the steroid prednisone, and the remissions were more common and more durable—but they were never permanent.

The missing piece came when Eli Lilly tried to sell the NCI vincristine, a new drug derived from periwinkle. Many experts, including Freireich's boss, thought the new drug was more likely to harm patients with ALL than to help them, but Freireich talked Zubrod into approving a tiny trial by arguing that even the worst poison couldn't harm the patients who were days away from death. The new drug produced an almost immediate remission in the first patient, and the second, and the third. The overall response rate in the first trial of vincristine on pediatric ALL was 55%, which was far more than any drug before it. Still, the cancer kept coming back.

That all changed when Freireich asked for permission to add vincristine to the other 3 drugs and give all 4 in a combination that came to be known as VAMP. Even Zubrod and Freireich's very adventurous colleagues at NCI thought it nearly mad to propose a 4-drug combination that included a virtually untested drug; yet, Freireich sold them on what became another big step forward. All but one of the first 12 children went into remission with a single course of the combination, delivered over 2 weeks.

Freireich, however, knew that even the most impressive remissions were no proof of cure, so he proposed something even more

radical: giving patients another 3 courses of the VAMP protocol while they remained in remission and appeared perfectly healthy. He again secured permission to proceed and produced one of the most celebrated trials in the history of cancer treatment. Most of the first 27 patients to receive the extra treatments still relapsed, but almost a quarter of them were permanently cured—a first in the battle against systemic cancer that would have been utterly unthinkable just a few years before.

Just a few months later, when Freireich should have been gracing magazine covers, he was effectively fired from the NCI. Zubrod had just moved on, and Freireich, for all his achievements, could not survive without his protector.

“If they gave the Nobel prize in medicine for clinical advancements, rather purely scientific discoveries, Emil J. Freireich—who's known to friends as J—would have been on at least 3 different prize-winning teams for the work he did at NCI. The thing is his run did not end there. After he jumped to MD Anderson in '65, he put together a team that leveraged his insights in combination chemotherapy and other areas to create treatments that have become curative for many other cancers,” said Bart Barlogie, MD, a Freireich protégé who has made breakthrough advances in the treatment of multiple myeloma and built a world-class myeloma institute at the University of Arkansas for Medical Sciences.

“He did as much as anyone to make Anderson the top cancer research center in the world. He attracted a huge amount of young talent that would have gone anywhere to work with him. He also made those researchers enormously productive by repeatedly urging them to be bold. Even administrators couldn't stop him and his team from pursuing what was in the best interest of patient care in the framework of translational research.”

Today, even Freireich's detractors acknowledge the importance of his breakthroughs, but it would be a mistake to think that any-

thing like universal acclaim greeted many of his breakthroughs. A large percentage of the nation's pediatricians, probably a majority, initially refused to use the VAMP protocol on grounds that it was inherently monstrous to poison children so aggressively. This was true even among pediatricians who specialized in cancer care. Medical journals published savage attacks on VAMP and the men who had created it.

Indeed, when Freireich went to MD Anderson to head the pediatric cancer division, the doctors who nominally worked under him refused to treat pediatric ALL with VAMP. Instead, they gave the medications individually, produced temporary remissions, and then let their patients die. When Freireich tried to change this, they argued that his lack of formal pediatric training made him unfit to care for children and they forced the administration to give him a different job. Part of this, no doubt, had no cause beyond the extraordinary novelty of combination chemotherapy and its horrific toxicity, but many believe that Freireich's tendency to denounce skeptics, rather than persuading them, reduced

his influence and kept him from achieving even more. Freireich, on the other hand, believes the blunt truth is a scientist's best friend and regrets nothing—except the proliferation of red tape that does ever more to hinder human accomplishment.

“Every time someone makes a mistake, someone else adds a procedure to prevent that particular type of mistake, and it has had a devastating effect on researcher productivity. Every minute a talented researcher spends filling in a form is a minute that researcher cannot use for actual research,” he said. “The other problem with all these procedures is they create both a terror of failure and a terror of any success that pisses off important people. I am not arguing that researchers should not weigh the potential costs and benefits of experiments. I am arguing that small groups can weigh such matters over the course of a few days as effectively as large ones can weigh them over the course of a few months. I am arguing that 10 lives lost to inactivity are worse than one life lost to an experimental treatment. And I'm arguing that the best way to spread knowledge is to speak the truth bluntly.” ■



MELANOMA

Antoni Ribas, MD

UCLA SCHOOL OF MEDICINE/JONSSON
COMPREHENSIVE CANCER CENTER

A key architect of pembrolizumab and other novel therapies

Cancer patients around the world are lucky that the graduate engineering programs in Spain require a large amount of high-level math. Had they been just a tad less rigorous, Antoni Ribas would never have become an oncologist and uncovered much of what we now know about using immunotherapy to combat cancer.

Ribas has spent the past 2 decades straddling the worlds of fundamental research and clinical trials, using his discoveries about what will and won't make the immune system target tumors to get the best responses in important drug tests. These days, with research dollars pouring into immunotherapy, Ribas is busier than ever, managing 23 researchers at his ever-growing laboratory at UCLA's Jonsson Comprehensive Cancer Center (JCCC).

"Toni didn't invent any of the individual checkpoint inhibitors that are in use or under investigation, but his research has made checkpoint inhibitors a practical treatment by giving us a better idea about who will benefit from them and, uniquely, studying not only their detailed mechanisms in people but also important aspects of molecular biology that impact therapy of melanoma. That has enabled him and others to design successful trials that get these incredibly promising treatments to real-world patients," said Kim Margolin, MD, an adjunct clinical professor at Stanford University's School of Medicine. "He's really everywhere in immunotherapy. Select a big paper at random and

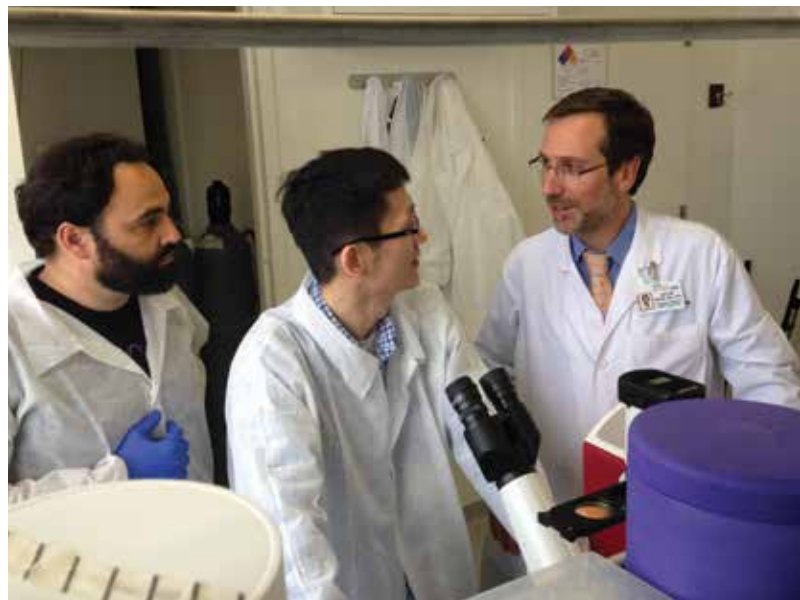
there's a good chance his name will be on it."

Ribas seemed destined for medicine from the day he was born. His father was a doctor. His grandfather was a doctor. His great-grandfather was a doctor. It would have been natural for Ribas to follow in their footsteps; however, he hoped to become an engineer instead. The challenge of finding elegant, mathematical solutions to unique material problems appealed to him more than medicine. Fortunately for cancer patients, the math eventually overwhelmed him and he shifted his focus to the less quantitative problems of human illness.

"I started engineering school and I realized pretty quickly that it was too complicated. There was just too much math. I needed something easier, and medicine was easier, at least for me, because it only really required the ability to remember a lot of stuff, and I was much better at that than advanced math," said Ribas, a professor of medicine (hematology and oncology) at UCLA's medical school and the director of JCCC's Tumor Immunology Program Area.

Ribas chose to follow his father into oncology, mostly because he had spent so much of his childhood hearing about the unique challenges of cancer and watching oncology grow from its infancy. He completed his residency at Hospital Vall d'Hebron in 1994 and began what could have been a comfortable lifetime of clinical practice in his native city. But Ribas still had the desire to solve problems, and he decided that he'd indulge it for a short time.

"When I finished my training, I had the prospect of doing more of what I had been doing, which was giving chemotherapy. There were no other real options for a medical oncologist in clinical practice in the mid 1990s. My other option was to do a research fellowship and try to discover something entirely new. I thought it would be more interesting to try to understand the disease better, so I applied for a postdoctoral fellowship at UCLA. I wanted



to work in the lab of a surgeon who was doing tumor immunology, which wasn't a standard clinical treatment back then and was actually pretty far out on the fringes of research," he said. "Before we left, I told my wife we were coming for 1 or 2 years. It's now 19 years later, and we're still here."

The surgeon at UCLA, James Economou, MD, PhD, had specialized in studying tumor types, such as liver cancer and melanoma, that responded poorly, if at all, to any treatment oncologists could throw at them. Ribas experimented on animals to see if he could find ways to stimulate immune system activity enough to use white blood cells to attack tumors. Ribas eventually discovered a technique for using dendritic cell therapy to make mice fight off melanoma, and his initial decision to stay on at UCLA stemmed from his desire to try the same technique in humans.

Dendritic cell therapy never worked in any significant percentage of melanoma patients, but when it did work, the results were spectacular.

“When I did my first melanoma trials, 1 in 10 or 1 in 20 patients who had this disease that had never responded to anything were effectively cured. Most of those responders are still with us today, more than 15 years later. The other patients, unfortunately, had no response at all and they died very quickly. Results like these led many to say that immunology would never work for any significant number of patients and that research should focus almost exclusively on the targeted therapies that looked so revolutionary with the responses in trials of Gleevec and Herceptin,” Ribas said.

“Perhaps I showed signs of discouragement because a mentor named John Glaspy, MD, MPH, made an argument for the importance of my work that I remember to this day. He said that I was like a person who went to the top of the Empire State Building, dropped 100 balls and found that 1 of them simply floated in the air rather falling to the ground. Those results wouldn’t be statistically significant either, but they’d be damn interesting, interesting enough to merit serious study.”

Immunology researchers like Ribas struggled to increase response rates by finding new ways to stimulate the immune system. Response rates remained depressingly low until James Allison, PhD, a professor at the University of California’s Berkeley campus and a 2014 Giants of Cancer Care recipient, had a world-changing idea. Immunotherapy might be more effective,

he reasoned, if it focused less on speeding up the immune system than on releasing the brakes that tumors put on it.

That insight led to the discovery of many tricks that tumors use to escape the immune system’s wrath. For example, Allison himself discovered that some tumors produce a substance called cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), which binds the cytotoxic T lymphocytes the immune system produces and, effectively, turns them off. Researchers developed experimental compounds that bonded with CTLA-4 and unleashed antitumor immune responses.

Not all antitumor immune responses were limited by this particular trick, however, so these experimental compounds could only prove themselves in trials in certain immunogenic cancers. Ribas did early research in this area and participated in the 2 first-ever phase I trial of a CTLA-4 antagonist. The design that Ribas created succeeded well enough to push the drug forward to the next trial and to spur development efforts at other drug companies. Trials of ipilimumab (Yervoy) resulted in eventual approval from the US Food and Drug Administration.

Ribas and his colleagues have done even more work to understand how different tumors produce programmed death cell receptor ligand 1 (PD-L1), which binds with programmed death cell receptor 1 (PD-1) sites on T cells and,





again, effectively turns them off so they cannot attack tumors. Their experiments helped demonstrate that melanomas often express PD-L1 on tumor surfaces as a mechanism of defense when attacked by T cells and that patients whose tumors do this would make good candidates for treatment with immunotherapies that prevented ligands from binding with PD-1. Ribas then translated these discoveries into practical medication strategies by running both the initial and the pivotal trials of pembrolizumab (Keytruda).

“The common aspect of nearly all of the immunotherapies I have worked with from the 1990s until now has been that people who respond to them have generally experienced extremely robust and durable benefits. The thing that has changed has been the response rates, which have gone from the anecdotal level to a substantial minority of all users,” he said.

“They should continue to increase as we keep studying tumor biopsies and learning more about what separates responders

from nonresponders. It’s clearly not just expressing PD-L1 on the tumor surface because we already test for that before using therapies like pembrolizumab and response rates are still below 50%. As we learn more, we’ll get better at separating responders from nonresponders in advance and, hopefully, getting more people to respond.”

Ribas works far longer hours than most people, but, by the standards of world-renowned researchers, he maintains an enviable work–life balance. He typically arrives in the office at 7:30 AM on weekday mornings and spends 12 hours at work before leaving the building and the job behind him. Ribas then dedicates his evenings—as well as his weekends—to his wife, his 15-year-old daughter, and his nonmedical interests, which range from hiking to gastronomy.

Ribas rejects the custom among high-achieving Americans to let vacation time go unused—he loves to travel—but he celebrates most other aspects of the nation’s scientific culture.

“This is a place that fosters innovation like no other because it is willing to spend serious money to support young investigators and to allow people to pursue ideas over long periods of time,” he said. “In other countries, grants tend to last a couple of years and they are expected to generate discoveries with immediate applications.” Researchers need to realize that, unlike their colleagues almost anywhere else in the world, “they have the opportunity to pursue such innovative dreams.”

Ribas has repaid the system for the opportunity it provided him by taking significant roles in various learned societies, sharing his discoveries at an endless series of conferences, taking



on fellows of his own, and collaborating with countless colleagues across the country and around the globe.

“Toni attends a daunting number of conferences, meets his obligations to endless organizational committees, gets a huge amount of funding for his lab, runs the lab and writes a huge number of papers—yet he still finds time to respond to e-mail almost immediately. It’s sort of scary,” said Margolin. “There are obviously many keys to his success, starting with the fact that he’s very bright, but the thing I hear discussed most often is his character. He hasn’t risen by forcing others down while he stands on their shoulders. He has risen by supporting his colleagues and inspiring their support. There are no losers when you collaborate with Toni, which makes a lot of people want to work with him.”

Ribas, in turn, has plenty of projects that he wants to pursue with collaborators inside and outside of his own lab. There’s always the ongoing investigation of the the fundamental interac-

tion between tumors and the immune system, of course, but the full list is almost endless. The incredible results from many recent immunotherapy trials have convinced countless organizations to invest big bucks, and Ribas hopes to translate that inflow into as many new discoveries as possible.

In addition to studying the basic science, he is beginning trials that use targeted therapies and immunotherapy in combination with each other: the first to destroy the dominant tumor biology and the second to mop up the surviving mutations that would otherwise survive and regroup.

“The most exciting thing, to me, is that we’re just beginning to understand how tumors escape the immune system,” Ribas said. “Hopefully, when we know much more than we do now, we will be able to do far, far more to trigger an immune response than we can now.” ■



MYELOID NEOPLASMS

Clara D. Bloomfield, MD

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

*Conducted groundbreaking work in chromosome changes,
including the Philadelphia chromosome*

One day after school, a second grader informed her mother that she was going to be a nurse when she grew up.

To this, her mother responded, “You’re going to be a nurse? Then you might as well be a doctor.”

That life-changing moment was the start of a monumental career path in myeloid neoplasms for Clara D. Bloomfield, MD, whose accomplishments include contributing to the discovery of the Philadelphia chromosome in patients with acute lymphoblastic leukemia (ALL), describing the rearrangement of chromosome 16q22 in acute myeloid leukemia (AML), and discovering that AML could be cured, even in elderly patients.

All took place on a road not easily traveled and often filled with criticism. Yet today, the veteran oncologist and 2015 Giants of Cancer Care Award recipient is known for not only changing practice in her field, but also for being an influential mentor who knows how to push past the tightest of boundaries.

A WORLD OF ACADEMIA

Leukemia had an effect on Bloomfield early on in her childhood.

“When I was in grade school, I had classmates who died of leukemia,” explained Bloomfield, who grew up in Champaign, Illinois. “When the child was diagnosed, he or

she would be sent off to the National Cancer Institute, because that was really the only place that was great for taking care of kids with leukemia.”

Time would pass, and Bloomfield and her classmates would be informed that another peer had died.

“This seemed, to me, like something that would be a great thing to be able to do something about—that I could really make a difference, that I could basically cure this incurable disease,” she said. “That is how I got interested in it.”

After her father’s duty in World War II, he began his academic career as a professor of Labor and Industrial Relations at the University of Illinois. Bloomfield, aged 4 years at the time, grew up and spent much of her time on the campus, describing it as a “tremendous academic environment.”

“When you grow up in academia, and you know what it’s all about—asking questions and discovering new things—it’s a big advantage,” Bloomfield said.

She attended the University of Wisconsin for her undergraduate work, where an interest in genetics peaked during her junior year studying fruit flies. She attended the University of Chicago for medical school. After she completed medical school and her internship, she moved to the University of Minnesota for her second-year medicine residency and a fellowship in medical oncology.

EXPLORING THE FIELD

Even if she did not recognize it, Bloomfield made a decision early in her career to research leukemias and lymphomas. During the second year of her fellowship, she was in the running for a national scholarship from the American Cancer Society. She was to be interviewed by a physician who treated patients with leukemia and had to describe her future research goals.

“I have to tell you, I never thought about it,” Bloomfield

recalled. “I thought, ‘I’m going to look terrible. I better come up with something in a hurry.’”

Bloomfield told the researcher she was interested in the characteristics of individual leukemic and lymphoma cells and how those might predict outcomes in response to treatment.

“That’s what I did, and have done the rest of my life,” Bloomfield said.

Though, in actuality, she originally planned to study Hodgkin lymphoma.

“There was a fellow ahead of me by a year, and he was doing Hodgkin lymphoma,” she said. “I was told that I couldn’t be doing it because he was researching it, but when he was gone I could start. Therefore, I started out by studying acute lymphoblastic leukemia.”

Her first project was to review 10 years of cases of adults with AML.

“I learned things from that study,” Bloomfield said. “All of the patients had died. But, I learned things that were very important that I immediately then began to investigate and publish on.”

One of these findings included Bloomfield’s discovery that AML could be treated aggressively and eventually cured. The disease was, at the time, believed to be incurable, especially in elderly patients.

Instinctively, the young, female researcher challenged this belief in a paper published in *JAMA*.

“All of a sudden, there was someone they had never heard of saying ‘that not treating older AML patients was wrong’, which was sort of a big deal,” Bloomfield said.

It was an even bigger deal when she was proven right.

In light of her finding and while still a fellow, the University of Minnesota tapped Bloomfield to lead the Leukemia/Lymphoma Service at the institution, which she ran until her departure in





1989. The center also promoted her from assistant to full professor within 7 years, making her the first female full professor of Medicine at the University of Minnesota.

Roswell Park Cancer Institute in Buffalo, New York, was Bloomfield's next career stop as the chair of the Department of Medicine. Following her stint at Roswell, in 1997 she joined The Ohio State University Comprehensive Cancer Center (OSUCCC) and James Cancer Hospital and Solove Research Institute, in Columbus, Ohio, where she became the third woman to ever direct a National Cancer Institute-designated Comprehensive Cancer Center.

At 73, she is one of the most achieved researchers in medicine at OSU, is a Distinguished University Professor, and a senior member of the OSUCCC advisory committee and the OSU President's and Provost's Advisory Council.

Outside the center, Bloomfield has a collection of hats she wears, including co-chair of the World Health Organization's (WHO's) Clinical Advisory Committee: WHO 2016 Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Systems. Moreover, she co-chairs the European LeukemiaNet AML Guidelines for patient management, which is said to have become the most widely accepted guidelines. A third co-chair role is with the AML Global Portal.

Bloomfield weaved through her remarkable and challenging career without any mentors.

Not one.

"The focus that is on mentoring these days just did not exist when I was young, especially having a concept of something like this for women," said Bloomfield. "It was more often a battle between men and women."

PUSHING THE ENVELOPE

A career in chromosome abnormalities did not fair easy. Proving that patients with AML could be cured was not Bloomfield's only battle in fighting for what she believed in.

"There were a number of things I discovered that no one else had found before," said Bloomfield. "My discoveries, a couple of them, were so unexpected and unaccepted that no one believed them. Those were really important for me, because I was immediately, at a very early stage in my career, in the middle of national controversy. It is good, from an academic point of view, when you turn out to be correct."

Cue Bloomfield's key role in the 1975 discovery of the Philadelphia chromosome in ALL, which emphasized the biologic heterogeneity of ALL. It showed that molecular characteristics had an impact on personalized therapy and other treatments.

When examining a patient with ALL who was believed to have chronic myelogenous leukemia (CML) because they had the Philadelphia chromosome, Bloomfield knew she was observing something important.

“This was something that was so unusual. This got me to study chromosomes,” she said. “I started to look for the Philadelphia chromosome in particular in patients with ALL, and as it turned out, I found a lot of them.”

Challenging the existing wisdom that the chromosome was only prominent in CML, Bloomfield again faced criticism from the oncology community, adding it was even worse than her earlier findings with AML.

“Researchers would say, ‘she doesn’t know what she’s talking about.’ But of course, as soon as they started to look, they found it themselves,” she said. “It put me on the map rapidly.”

She was approached to give national lectures where senior hematologists would debate Bloomfield and argue her findings.

Her strong-willed attitude came in handy again when she described the rearrangement of chromosome 16q22 in AML.

“The main point was that it was found in a very specific type of AML,” Bloomfield said. “In this case, I subsequently discovered that this type of AML was particularly sensitive to high-dose cytarabine treatment compared to many other AML subgroups. Going along with that is the discovery that high-dose cytarabine is more important in AML with translocations involving chromosomes 8 and 21. We are talking of a cure rate now approaching 80%.”

These pivotal moments were all part of Bloomfield making her way through a “male-dominated field.”

“It takes a certain personality to go against the grain, just being a woman at that point in medicine,” she said. “It was going against the dogma. It’s not like today, where 50% of your medical school class is women. Women just didn’t belong in medicine; it was considered a man’s field. So, I was pretty used to fighting the establishment from that point of view. For me, this didn’t bother me at all. When you see something and you’re sure you’re right, then you stand up for that. Don’t worry about what the dogma is at that time. I still spend a lot of time teaching trainees and younger faculty that that’s what they have to learn to do.”

Bloomfield credits this drive to her academic background.

“It definitely makes you more comfortable continuing to believe in additional things that others may not believe in,” she added.

Her take-charge initiatives have also had an impact in gender equality in the medical field, such as equalizing salary for women.

“I was able to see that women were put on important national committees and have gotten awards,” Bloomfield said. “When I chaired the American Society of Clinical Oncology (ASCO) program committee I made it 52% women.”

Although she grew up with none of her own, mentorship is



important to Bloomfield and she teaches senior faculty how to fight the status quo.

It goes along with her favorite saying: “Believe what you see or find, not what others have claimed.”

“I really tell people that all the time,” she added.

There is truly something special about those relatively rare cases when you discover something new, Bloomfield said, looking back on her career. Today, that boost of adrenaline may come from the development of a novel targeted therapy. Though she is not directly involved with drug development, the news still excites her.

“It’s a rush, so to speak, when you have learned something that is going to improve the clinical outcome for patients,” said Bloomfield.

There are plenty of goals she still has for the field of myeloid neoplasms, such as to witness the majority, if not all, of patients with AML being treated with appropriate curative therapy. Her vision is that AML will become a mainly cured disease.

“When I started, the average survival for 1 type of AML, acute promyelocytic leukemia, was 2 weeks. Now, 90% are cured,” Bloomfield said. “I think that’s possible for the rest of AML and we just need to work on it.”

When asked about hobbies outside of work, Bloomfield quietly laughed and admitted she has none, adding the last time she saw a movie was 5 years ago when her fellows took her to one presented especially for her.

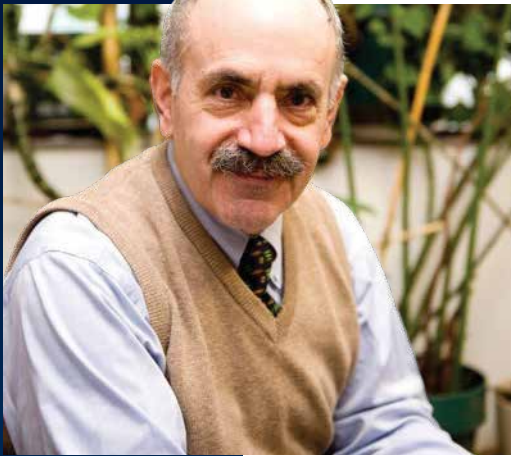


However, she does enjoy tandem bike riding and regularly takes part in the OSUCCC’s annual fundraiser: a 25- to 180-mile ride.

Though she has limited free time, Bloomfield said she would not change a thing about her work. Perhaps she would focus her research on pancreatic cancer, she said, if she were just starting out in medicine today.

But the pioneer who has always pushed the envelope has no plans to quiet down, even if she did have a more flexible schedule.

“Maybe I’d take a half day off a week,” Bloomfield laughed. “I’m always working, and I’ve never learned how not to work.” ■



SCIENTIFIC ADVANCES

Robert A. Weinberg, PhD

MASSACHUSETTS INSTITUTE OF
TECHNOLOGY/WHITEHEAD INSTITUTE

Landmark discoveries on signaling pathways in cancer

When Robert A. Weinberg was a boy, he loved dissecting what was complicated and figuring out what made it work.

When he wasn't taking apart electric trains, he was studying genealogy, tracing the branches of his family tree.

But during those years in Pittsburgh, Pennsylvania, Weinberg had no idea where that passion might lead him.

He attended the Massachusetts Institute of Technology (MIT) because friends of his parents had gone there. He pursued medicine because "in those days, young Jewish boys became doctors" and switched to biology when he made the alarming discovery that "doctors had to stay up all night taking care of patients."

"I'm not a person who's planned out his course in life," said Weinberg, 72, a renowned oncology researcher whose work has changed the world's understanding of cancer. "I just stumble from one steppingstone to the next."

Through a combination of talent and circumstance, that series of stepping-stones has coalesced into a long and successful career for Weinberg, who changed the course of oncology research by discovering the first mammalian oncogene, shedding light on what causes normal cells to form cancerous tumors.

A member of the US National Academy of Sciences, Weinberg was presented with the

National Medal of Science by President Bill Clinton in 1997 and named Scientist of the Year by *Discover* magazine in 1982. In 2013, he won a Breakthrough Prize in Life Sciences, whose creators include founders of Google and Facebook. Given to honor those conducting excellent research aimed at curing diseases and extending life, the honor came with a \$3 million award for “past achievements in the field of life sciences, with the aim of providing the recipients with more freedom and opportunity to pursue even greater future accomplishments,” according to the website of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, which is home to Weinberg’s lab.

This year, Weinberg was named a Giant of Cancer Care by OncLive in the Scientific Advances category, for his landmark discoveries on signaling pathways in cancer.

“I’m flattered,” he said of his selection for the award. “There are a lot of very prominent and world-recognized people among them, and I’m flattered to be included among them.”

ONCOGENE RESEARCH REMAINS A PASSION

Weinberg’s discovery of the first cellular oncogene in mammalian cells, Ras, provided researchers with a deeper understanding of cancer that helped pave the way for the growing tide of targeted cancer therapies. Weinberg and his colleagues made another landmark discovery when they became the first to figure out what makes a normal, dormant gene change into a virulent oncogene. His lab also discovered the tumor suppressor retinoblastoma protein, opening the door to the isolation and study of genes that prevent the onset of cancer.

In 2000, Weinberg shared his comprehensive insights into what makes cancer cells abnormal by co-writing the seminal paper “Hallmarks of Cancer,” the most cited *Cell* article of all time.

“I’m driven by trying to figure things out,” Weinberg said. “It’s

an unrelenting drive leading to occasional ‘Eureka’ moments, with a lot of grunt work in between.”

Weinberg is director of the Ludwig Center for Molecular Oncology at MIT, where he is also the Daniel K. Ludwig Professor for Cancer Research. He joined the staff of his alma mater in the early 1970s, when he became part of its newly formed Center for Cancer Research. Nearly a decade after that, Weinberg became a founding member of the Whitehead Institute.

His team’s work there focuses on the cellular mechanisms that cause cancer to grow and to metastasize—dynamics including epithelial-stromal interaction and the properties of cancer stem cells. Recent papers that include Weinberg as an author focus on both of those topics; one published in January 2015 in the journal *Cancer Discovery* is titled “How does multistep tumorigenesis really proceed?”

Although Weinberg says he hasn’t “touched a test tube in 35 years,” he attends scientific meetings nearly every day in his own lab or with other colleagues to discuss results, offer critiques, and suggest additional experiments. In 2007, Weinberg published a graduate-level textbook, *The Biology of Cancer*, of which he remains very proud; the work is in a second edition after he revised it four years ago, and he is now updating it for a third edition. Weinberg also gives talks at about 25 scientific meetings each year, and at MIT spends about 15% of his time teaching half a course in introductory biology for undergraduates, along with half a graduate course in cancer biology.

In front of the classroom, Weinberg likes to entertain his undergraduates by revealing that he got a “D” in introductory biology, a course he didn’t enjoy when he took it at MIT. And he passes on this wisdom: “Most of the young people in high school have the conviction that biology is all about memorizing facts, when, in fact, it’s a very logical science with a lot of interesting

questions that remain unexplored. It's a very intellectually challenging field."

THE PATH TO UNDERSTANDING

While Weinberg wasn't excited by his initial coursework during his days as a biology student, he found himself in the right place at the right time.

"The revolution in microbiology was just erupting," Weinberg said. "As a junior, I was exposed to the genetic code, which was just being deciphered. All of a sudden it got very interesting, so I became interested in a serious way in the new biology—molecular biology—[and] in taking apart complicated things into their component parts, just like taking apart old electric motors."

Yet at the same time, another revolution was in progress, and it pulled Weinberg away from his studies. In 1965, after a year of graduate school, Weinberg left MIT to teach at Stillman College, a predominantly African-American institution in Tuscaloosa, Alabama. The city had just been ravaged by a hurricane, and the fight for desegregation was in full swing.

"I did feel I needed to do something for the world, and it was a time when people with my talents were needed," said Weinberg. "I was the undergraduate biology department in that college that year. On weekends, I would buy sacks of flour and rice and beans and carry them out to the tent cities of sharecroppers in Greene County, who'd been evicted from their land because they'd registered to vote."

"Everybody was sure I'd stay in Alabama or end up getting buried under a dam, which had happened to some civil rights workers the year before," Weinberg added. "But much to everyone's surprise, I came back to MIT in 1966 and finished my PhD work."

Weinberg went on to complete two postdoctoral fellowships:

one with Ernest Winocour, PhD, at the Weizmann Institute of Science in Rehovot, Israel, where Weinberg enjoyed meeting and spending time with relatives; and the other with Renato Dulbecco, MD, at the Salk Institute for Biological Studies, in La Jolla, California, where Weinberg worked with the DNA tumor virus SV40 to study RNA metabolism.

Weinberg was at the Salk Institute when he received a visit from his future. It came in the form of Salvador Luria, MD, a pioneer molecular biologist who was on staff at MIT.

"He told me I was going to be part of a new MIT cancer center he was founding," recalled Weinberg. "He didn't ask; he just told me. After a couple of days I said 'OK,' so I ended up coming back to MIT—not because I'd planned to do so. It just happened."

In his first year at the cancer center, Weinberg worked as a research associate to David Baltimore, PhD, who had just discovered reverse transcriptase—a revelation that, three years later, would earn him the Nobel Prize, which he shared with two others, including Dulbecco. Intrigued by Baltimore's work, Weinberg decided to explore retroviruses in his own lab.

"Around 1977, we became involved in studying viral oncogenes, and that led to us discover, in 1979, the first cellular oncogene in mammalian cells," Weinberg said. "It was the most important thing that ever happened in my lab."

The experiment involved taking genes from cells that had been exposed to a chemical carcinogen and putting those genes into normal cells. The result was that the normal cells became cancerous, proving for the first time that cancer is a genetic disease. The finding led to the discovery of additional oncogenes by other labs, opening the door to the possibility of targeted cancer therapies.

"It's not as if somebody else would not have done it a year or two later," a modest Weinberg said of his finding. "But that was my moment in the sun."

LAB WORK CONSUMING

The achievement didn't escape the notice of Baltimore, who appointed Weinberg as a lab head when he founded the Whitehead Institute in 1982. It turned out to be a wise decision. During Weinberg's first year at the Whitehead Institute, he experienced the biggest "aha" moment of his career.

He and his colleagues converted a normal gene into a cancer-causing bladder carcinoma oncogene, demonstrating for the first time how a healthy, dormant gene can be transformed into a virulent oncogene.

The cause of the cancer, Weinberg was fascinated to find, "was a point mutation, a single letter or base of DNA among the thousands of bases that, together, constitute a gene."

Eight years later, Weinberg shared his comprehensive understanding in "The Hallmarks of Cancer," which was co-authored by Douglas Hanahan, PhD. The article discussed "six principles, or hallmarks, that turned out to be a very useful conceptualization that explains much of what makes cancer cells abnormal," Weinberg said. He and Hanahan updated the article in 2011, adding information about more recently identified biological mechanisms that contribute to the creation of tumors.

In addition, Weinberg continues to unravel the mystery of cancer in his lab, where he and colleagues are researching the molecular mechanisms that control carcinoma progression and metastasis.

A major focus of their research is the interaction between the epithelial and stromal cells that are often situated in separate layers in the tissues of humans and other mammals; specifically, Weinberg's team is investigating the mechanism by which epithelial cells recruit stromal cells in the development of a cancer. Further, the group is looking at how tumors seem able to reactivate proteins that remain in the body from the process

of embryonic development, stimulating them to contribute to cancer metastasis. In related work, they are studying cancer stem cells, which are self-renewing, can survive chemotherapy, and can cause tumors to grow.

"We will not succeed if we wipe out only the cancer stem cells, we will not succeed if we wipe out only the nonstem cells," he said. "Both populations of cells need to be targeted in order to hope to achieve a durable clinical response, given the plasticity and the bidirectional interconversion between these two different cell types."

Taking the broad view, Weinberg points to immunotherapy of tumors as the most exciting strategy on the horizon within his field. But he fears it will be more difficult than it needs to be for scientists to pursue that goal.

"Funding of basic cancer research is increasingly being marginalized through the headlong rush into translational research," he said. "Those enthusiasts of translational research have long ago forgotten that the pipeline of discovery needs to be continuously filled by basic preclinical researchers who are increasingly under threat."

For his own part, Weinberg describes his work as all-encompassing—not so different, ironically, from the prospect of all-night patient care that discouraged him from pursuing a medical degree during his days as a student. Still, the pioneering researcher has no intention of slowing his pace.

"I don't have time to read a book or to listen to music, which I love doing, so that's been a real sacrifice. It's been going on for 40 years, and I can't get them back," the scientist said. "Still, I feel blessed. Ninety-five percent of the people in the world don't enjoy what they're doing, so my career has been a stroke of good fortune, a gift which I've never taken for granted." ■



SUPPORTIVE/ PALLIATIVE CARE

Charles L. Loprinzi, MD

MAYO CLINIC

Explored better ways to manage treatment-related toxicities

Charles Loprinzi may have landed somewhat accidentally into the world of symptom management research, but once he arrived, he was there to stay.

Loprinzi has dedicated his medical career to oncology, including more than three decades at the Mayo Clinic in Rochester, Minnesota, where he currently serves as the Regis Professor of Breast Cancer Research. Underpinning much of his work—both at the bench and the bedside—has been a dogged pursuit of interventions to provide patients with relief from the debilitating symptoms that often accompany a cancer diagnosis and its treatment.

“I was going to become a surgeon when I was in the first year or two of medical school ... but the very first clinical rotation I had was internal medicine, and I found that that was much more fun than sitting in medical school classes,” Loprinzi explained.

He said that he liked all of internal medicine’s subspecialties, and oncology offered him a way to touch upon many of them. Moreover, oncology was a field where the challenges were plenty: “We needed progress—there were a lot of questions that needed answering.”

Throughout his life, Loprinzi relished such challenges. Enter Charles “Chuck” Moertel, Loprinzi’s colleague and mentor, when he came to the Mayo Clinic during the mid-1980s. Moertel also chaired the North Central Cancer Treatment Group and was looking

for someone to lead symptom control research under the auspices of the Community Clinical Oncology Program (CCOP), because, as he told Loprinzi, “the treatment people don’t want to deal with such research.” Loprinzi put the prevailing sentiment at the time more bluntly when he recalled while as an oncology fellow at the University of Wisconsin, a highly respected colleague said to him, “We don’t do puke studies here.”

Nevertheless, symptom management fit into the CCOP’s work in the area of cancer prevention and control, and Moertel saw in Loprinzi a promising researcher well-suited to lead the effort.

Loprinzi agreed and has never looked back.

PRIORITIZING SYMPTOM RESEARCH

A native of Portland, Oregon, and the second of 10 children borne over a span of only 11-and-a-half years, Loprinzi said he learned early on how to make his own way and to figure things out. He worked at a young age, learned to save the money he needed for his education, and set off for college at Oregon State University, sight previously unseen, with only two “banana boxes” of belongings.

These early experiences helped to set the stage for a career dedicated to problem-solving and tackling the side effects that patients with cancer often confront, and who for some, persist long after their therapy ends.

Symptom management trials were virtually nonexistent when Moertel first approached him to lead some, but since that time, Loprinzi has authored hundreds of studies, focusing on oral mucositis, anorexia/cachexia, hot flashes, and chemotherapy-induced neuropathy, to name a few.

Randomized clinical trials he conducted early in his career demonstrated that megestrol acetate can improve appetite and lead to weight gain in patients with anorexia/cachexia; the re-

search also illuminated the agent’s toxicity profile. Later research he led found that megestrol acetate was helpful at low doses to relieve hot flashes in women with breast cancer, another principal focus of his research over the years.

Loprinzi also sought to find a solution to oral mucositis, a frequent and debilitating side effect of 5-fluorouracil (5-FU) and other chemotherapies. Following up on a suggestion of one of the nurses he was working with in the early 1990s, he led a study giving patients snow cone–like ice chips starting 5 minutes prior to 5-FU administration and continuing for 30 minutes. The result: a 50% reduction in mucositis, according to patient-reported outcomes; ensuing studies replicated the benefit. Cryotherapy is now recommended in guidelines of the Multinational Association of Supportive Care in Cancer—not only for patients receiving 5-FU, but for other chemotherapeutic agents as well.

Currently, Loprinzi’s research is largely focused on chemotherapy-induced peripheral neuropathy (CIPN), a big problem, he said, that can be particularly hard on patients when it persists after treatment ends. He has led multiple randomized clinical trials testing promising-appearing agents for prevention of CIPN and/or treatment of established CIPN, but, “unfortunately, neuropathy remains a major clinical problem, to date.”

“There is a substantial minority of patients who have problems [with CIPN] later on, which can be crippling for them,” he explained, which means it is very important to watch these patients closely as they are receiving potentially neurotoxic chemotherapy, and identify those more prone to it early on. At times, stopping neurotoxic chemotherapy is in order.

Loprinzi and colleagues are exploring scrambler therapy, a nerve stimulation process that has shown some promise in initial CIPN studies. His research team has also evaluated a potentially effective drug traditionally used in the treatment of acne—mino-

cycline—which they tested in a pilot, placebo-controlled, randomized trial; patient accrual has been completed and results are eagerly awaited.

Since those nascent studies he conducted with Moertel, the field of symptom control research has grown steadily. Grounding those trials in strong science is essential, stressed Loprinzi. That means employing scientifically rigorous methodology, pursuing findings that are publishable in prominent clinical journals, and keeping their practice-changing potential top-of-mind—not only by defining new syndromes and treatments, but also by delineating those interventions without benefit or those which may actually cause harm.

Loprinzi has received numerous awards for his research, including the Susan B. Komen Foundation Brinker Award in 2002 and the 2006 Clinical Research Award from the Association of Community Cancer Centers. He has been appointed as an ASCO Fellow and he delivered the Charles G. Moertel Lecture, established in honor of his mentor, in 2013.

THE ART OF ONCOLOGY

Loprinzi came to understand early in his career that cancer treatment was both a science *and* an art. He found a forum to showcase the latter in the “The Art of Oncology” section of the *Journal of Oncology* (JCO). Now in its sixteenth year, it remains a favorite among many oncologists—offering succinct, compelling glimpses into the human side of the oncologist’s everyday practice. He is the section’s founding editor, having served in that role from 2000 to 2011.

Loprinzi said that at first he hesitated when JCO recruited him to be the section’s consulting editor: “I was thinking, ‘I am too busy,’ but then I realized this was an offer too good to be true, and I should just do it. It turned out to be a very educational and rewarding experience.” In addition to the regular feature in JCO, Loprinzi edited two anthologies of selected essays from the series, *Art of Oncology: Honest and Compassionate Responses to the Daily Struggles of People Living with Cancer*, which are available as Kindle e-books.

COMPASSIONATE HONESTY

Loprinzi’s office at Mayo is on the 10th floor, but he rarely uses the elevator to get there. He said that he does some of his best thinking while being physically active, preferably outdoors. For the last few years, he has vacationed with Margie, his wife of more than 30 years, and other couples on week-long walking tours in Great Britain.

The father of three grown children who all live nearby him—two following his footsteps into healthcare careers—also likes to split firewood.

“I cut all of my own firewood, even in the middle of winter when it is below zero degrees outside. This is good thinking time.” He notes that when it is really cold outside, the wood splits better. It is often on these occasions that Loprinzi finds he can reflect on some of the practice and research challenges he faces every day.

Breaking issues down is a strategy that has helped him throughout his career. A case-in-point: how to determine—and convey to the patient and family—what treatment approach is right for each individual. For some



MERCK

Giants
OF Cancer Care



ive



TIS

Onco

NOV

Giants
OF Cancer Care

OncoLive
PRESENTS

Giants
OF
Cancer Care

individuals, the goal of treatment is to try to cure the patient. For other patients, this is not a realistic goal, however, noting that in oncology you ‘never say never and never say always.’ For patients where cure is not the goal, he explains that the goal is to have the patient ‘do as well as is possible for as long as is possible.’ He further notes that this can be broken down into four items:

“First, we want you to have the fewest side effects as possible from the cancer for as long as possible. Second, we want you to have the fewest side effects as possible from the treatment. Third, we want you to have the longest life, and fourth, we want you to have the best quality of life.”

Loprinzi said that he does not determine which one of these 4 components is most important for each of his patients, but rather, sees this approach as a framework to help guide these conversations for physicians, and, importantly, it explains the issues in a way that patients and families can understand. It also can stimulate reflection on the risk–benefit profile of certain therapies—not only when to start them, but also when to stop.

“I think that there is a tendency for some physicians to treat too many patients, for too long, for too little benefit, without patients knowing it and without physicians admitting it,” he said.

“There is a time for stopping cytotoxic therapy. I am convinced there is a time when chemotherapy causes net harm if it is used for too long, causing survival to be shorter than it would be without it; we do not know exactly when that is.”

The lodestar for Loprinzi’s work in caring for his patients when cure is not a realistic option is one of “compassionate honesty.” This means sitting down with his patients in the clinic, where he still spends about 20% of his time, to ascertain what their goals are as he provides a realistic assessment of their prognosis.

ALWAYS MORE PUZZLES TO SOLVE

Loprinzi currently leads the symptom control program of the Alliance for Clinical Trials in Oncology Group. Among its latest projects is a new multisite trial led by Jennifer Temel of Massachusetts General Hospital. Temel was the lead investigator on the seminal study demonstrating a survival benefit when early palliative care was provided to patients with metastatic non–small cell lung cancer (NSCLC) published in the *New England Journal of Medicine* in 2010.

The new trial (NCT02349412), which is rapidly accruing patients, noted Loprinzi, is examining the effect of early palliative care beyond the NSCLC setting to include patients being treated for other advanced lung and gastrointestinal cancers.

“When I started my career, very few people were focusing on symptom management,” recalled Loprinzi, “but now, it has become more popular. I can tell you that a number of practicing oncologists are very happy to hear the results of many symptom control studies, which influences their clinical practice.”

Still, he underscored, one trial will not give a researcher all of the answers, and as one question gets answered, 10 more are likely to emerge, which is one of the features of oncology research and practice that attracted Loprinzi in the first place:

“I have been very fortunate to have been associated with a number of clinical trials which have described interventions that have actually influenced clinical practice.” ■

2014 INDUCTEES



OUTREACH
Edith A. Perez, MD
Mayo Clinic



MELANOMA
Jedd D. Wolchok, MD, PhD
Memorial Sloan
Kettering Cancer Center



LUNG CANCER
Paul A. Bunn Jr, MD
University of Colorado
Cancer Center



MYELOMA
Kenneth C. Anderson, MD
Dana-Farber Cancer
Institute/Harvard
Cancer Center



PROSTATE CANCER
Patrick C. Walsh, MD
Johns Hopkins
University



LYMPHOMA
Riccardo Dalla-Favera, MD
Columbia University
Medical Center



BREAST CANCER
Dennis J. Slamon, MD, PhD
UCLA Jonsson
Comprehensive
Cancer Center



EDUCATION
John R. Seffrin, PhD
(retired)
American Cancer
Society



**HEAD & NECK
CANCER**
Kie Kian Ang, MD, PhD
(deceased)
The University of Texas
MD Anderson Cancer
Center



SUPPORTIVE CARE
Jimmie C. Holland, MD
Memorial Sloan
Kettering Cancer Center



**GENITOURINARY
CANCER**
Philip W. Kantoff, MD
Dana-Farber Cancer
Institute/Harvard
Cancer Center



**DRUG
DEVELOPMENT**
Howard A. Burris III, MD
Sarah Cannon
Research Institute



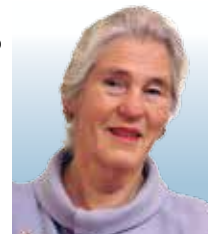
LEUKEMIA
Hagop M. Kantarjian, MD
The University of Texas
MD Anderson Cancer
Center



**GASTROINTESTINAL
CANCER**
George D. Demetri, MD
Dana-Farber Cancer
Institute/Harvard
Cancer Center



**SCIENTIFIC
ADVANCES**
James P. Allison, PhD
The University of Texas
MD Anderson
Cancer Center



GENETICS
Janet Davison Rowley, MD
(deceased)
University of Chicago

2013 INDUCTEES



BREAST CANCER
Bernard Fisher, MD
University of Pittsburgh



GASTROINTESTINAL CANCER
Bert Vogelstein, MD
Johns Hopkins Medicine



GENETICS
Elizabeth H. Blackburn, MD
University of California, San Francisco



GENTOURINARY
Lawrence H. Einhorn, MD
Indiana University



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



LEUKEMIA
Brian J. Druker, MD
Oregon Health & Science University



LUNG CANCER
Thomas J. Lynch Jr, MD
Yale Cancer Center



PROSTATE CANCER
Charles L. Sawyers, MD
Memorial Sloan Kettering Cancer Center



SCIENTIFIC ADVANCES
Judah Folkman, MD (deceased)
Harvard Medical School



LYMPHOMA
Vincent T. DeVita Jr, MD
Yale Cancer Center



MELANOMA
Steven A. Rosenberg, MD, PhD
National Cancer Institute



MYELOMA
Robert A. Kyle, MD
Mayo Clinic





INDEX

NAME

CATEGORY

B

Bast, Robert C. , Jr
Bloomfield, Clara D.

Gynecologic Malignancies 34
Myeloid Neoplasms 64

F

Freireich, Emil J.
Freeman, Harold P.

Lymphoid Neoplasms 50
Community Outreach/Education 16

H

Hortobagyi, Gabriel N.
Hussain, Maha H.

Breast Cancer 10
Genitourinary Cancer 28

J

June, Carl H.

Immuno-Oncology 40

L

Loprinzi, Charles L.

Supportive/Palliative Care 74

M

Mayer, Robert J.
Minna, John

Gastrointestinal Cancer 22
Lung Cancer 44

R

Ribas, Antoni

Melanoma 58

W

Weinberg, Robert A.

Scientific Advances 70

