LUDWIG
CANCER
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Women in science

PERSPECTIVES FROM LUDWIG LEADERS

WELCOME

Voices in a vital conversation

Recent events have combined to raise issues related to women in science to a prominent place in the global discourse. Among these are the gender disparities that continue to trouble the professional lives and prospects of women in science. A study published in 2021 by the National Academies of Sciences, Engineering, and Medicine, for instance, documented how measures like shutdowns early in the pandemic exacted a far greater toll on the careers and mental wellbeing of women scientists than those of their male peers. Another recent study, this one examining diversity at 103 cancer centers affiliated with the Association of American Cancer Institutes, found that women are underrepresented in all leadership positions, ranging from 16% for center directors to 45% for associate directors. Imbalances extend to the level of research program leaders, of whom only 39% are women. In all categories, these disparities are especially marked for racial and ethnic minorities.

Edward A. McDermott Jr.
President and Chief Executive Officer

Chi Van Dang
Scientific Director

To contribute to this ongoing conversation, we spoke with some of the women leaders of Ludwig Cancer Research—principal investigators, advisors, directors—about their lives, careers and views on gender-related issues. What emerged from our interviews is a celebration of women leaders in our community and their insights on matters ranging from science to leadership to family.

Many spoke about how essential it was for them, early on, to develop confidence in their scientific acumen, and all recalled with gratitude the mentors who shaped their careers. Several also described how they try to open doors and extend opportunities to other talented women in their field.

Much of the advice they gave is relevant to any gender: to be prepared to accept the opportunities for advancement that come your way, for example, or to take educated risks and remain unperturbed by the failure of experiments. Almost all the Ludwig women leaders spoke about the importance of reserving time and attention for family. In line with that, most explicitly advocated for more institutional support for scientists—men and women—raising young children or caring for elderly parents.

Of course, we also enjoyed hearing the stories these Ludwig scientists shared with us about their lives, their "Aha!" moments and the fascinations and friendships that fueled their careers. We hope you do as well, and that you join us in celebrating the contributions of these outstanding Ludwig leaders.

Sincerely,

Edward A. McDermott Jr.

Chi Van Dang

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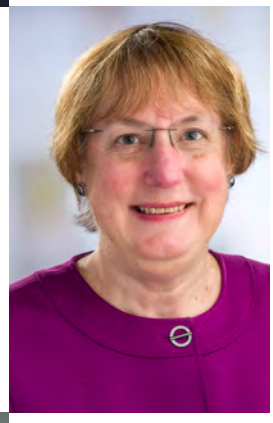
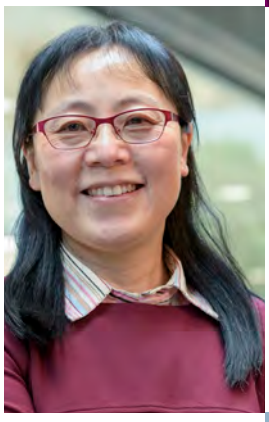
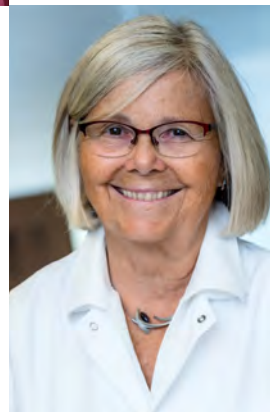
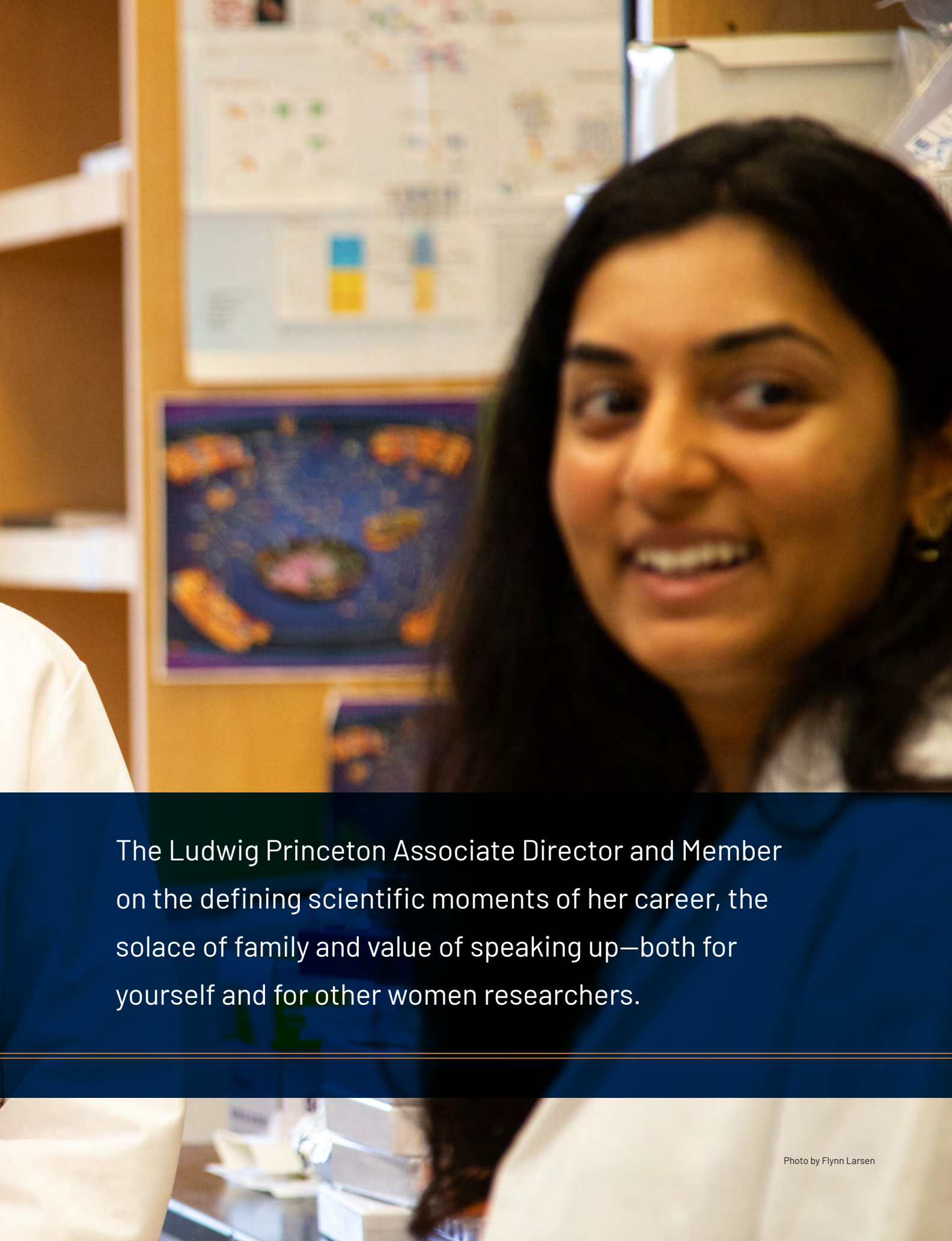






Eileen WHITE



The Ludwig Princeton Associate Director and Member on the defining scientific moments of her career, the solace of family and value of speaking up—both for yourself and for other women researchers.

Photo by Flynn Larsen

A brand new postdoc in Bruce Stillman's group at Cold Spring Harbor National Laboratory in 1983, Eileen White couldn't believe her good fortune when her new boss handed her a viral oncogene and told her to figure out what it does.

Eileen White in 1983

Scientific dogma at the time held that oncogenes do just one thing: drive cell proliferation. But White's viral oncogene—E1B—apparently hadn't received the memo. "This oncogene seemed instead to be preventing cells from dying," says White, who is today associate director of the Ludwig Princeton Branch. "People didn't believe it, but I could see what was happening with my own eyes. I knew I was right."

Collaborating with Harvard scientist Stanley Korsmeyer, White pressed ahead with the experiments required to prove her hypothesis. Those studies were completed after White set up her own lab at Rutgers University, where she is currently chief scientific officer and deputy director of the Rutgers Cancer Institute of New Jersey. They confirmed that oncogenes can function by inhibiting programmed cell death, or apoptosis, and helped launch a field of study that continues to inform new strategies and drugs for cancer therapy. And that was just for starters. While exploring the suppression of apoptosis in cancer, White and her colleagues made the serendipitous observation in the late 90s that cultured malignant cells could survive extreme starvation. Her laboratory's investigation of the phenomenon yielded yet another transformative discovery: that cancer cells depend on autophagy—in which cells cannibalize their innards—to survive.

White's lab has since demonstrated in mouse models the importance of autophagy to lung, prostate, breast and melanoma tumors, and shown that both cancer cell and systemic autophagy are essential to tumor growth. Her work, often done in collaboration with Ludwig Princeton Director Joshua Rabinowitz, has elucidated metabolic reasons for this dependency and shown, more recently, how autophagy can additionally support tumor survival by suppressing anti-cancer immune responses. These discoveries and the ongoing research they've inspired hold considerable promise for the development of new treatments and therapeutic strategies for cancer.

WELLS OF CONFIDENCE

A native of Long Island, White had always been interested in biology. After obtaining her bachelor's degree at the Rensselaer Polytechnic Institute in New York, she completed her graduate studies in Eugene Katz's laboratory at the State University of New York, Stony Brook, studying developmental genetics. Aside from Katz, White found excellent mentors in her department chair Arnie Levine, who had co-discovered p53—the apoptosis-inducing tumor suppressor that is mutated in half of all cancers—and Joan Brugge, who had discovered and characterized the viral oncogene Src and is today co-director of the Ludwig Center at Harvard (see profile, page 48).

"Joan was a symbol of a successful woman in science," says White. "She is a brilliant scientist and was a role model in that she

demonstrated that what I was trying to achieve was actually possible."

Confidence in her own possibilities—and capabilities—came from other sources as well. As she progressed through her scientific training, White recalls that she noticed senior researchers often asked the same questions at seminars that she had in her head. "Knowing that I could carry my weight with leaders in the field gave me the confidence to speak up," says White. "So, then it wouldn't be the famous older scientists asking the question, it would be me."

Today, when asked by young researchers, especially women, for advice on how to succeed as a scientist, White encourages them to believe in their own abilities and informed hunches, to speak up. Self-confidence was, after all, what empowered her to discard dogma and prove that her viral oncogene suppressed apoptosis. "I tell them, 'Let your voice be heard and don't be afraid,'" White says. "If you occasionally say something wrong, people will forget about it. If you know what you're doing, there's no downside to making your voice heard."

INGREDIENTS OF SUCCESS

What you're speaking up about also matters, of course. White notes that, as a postdoc, she was not only working on a problem she was passionate about, but one that was of some significance to both basic science and medicine. She often advises young researchers to carefully consider the problems they pick. They have to be intellectually stimulating to you—science is hard and fascination an important element of motivation—but the answers should also be of sufficient importance to science or health. And the problems absolutely must be technically tractable. "All these pieces have to come together," she says.

Taking time for a personal life also matters. In White's case, that desire additionally served

Photo by Flynn Larsen

> "Let your voice be heard and don't be afraid. If you occasionally say something wrong, people will forget about it. If you know what you're doing, there's no downside to making your voice heard."

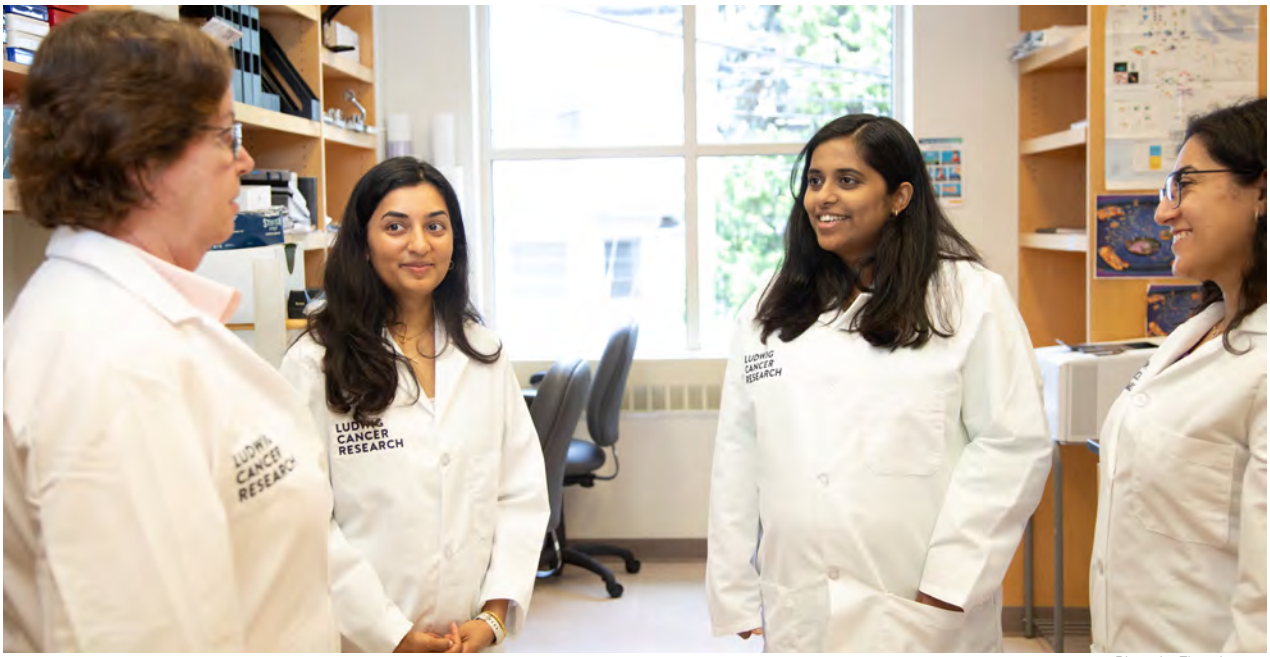


Photo by Flynn Larsen

Eileen White with, from left, PhD student Maria Ibrahim, research associate Akshada Sawant and postdoctoral fellow Maria Gomez.

as a kind of incentive. "I got married while I was a graduate student, and I wanted to have a family, but I knew it was going to be extremely hard to do that and be a scientist at the same time," she says. "I thought, if I'm going to be sacrificing myself, and asking my family to sacrifice themselves, I'd better make it count." Ultimately, she says, fulfilling both those ambitions depended a great deal on her husband's support and entailed much coordination.

Not that family was an encumbrance. Quite the opposite. "Spending time with the family was a good outlet," White says. "If things in the lab are terrible, and you go home and you play with your children, it sort of makes the bad things go away. Not being a scientist 24 hours a day, and setting aside time to do something completely different, like watch my child play soccer, was very important to my mental wellbeing."

White recalls that some senior scientists she came across at the time assumed that a woman who chose to become pregnant wasn't serious about her career. But she had enough support from mentors and like-minded peers and was sufficiently self-assured to be unaffected by such biases.

WOMEN IN SCIENCE

Other manifestations of sexism were more systemic. White notes that, early in her career, the insights and opinions of women scientists were often accorded less weight than those of their male counterparts. That attitude also influenced professional events in tangible ways. "I would be invited to speak at a meeting and I'd notice that I was the only woman on the program, and I would confront the organizers of the meeting, saying, 'Why are there no other women on the agenda?'" White recalls. On one such occasion, she was told by the organizers that they couldn't think of any other women in the field worth inviting as speakers. She responded by offering them a list of women scientists she said were at least as, if not more, worthy of the honor.

This, she says, has changed in recent years. Many institutions that host or fund conferences, like the National Institutes of Health and Cold Spring Harbor, now routinely scrutinize the roster of invited speakers for gender disparities. "That was an evolution, and a resolution of this problem was to raise awareness about the bias we were seeing in scientific conferences," says White. "It started mostly with gender equity because it was so obvious. But now it has transcended to other types of diversity issues, and I think that's a great evolution." Still, White continues to encourage young scientists to champion women in their field.

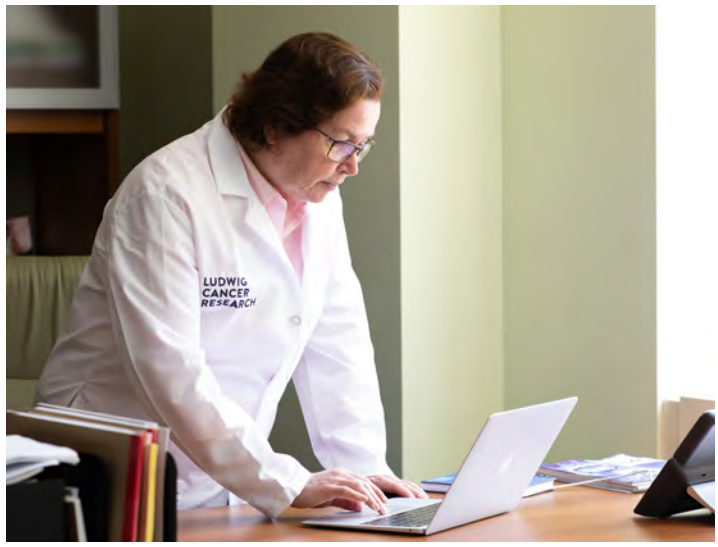


Photo by Flynn Larsen

LOOKING AHEAD

Though sexism is now far less pervasive in science than it was in the early 1980s, White notes that it is also much harder today to establish a scientific career, a difficulty exacerbated by the COVID-19 pandemic, which has exacted a disproportionate toll on young researchers and women. More needs to be done to support women—and men—starting out on a scientific career, says White. One important step would be to increase salaries for young researchers. "Being a scientist can be very exciting but I think, more so than in other fields, the money you're paid early in your career is very, very low," she says. This discourages people who are starting families, as many are at that stage of their lives, from pursuing a life of science. The low pay particularly disincentivizes women, minorities and people of limited means, all of whom are typically already dealing with a mix of other structural and economic challenges.

This, says White, is particularly true given the ever-increasing time it takes for researchers to obtain their first R0-1 grant. Many don't get these foundational grants until they're in their mid-40s. Addressing that will require larger changes to funding in biomedical research. For now, however, White suggests research institutions can support young scientists in other ways, by offering daycare support, for example, or giving researchers more time to complete the work necessary to achieve tenure. White notes that organizations like Ludwig can help address some of the difficulties, like the high expenditure of time and money that goes into childcare—which are burdens to all young researchers, but often disproportionately borne by women.

Many of the required changes will depend on more generous funding for research from government treasuries, White admits. But she argues that such funding is also eminently justifiable, given the economic, medical and societal rewards that demonstrably flow from public support for scientific research. For now, she encourages young researchers not to lose faith in their career choice.

"Perseverance is an important part of the job, but I would say that if you make great scientific discoveries, it's worth it," White says. "Those discoveries don't happen every day but if you persevere, ask the right questions and answer them, the grants will come, the papers will come and your trainees will be excited about their work. It can be a very satisfying career."

Sangeeta BHATIA

The Ludwig MIT investigator on the importance of childlike curiosity to a scientific career, her long-standing advocacy for women as scientists and entrepreneurs and making science fit her life—not the other way around.

Photo by Len Rubenstein

By the time Sangeeta Bhatia was in high school, she and her father—immigrant, engineer, entrepreneur—had worked out a plan for her life.

"The idea was that I would get a bachelor's degree, and a master's, and then I would go be a captain of industry," says Bhatia, who is today a member of the Ludwig Center at MIT. That plan, she confesses, "evolved a lot along the way."

Yet its contours remain distinctly visible in her biography. Bhatia indeed obtained a BS in engineering from Brown University and an MS in mechanical engineering from MIT. But she also went on to earn a PhD in biomedical engineering from a joint program of Harvard University and MIT and added to that an MD from the former. As for being a captain of industry, she chose instead to become a scientist and inventor—who has so far launched six biotechnology startups, received the 2014 Lemelson-MIT Prize (a.k.a. the "Oscar for inventors") and is a member of the National Academy of Inventors. Her accomplishments in fields ranging from oncology, hepatology and infectious disease to nanotechnology and tissue engineering have earned her the extremely rare distinction of election to all three of the U.S. National Academies (Medicine, Science and Engineering), as well as the American Academy of Arts and Sciences.

Scientific achievement isn't the only thing that distinguishes Bhatia. She has also emerged as a leading advocate for gender equity in fields related to science, technology, engineering and mathematics (STEM).

FINDING A NICHE

As an undergraduate at Brown in the mid-1980s, Bhatia worked as an intern in the laboratory of the tissue engineer Patrick Aebischer, trying to apply piezoelectric materials to support nerve regeneration. Bhatia grew fascinated with the possibility of devising materials that communicate with living tissue for therapy. After a gap year at a drug company, she enrolled in the Harvard-MIT Health Sciences and Technology (HST) program . "I was one of two women in a class of about 40 students," she recalls.

The HST program required students to take a year of classes at Harvard Medical School, and it was there that Bhatia "fell in love with the human body" and decided she'd become a doctor as well. For her graduate research, meanwhile, Bhatia developed microfabrication technology to grow liver tissue on a chip in Mehmet Toner's lab at Massachusetts General Hospital. Toner would prove to be an influential mentor to Bhatia. "He saw more in me than I saw in myself," says Bhatia. "He was the one who said I should at least consider interviewing for faculty positions. He saw that I had leadership potential and gave me that nudge of encouragement."

Taking his advice, Bhatia accepted a tenure-track position at the University of California, San Diego, where she set up her first lab as she completed her medical training, and her husband—systems biologist Jagesh Shah—took up a postdoctoral fellowship. "I actually was not sure I wanted to be a professor," she says. "My husband said to me, 'Let's just go try it out.'" As it turned out, Bhatia loved training young scientists and found herself surrounded by supportive colleagues.

"I didn't feel that pressure to succeed as a junior faculty member where my whole life was on the line," she says. "That allowed me to take more

Sangeeta Bhatia speaks at *TED Talks Live—Science and Wonder* in 2015.

Photo by Ryan Lash/TED

risks scientifically and follow my curiosity into new spaces." One of those spaces was nanotechnology, a brand new field at the time. Bhatia began collaborating with Erkki Ruoslahti, president of the Burnham Institute in San Diego, to devise targeted nanoprobes for medical imaging. A paper out of that collaboration, she notes, remains among the most highly cited of her publications.

Bhatia drew an important lesson from that experience. "The reason to be in this profession is to do things that other people aren't also doing," says Bhatia. "Science can be scary. We train a really long time, and it feels like the stakes are high. And so, people can become overly strategic. They think, 'What is my one reagent? Which experiment am I going to take to my lab and build my lab around.' I ask them, 'What are you curious about, like when you were a kid?' That spirit, in my opinion, is the most important thing to hold on to." Though obtaining funding can feel like a consuming challenge these days, Bhatia notes, things aren't quite hopeless. "We all think about going to the NIH, which is a wonderful mainstay, but there are also a lot of philanthropic and foundation sources," she says. "There's sponsored research from companies which, if done carefully, can also provide insights into knowledge gaps that are not obvious in the public domain. We have to teach our trainees to think a little bit broader about funding so that they can get going with their great ideas earlier in their career."

HOMING INSTINCTS

As her career took off in San Diego, Bhatia became pregnant with her first child. There

> The more comfortable you are being yourself, the more successful you're going to be as a leader."

Photo by Bill Gallery

was uncertainty about departmental policies in addressing pregnancy and childcare, since the issue had never come up. "So, I said, 'Okay, I'm going to learn about best practices and recommend them to the department,'" she recalls. "And that's what we did." She was also greatly helped by a Packard Fellowship, which allowed her to use $10,000 of her stipend every year for childcare. "That may sound small in the scheme of a grant, but it was just life changing for me as a young investigator," she says, adding that she still pushes the institutions she interacts with to adopt similarly supportive childcare policies.

Though she loved her work and colleagues at San Diego, Bhatia felt the urge to move back to Boston "After my husband and I had our first daughter, we felt this enormous pull to be near family again," she explains. "We both come from big Indian families. A lot of what I've done since having kids has been around being the mother, wife, daughter and sister I want to be. Those things take time. I've made a lot of choices to have science fit in my life and not the other way around."

In 2005, Bhatia accepted a position at MIT where she is today John J. and Dorothy Wilson Professor of Health Sciences and Technology and of Electrical Engineering and Computer Science. Her lab had now expanded from the engineering of liver tissue and microfabrication to nanotechnology and then oncology, where she saw huge potential for the use of nanomaterials for diagnosis and therapy. She has sought to recreate in her lab the ethos of scientific freedom she enjoyed as a young professor in San Diego. She lets her trainees spend 20% of their time tinkering, for example. "They call it submarine time, where they can try something out that they are curious about," she explains. "It doesn't have to be anything to do with their project. Science is full of failure, so you have to have those fun moments."

That culture has probably contributed something to the launch of five biotechs out of Bhatia's lab, not to mention the many more established by her trainees. Most recently, Bhatia has co-founded a company—Glympse BIO—developing a sensor technology for the noninvasive detection of disease, including cancer. Another, Satellite Bio, which recently launched with $110 million in funding, builds on her work engineering liver tissue to advance a new approach to regenerative medicine.

THE ADVOCATE

Between running her lab and launching

companies, Bhatia—a mother of two STEM-inclined girls, as she puts it—actively advocates for gender equity in science. Her efforts date back to 1993, when she and other women graduate students at MIT started a program, Keys to Empowering Youth, to inspire middle school girls to set their sights on STEM-related fields. "Young girls drop out of science disproportionately," says Bhatia. "It starts at age 11 and is especially notable in subfields of engineering, math and physics." Keys to Empowering Youth, is now run by an undergraduate Society of Women Engineers, for which Bhatia serves as an advisor. Bhatia also advocates for measures to promote gender equity further along the career path, such as deliberately ensuring parity in faculty and postdoctoral pay and recruitment, and in selecting speakers at conferences. "There's a long list of best practices," she says. "The NSF Advance Program has entire slide decks that you can download for your institution, and you can just adopt those policies."

In a field as dominated by males as engineering, Bhatia recalls it took some time to feel at ease being herself. "I felt like an imposter in the room, and I was watching myself and picking my moment to speak," she recalls, describing what is commonly referred to as "imposter syndrome." She compensated by burying her femininity—avoiding makeup, wearing pantsuits. That, she says, changed after she read about the phenomenon and as she gained confidence in herself and came to appreciate her differences in ways she hopes other young women researchers do as well. "I realize that I manage differently, I do science differently, I start companies differently, I mentor differently, and that's actually a strength," she says. "The more comfortable you are being yourself, the more successful you're going to be as a leader."

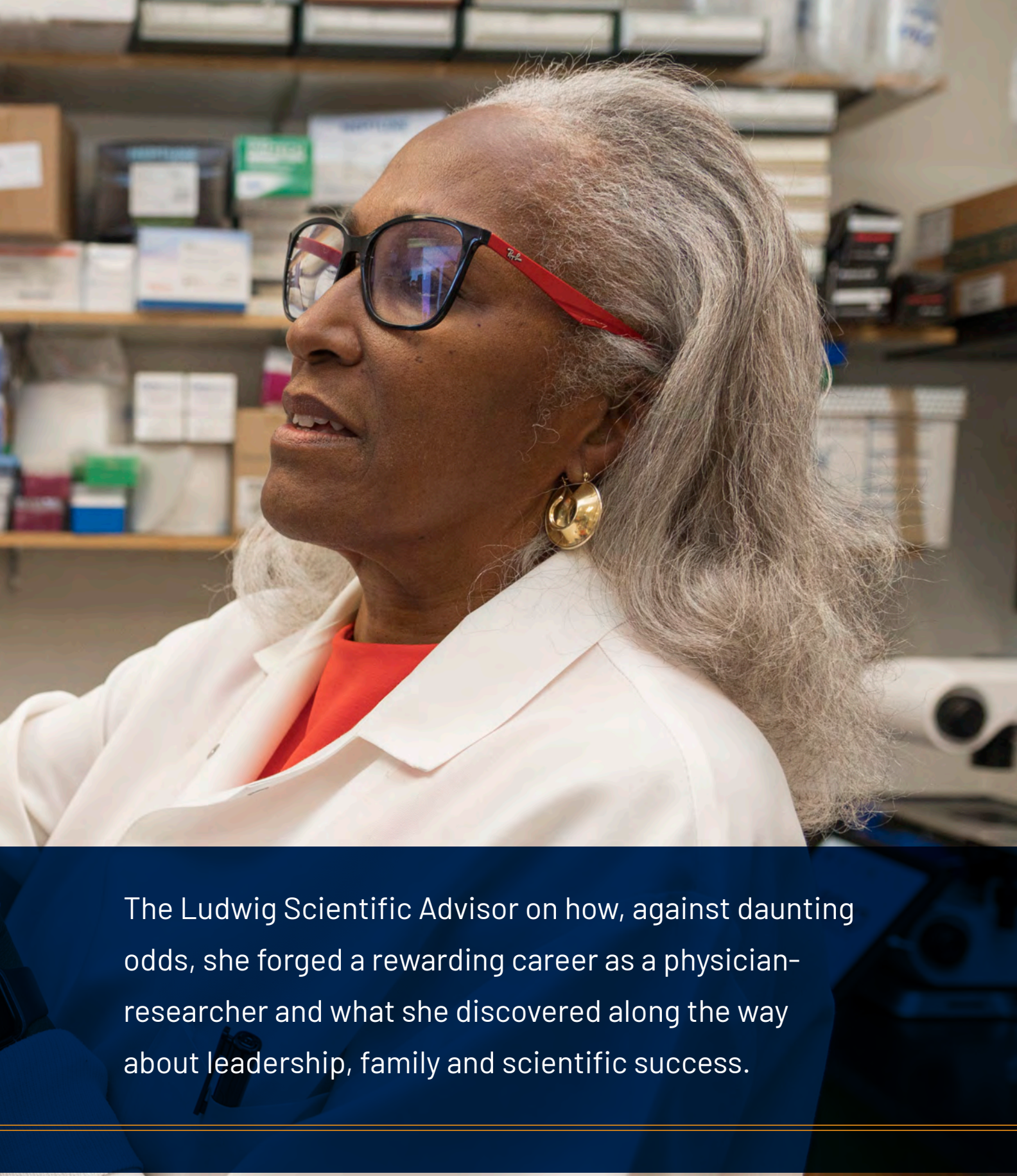
Lately, Bhatia has aimed her advocacy at the highest rungs of the biotechnology ladder. With her friend and mentor Nancy Hopkins—a molecular biologist who famously led an influential study in the late 1990s documenting gender discrimination across the School of Science at MIT—and Susan Hockfield, a former president of the university, Bhatia launched in 2018 the Boston Biotech Working Group (BBWG). Its aim is to bring gender parity to the notoriously male-dominated venture capital (VC) industry, which funneled just 2% of total funds to firms launched exclusively by women in the U.S. in 2021, according to the research firm PitchBook. A report put together by BBWG showed that less than 10% of the 263 start-ups spun out of seven departments at MIT had been founded or co-founded by women between 2000 and 2018, a period in which women comprised 22% of the faculty.

The BBWG hosted a series of dinners with VC and healthcare industry leaders to generate ideas about how to address these disparities. This exercise gave rise, among other things, to the Future Founders Initiative sponsored by Northpond Ventures, which recently underwrote a competition between aspiring women entrepreneurs for an incentive prize.

"We had nine women compete," says Bhatia. "We created a cohort so they could support each other. We gave them world class mentors." The winner received $250,000 in discretionary funds, and the two runners up won $100,000 each. But the others too benefited from the experience. "Eight of the nine are planning to start companies now," Bhatia notes. BBWG's aim is to cultivate an "ecosystem" that empowers women entrepreneurs, says Bhatia. "We have data gathering projects, mentoring projects, and initiatives to get more women on boards," she says. "We have all kinds of experiments to accelerate the pace of change."

If Bhatia's track record is any indication, their results will be as useful as they are enlightening.

Juanita MERCHANT



The Ludwig Scientific Advisor on how, against daunting odds, she forged a rewarding career as a physician-researcher and what she discovered along the way about leadership, family and scientific success.

Photo by Noelle Haro-Gomez

As far back as Juanita Merchant can remember, her mother drummed into her and her brother the indispensability of a good education.

A woman of preternatural will, she had escaped the virulent racism and poverty of rural Oklahoma in the 1930s and earned a bachelor's degree from a Historically Black College near Tulsa. She then repeated that feat at another college in California—and earned a master's degree as well—to qualify for a teaching job in Los Angeles, California, on which she raised her two children alone after her husband, a World War II veteran suffering from alcohol dependency, left the family when Merchant was about eight years old.

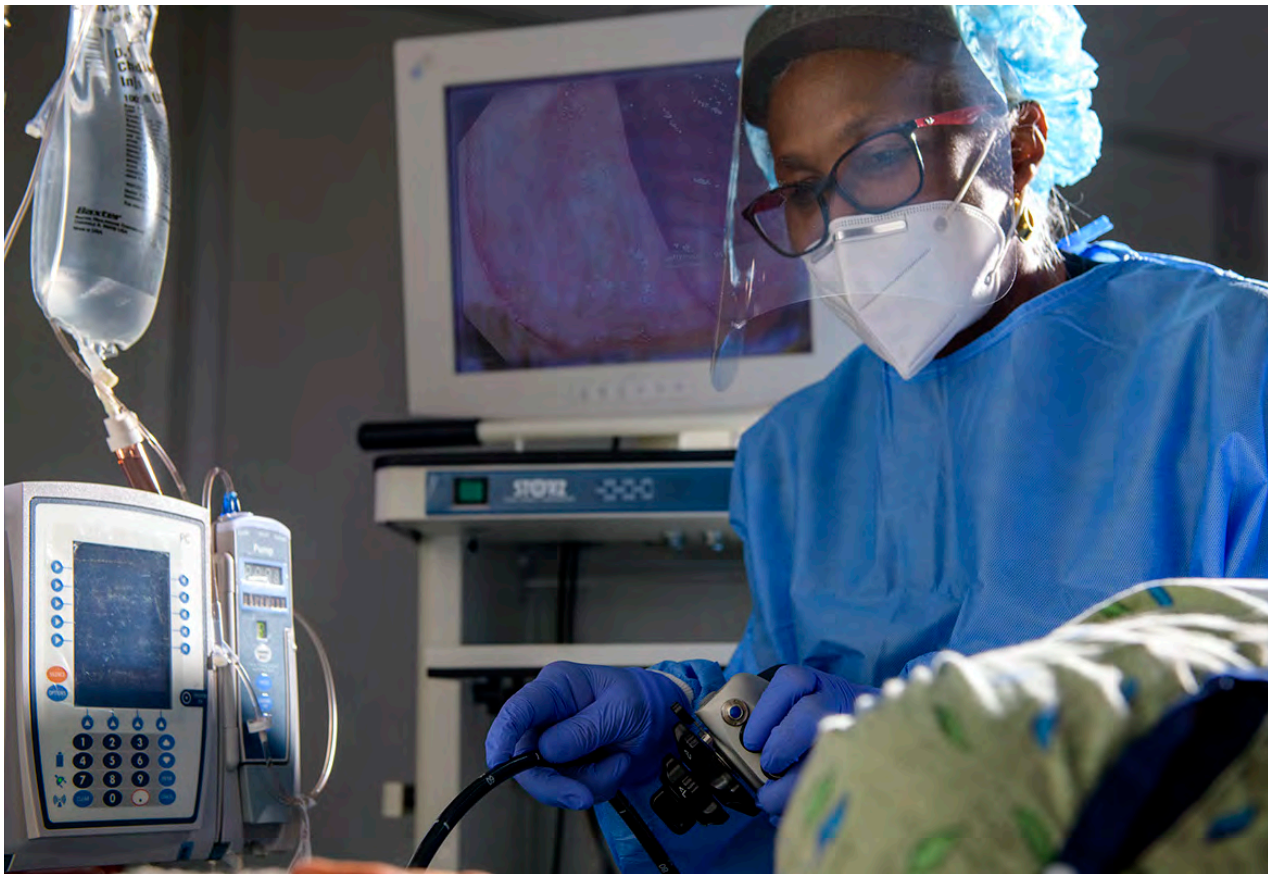
Little wonder, then, that when Merchant finished middle school, her mother made sure she was bussed to a high school that offered college prep classes. But the counselors of the LA school system had other ideas. They pushed Merchant into home economics, where she would learn to sew, cook, knit and type. "This was the mid-60s, and there just wasn't any expectation that someone like me was going to go to college, and certainly not that I'd go into science," says Merchant. Undeterred, Merchant took college prep courses in summer school, got admitted to Stanford University in 1973 and then went on to earn an MD and PhD from Yale University.

In 2018, after "retiring" from a rewarding 27-year academic career at the University of Michigan, Merchant joined the University of Arizona, Tucson, where she is today the Regents Professor and chief of the Division of Gastroenterology and Hepatology at the College of Medicine. Over the past three decades, Merchant—who is also a scientific advisor to the Ludwig Institute for Cancer Research—has compiled a rich portfolio of research on the molecular biology of gastric cancers and the regulation of gastrointestinal growth and colon cancer by a transcription factor she isolated named ZBP-89. Still, the home economics experience may not have been entirely pointless. Some ghost of that education, Merchant muses, may have recently helped inspire her to devise a program in healthy cooking for people with gastrointestinal issues—one in which she currently cooks with patients in Tucson.

Juanita Merchant as a postdoctoral GI fellow at Massachusetts General Hospital out for dinner with other GI research fellows.

FORGING A PATH

At Stanford, where Merchant majored in



Juanita Merchant demonstrating an upper endoscopy at the University of Arizona.

Photo by Kris Hanning

biology, she met her first and perhaps most formative mentor, Renu Heller, in whose lab she researched cholesterol metabolism in the small intestine. Merchant credits Heller, a biochemist of Indian origin, with opening her eyes to the challenges women, especially minority women, were likely to face pursuing academic careers in science and medicine. She pushed Merchant to build up her qualifications. "She said, 'if you want to be successful, you should get both an MD and a PhD,'" says Merchant. "The point she was making was that women need to be overqualified because they are not considered competitive if they don't really stand out." Heller also pushed Merchant to apply to her alma mater Yale University, which was then one of the few schools offering an MD-PhD program.

Merchant's PhD research at Yale involved the characterization of an enzyme isolated from the duck salt gland, a relatively obscure subject involving endless hours of electron microscopy. When Merchant found she would need to study the phosphorylation—a key chemical modification—of the Na,K-ATPase enzyme, Fred Gorelick, a gastroenterologist who had a lab next door offered his help. Over several days, he met with her at 6 A.M., prior to starting his clinical endoscopic procedures, to show her how to assay protein phosphorylation. He would be a lifelong friend and mentor to Merchant, who became the first African American to complete an MD-PhD in Yale's Medical Scientist Training Program.

Merchant met another important mentor when she began her residency at Massachusetts General Hospital (MGH) in 1984. During her second year, she and another resident were the only African Americans

> Women need to be overqualified because they are not considered competitive if they don't really stand out."

in the program when they were approached by the Chair of Medicine, John Potts, who wanted to understand why Harvard's Black medical students weren't doing their rotations at the hospital. When the pair answered that they did not know, Potts asked them to arrange a pizza dinner with minority students to discuss the matter. "After that meeting, the very next year, they started turning up for rotations at the hospital," says Merchant. The episode was to Merchant a lesson in proactive leadership. "John was very forward thinking in even asking that question, and I really appreciated that," says Merchant. "He was very supportive and wanted to understand how to increase diversity in clinical training at MGH."

After completing her residency in 1987, Merchant began a three-year fellowship in Stephen Brand's laboratory at MGH, where she learned molecular biology. Her project involved exploring the DNA elements associated with the expression of gastrin, a hormone that drives acid production in the stomach. By the second year of her fellowship, Merchant published her first paper on the subject and won a four-year career development grant, both of which worked wonders for her self-confidence. The gastrin project would also become the longest running research program in her lab, spawning over the next 27 years many new avenues of research, including her studies on ZBP-89 and gastrin's role in gastric cancer initiated by *H. pylori* infection.

That project also took Merchant to a scientific meeting in Montreal, Canada, where she met the most important mentor of her career, the late Tadataka "Tachi" Yamada, a prominent researcher in her field and chair of internal medicine at the University of Michigan, Ann Arbor. After Merchant completed a fellowship in gastroenterology at the University of California, Los Angeles, in 1991, Yamada recruited her to his department, including with the formal offer a handwritten note: "I am committed to seeing you successful in your career." He remained true to his word, nominating Merchant for awards and membership to influential committees, helping to enrich and advance her career.

GETTING AHEAD

Indeed, getting a seat in professional decision-making bodies—like editorial boards and academic committees—is a critical component of career advancement, Merchant notes, and not just because it enhances your professional profile. "If you aren't at the table, you're on the menu," she says, quoting her longstanding friend Ivor Benjamin, a past president of the American Heart Association who was an intern at Yale when she was a student there and is today director of the Cardiovascular Center of the Medical College of Wisconsin. Further, she notes, women at the table can also help level the playing field—say, by inviting other women to speak at conferences, advocating for their hiring to faculty positions or appointment to leadership posts, or assigning journal essays and reviews to them.

Merchant has, of course, faced her share of challenges in leadership. She notes, for example, that bias frequently shapes the experience of women in such positions. "There are still challenges for women, regardless of the accolades they may have," she observes. "Women's leadership style is often different from that of men. It's usually not as top-down, but a bit more collaborative. Sometimes I find that people will try to push the woman leader to see how hard she will push back. You have to learn how to draw that line in the sand."

Photo by Noelle Haro-Gomez

> “There are still challenges for women, regardless of the accolades they may have. ... Sometimes I find that people will try to push the woman leader to see how hard she will push back.”

Merchant also emphasizes that a history of excellent research and publications in top-notch journals is necessary but not sufficient for career advancement, especially into leadership positions. “You have to get out and sell your work,” she says. “When you get invited to deliver important, high-profile talks, you need to show up.”

This can be an issue for researchers who have children, especially women, who may worry about not being with them enough, Merchant concedes. But Merchant, who raised her daughter alone—admittedly with plenty of mutual support from a network of friends in Ann Arbor—tells young parents that, in her own experience, what children value and remember most is the quality time you spend with them. If you’re there when it counts, she believes, children appreciate why you have to be absent at other times. For Merchant, this meant helping her daughter with her homework and being present for major social, educational or sport events. But it also sometimes meant taking her to meetings to far flung locations, like Copenhagen or Istanbul. Such experiences, Merchant says, enriched her daughter’s life in countless ways.

Finally, self-confidence is a vital ingredient of success, says Merchant. Mentors and advocates can help you build that confidence. She recalls, for example, that when she returned to the clinic after completing her doctoral research at Yale, Benjamin, an intern at the time, helped shore up her confidence in her abilities. But more often, Merchant notes, you have to help yourself. “I do a lot of yoga, so I think of it as ‘strengthening your core,’” she says. “Having confidence and believing in yourself.”

Passion for your work goes a long way in having a successful academic career, Merchant says. It can carry you through the many failures—and ensuing self-doubt—that are typically par for the course in a life of scientific inquiry. “This is why I tell trainees that, above all, you have to feel the love for whatever it is you plan to pursue in your career,” she says. “In the end, even though I’m clinically trained and seeing patients, what really gets me up in the morning is, first, that I love to talk about science and, second, I love teaching and mentoring trainees. I just love seeing that light bulb turn on, that look in somebody’s eyes that says, ‘I really get it now.’”

Johanna JOYCE

The Ludwig Lausanne Member on her good luck in teachers and mentors, the dire need for childcare and technical support programs for researchers starting families and stanching the flow of young scientists out of academia.

Photo by Hugues Siegenthaler

With a talent for deductive reasoning and inspired by a couple of gifted chemistry teachers, Ludwig Lausanne Member Johanna Joyce had little doubt which career path she wanted to pursue by her final year of high school.

Johanna Joyce in 2005

Her parents, who had moved their family from London to a farm near Dublin a few years prior, hoped she would become a physician. "But I said, 'No. I want to be in a lab, I want to discover; I want to be a scientist,'" says Joyce. That's also what she told the career guidance counselor at her high school, when she dropped by his office for a required consultation. The idea was met with skepticism. "He said, 'Do you think maybe you should reconsider that and pick something that might be easier for a girl to do?'" Joyce recalls.

"I just mentally rolled my eyes and obviously ignored him," says Joyce, who is today, in addition to her Ludwig appointment, also a professor at the University of Lausanne. "When somebody tells me I can't, or shouldn't, do something—it generally has the opposite effect!"

The effect, in this instance, propelled Joyce into the elite ranks of budding scientists at Trinity College, in Dublin, where she completed an honors program in genetics led by scientists she considers the best teachers she ever had. Fascinated by genomic imprinting, the subject of her honors undergraduate thesis at Trinity, Joyce next made her way to the University of Cambridge where she earned her PhD in Paul Schofield's laboratory exploring how the faulty regulation of imprinted genes causes a disorder that predisposes children to cancer. Eager to delve more deeply into the molecular and cellular

Joyce hiking with her children in Rochers de Naye, shortly after moving to Switzerland.

complexity of cancer, she subsequently moved to the University of California, San Francisco, for postdoctoral studies in the laboratory of Douglas Hanahan (now once again a colleague of hers at Ludwig Lausanne), exploring a family of proteins named cathepsin proteases and their involvement in the progression of pancreatic cancer.

Joyce opened her own lab at New York's Memorial Sloan Kettering Cancer Center in early 2005 and began studying tumor-associated macrophages (TAMs), immune cells that can, depending on their state, either support the growth of tumors or target their constituent cancer cells. In 2013, her laboratory made a key discovery that had

significant implications for our understanding of gliomas. She and her colleagues reported that when TAMs, which abet glioma growth in mouse models, are exposed to an inhibitor of the CSF-1 receptor (CSF-1R)—whose activity is normally essential for macrophage survival—they don't die off, but are instead "reeducated" to target the cancer cells.

Since then, Joyce's exploration of the immune cells of the tumor microenvironment (TME) has only grown in its scope and sophistication. She and her team have revealed, among many other things, how anti-CSF-1R therapy alters the gene expression and activity of TAMs and microglia (the brain's resident macrophages), shown how resistance to such therapy develops in brain metastases of breast cancer and developed therapeutic strategies to defeat those mechanisms. Her lab has uncovered how radiotherapy alters TAMs to drive therapy resistance and growth of gliomas, and interrogated the immune landscapes of primary brain tumors in patients, comparing them to those of various brain metastases. She and her colleagues have developed and freely shared powerful new methods to map the TME and, most recently, to watch its evolution in real time during glioma progression and following therapy by literally looking inside the brain. With its breakneck pace of discovery and collaborative generosity, the Joyce lab is today at the forefront of a field that has dramatically enriched our understanding of tumor biology and promises to revolutionize the treatment of some of the deadliest manifestations of cancer.

FAMILY SUPPORT AND MENTORSHIP

What, apart from a knack for scientific reasoning and creativity, accounts for all this success? Joyce credits her parents first and foremost, who shaped her, equipped her with a vital self-confidence and offered their unconditional support no matter what she chose to do, or how far her pursuits took her from home. Her husband, a neuroscientist,

Joyce in the lab with postdoc Daniela Quail, now an assistant professor at McGill University in Canada.

has been equally important. "I think having a supportive life partner, as a woman scientist and a mother, is key," she says. "It could arguably be the most important thing."

Joyce was also fortunate in her science teachers and mentors. She was, she notes, blessed with the best instructors—almost all of whom were male. "Never, not once, was there anything my mentors said or did that made me feel that I, or anybody in the lab, was any different from anyone else. It just never, ever came up," she says. Ditto for her professors. "Honestly, it was never seen as a problem, or as something we even talked about much as undergraduates, PhD students or postdocs. We were all genders, all ethnicities, all cultures just coming together in the shared pursuit of scientific discovery."

Joyce in the lab with postdocs Alberto Schuhmacher and Leila Akkari, now assistant professors in Spain and the Netherlands, respectively.

> When somebody tells me I can't, or shouldn't, do something—it generally has the opposite effect!"

BEING A WOMAN SCIENTIST

This is not to say, however, that Joyce believes her early experiences were necessarily typical or that sexism in science is a thing of the past. She is acutely aware that gender parity is today a prominent issue in scientific circles, especially in academia. Part of the reason for this, she ventures, is considerable disappointment with the slow pace of change. She recalls that when she was a PhD student, she was led to believe that gender discrimination in the field was a problem of the past. "Yet here we are, more than 20 years later, and we're still talking about the exact same problems," she says. "It certainly hasn't changed as much as we all expected. I think that's part of the frustration—that change happens incredibly slowly, and now as a result of the pandemic, we are regrettably seeing many of those hard-won advances for women actually slide back again. This concerns me tremendously."

Joyce also worries that while greater awareness of sexism in the field is commendable, and of course critical, one downside is that it may discourage some women from pursuing scientific careers. "I point out to the young women who worry about this that many of us senior women have advanced despite implicit, and sadly all too often explicit, sexism—and that we are trying to forge a path forward for all the women who come after us. We are really trying our utmost to make it less challenging."

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FUTURE SCIENTISTS

One way she does that is by advocating for young scientists, especially women, and recommends that they, for their own part, cultivate a network of advocates. Joyce, for example, receives many more invitations to speak at conferences and write reviews than she can accept. So, she keeps a list of people she has trained—or met and been impressed by at conferences and other venues—who she then puts forward as alternatives every time she has to turn down such invitations. “It’s very simple to do, and it can really help many young scientists who are just starting out,” says Joyce. “Organizers are delighted to have alternatives, and they frequently then do invite those people.” Similarly, she encourages young scientists to develop a network of mentors who can advise them on a range of matters beyond the nitty-gritty of their research, like writing grant proposals and hiring laboratory staff. “At the University of Lausanne, for example, we have a mentoring program that pairs female postdocs with senior faculty, which is a great way to get advice from someone other than your PI—particularly if there might be issues or concerns, so that these can be discussed in a supportive and confidential manner to identify constructive solutions.”

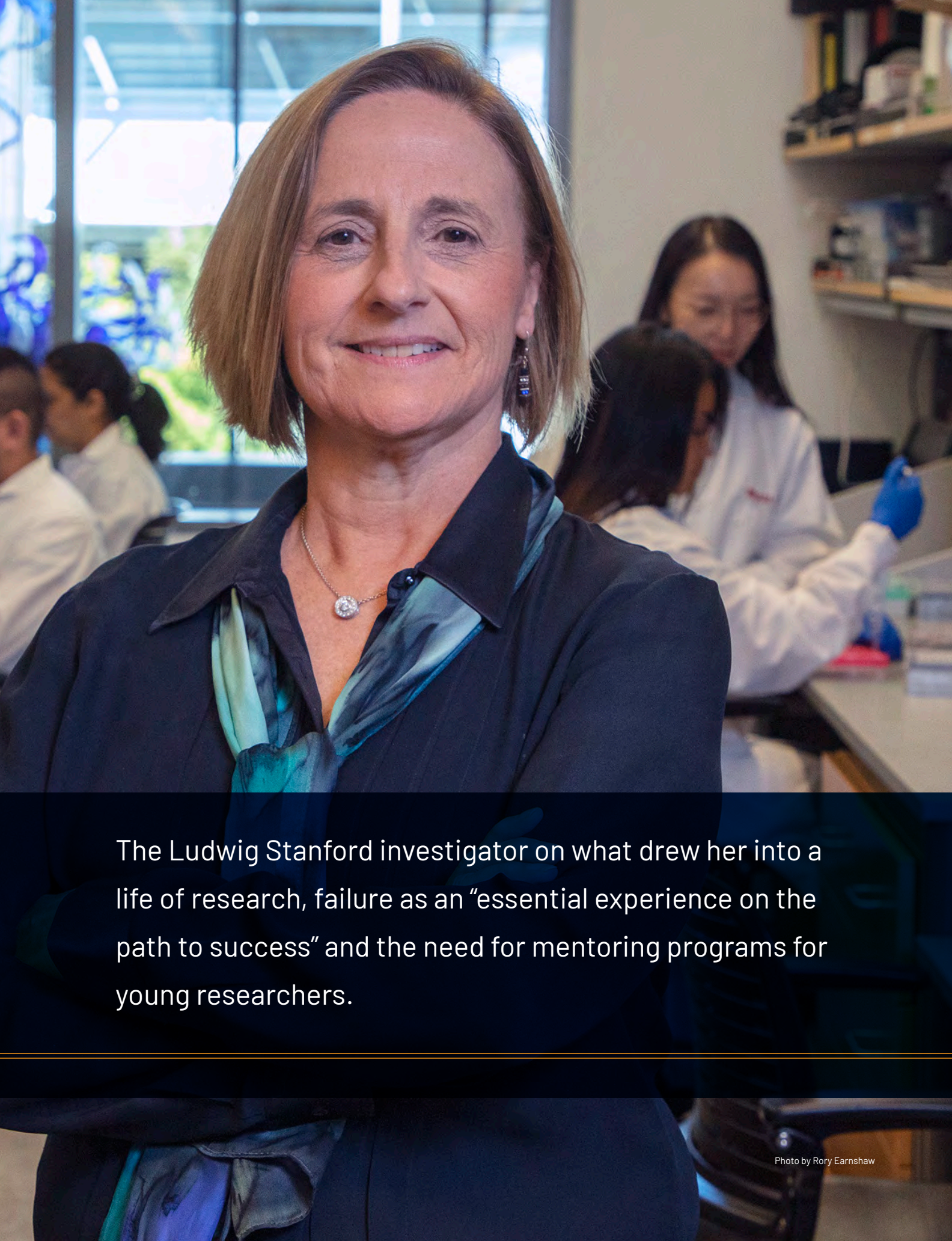
On a higher level, Joyce says institutions can support young researchers by providing affordable, subsidized or free childcare. By the time people begin stints as research fellows, many are at an age where they’re starting families. “Access to affordable childcare is a big challenge for many young scientists,” she says. “Some institutes do provide that support, and I see that the postdocs and students in those environments are very happy.” Joyce further cites another beneficial program in Lausanne, which gives parent scientists the opportunity to apply for technical support. “I think this is key—the scientist can train the technician before going on parental leave, and in this way experiments can still continue during those months,” she says. “For researchers working with animal models, for example, this can have a critical impact in enabling their long-term experiments.”

On a still higher level, she believes the field at large needs to pay postdocs much more than is now customary. Not doing so, she worries, could precipitate the global and growing trend of young researchers leaving academia for more remunerative careers because their salaries simply do not cover the cost of living, especially when that includes paying for childcare. This is likely to significantly affect the future of biomedical research, not to mention the prospects of young PIs starting up laboratories that depend on recruiting qualified research fellows. As an example, Switzerland, says Joyce, has set pay standards for PhDs and postdocs relatively high and, consequently, she has not seen a similar drop-off in postdocs applying to her lab.

“As institutes, and as individual group leaders, we must respect our lab members, treat them fairly and equitably, and value them as highly-qualified young scientists,” says Joyce.

And those suggestions apply, of course, whatever the scientist’s gender happens to be.

Crystal MACKALL



The Ludwig Stanford investigator on what drew her into a life of research, failure as an “essential experience on the path to success” and the need for mentoring programs for young researchers.

Photo by Rory Earnshaw

From a young age, Crystal Mackall knew she wanted to be a doctor. She even had an inkling that she wanted to be an oncologist.

Mackall attributes her younger self's rare clarity of purpose to the feeling of dread that she and others around her associated with cancer while growing up in East Palestine, Ohio. "It was 'the emperor of all maladies,'" says Mackall, a leader in translational immuno-oncology at the Ludwig Center at Stanford University, where she is Ernest and Amelia Gallo Family Professor of Pediatrics and Medicine. "And so becoming a physician who had an impact on cancer was always the most compelling story for me. And that hasn't changed."

Mackall was aided by supportive teachers in middle and high school, especially Karen Peters, her seventh-grade science teacher who, she says, was "the first really strong-willed woman I had met." It also helped that Mackall's parents—her father was a steelworker, her mother an office worker—encouraged healthy debate among their children at home.

"You could say we were an argumentative family," jokes Mackall, who is also the founding director of the Stanford Center for Cancer Cell Therapy. "We really believed in ideas, and we weren't afraid to challenge ideas, both within the family and without. As a result, I find that I'm a little more fearless than maybe some folks who grew up in more rarefied circumstances, where the hierarchies were kind of set."

Mackall specializes in creating immunotherapies for pediatric cancers. Her group was among the first to show the effectiveness of the chimeric antigen receptor (CAR) T-cell therapies CD19-CAR and CD22-CAR against childhood cancers. Her lab has also pioneered efforts to apply CAR T-cell therapy to brain tumors—most notably in a recent collaboration with Ludwig Stanford's Michelle Monje—and is developing novel approaches to prevent and reverse T-cell exhaustion, a central challenge of cancer immunotherapy.

THE CULTURE OF SCIENCE

After high school, Mackall enrolled in a six-year medical school program at the University of Akron in Ohio. "It was sort of the European model," Mackall explains. "You got your bachelor's degree in two years, and then you automatically went into medical school."

Mackall's plans to leave Ohio after medical school were upended by an encounter during her residency at Akron General Hospital. "I met the love of my life at that time," Mackall says. "We are still together 43 years later." She notes that the support of her wife, a radiation oncologist, has been critical to her ability to pursue a scientific career.

In 1984, during her residency, Mackall read a study led by Steven Rosenberg, describing the treatment of metastatic melanoma with interleukin-2 — one of the first demonstrations of effective immunotherapy for human cancer.

"I thought, 'Wow, now that is cool,'" Mackall says. Interested now in conducting medical research, Mackall applied for a fellowship at the National Cancer Institute (NCI), where she would spend the next several years learning how to be a scientist. "There was a lot of, obviously, practical techniques and intellectual training, but there was also a

Photo by Rory Earnshaw

Crystal Mackall with lab members Alex Doan, seated, Patrick J. Quinn, and Tara Murty, right.

cultural training that I needed to go through," Mackall says.

Her guide and scientific mentor during this time was Ron Gress. "Ron took me into his lab and mentored me over the next six years. He taught me not only about how to think like a scientist, but also about the culture of science," Mackall says. Gress saw Mackall through a series of critical early successes—and failures. "After 14 revisions with his help, and about three years of science, I submitted my first paper to *Blood*, and it came back with reviews that all said, 'The science is sound, the controls are great, it is well written, we just don't think it's very interesting,'" Mackall says. "I was just so demoralized, but it taught me a very important lesson: that you need to sell. As a scientist, part of what you do is you sell. You sell hope that what you're studying has value."

Mackall was also inspired by the person who hired her, Phil Pizzo, chief of the Pediatric Branch of NCI and a former Ludwig Board member, whose research focused on children with cancer and AIDS. "Pediatricians tend to be very conservative," she says. "So, when I was getting into a position where I could make more decisions, what I found was a community that wasn't particularly forward

> I really want people to know that many of the people who they look at today as successful at one time felt exactly like they do. And that the most important issue that has to be addressed is believing in yourself and giving yourself enough of a chance to succeed."

leaning, wasn't openly willing to try new things. Phil, on the other hand, really taught me to be bold and gave me license to do that," Mackall says. "And that is the way I've conducted my career—I think of the problems from the patient's vantage point, and I go after problems that are so difficult that I know that the patients and their families want me to be taking risks."

Mackall's group at the NCI, for example, wanted to begin a trial that targeted CD22 in children with leukemia who had become resistant to CD19-CAR therapy. Ethicists on the advisory committee of the National Institutes of Health (NIH) pushed back, arguing that the trial needed to be conducted in adults first. But an adult trial would take years, and there was a large population of children who could benefit from the treatment now.

"And so I used every ounce of my power, and influence, and logic, and everything else I could throw in there to make the case that, no, there was no moral or ethical imperative for waiting, the children needed it now," Mackall says.

Her team eventually prevailed: the CD22-CAR therapy turned out to have a 70% complete response rate in children and received Breakthrough Therapy Designation from the FDA.

PATTERNS OF BIAS

When Pizzo left the NIH in 1996 for Harvard University, Mackall was offered a tenure track faculty position at NCI. She would spend the next decade running her own lab, developing a translational research program, and eventually becoming chief of the pediatric oncology branch of the NCI, which was the job Pizzo held when he had hired her.

"The beauty of the NIH is you really can do medicine and translation hand in hand. And I'm a translational scientist," Mackall says. "I take ideas from the bench to the clinic. I feel that I'm able to bring those cultures together."

Mackall says she never felt that being a woman limited her opportunities as a young investigator, but as her accomplishments and accolades accumulated, she began noticing "glass ceilings" for herself and her women colleagues. "It was always subtle enough or veiled enough that it was kind of hard to pin down," Mackall says. "And if you were a Pollyanna, you could have talked yourself into, 'Oh, this isn't really happening.'"

Over the course of a career spanning more than three decades, Mackall learned to spot recurring patterns of subtle bias. "I think, for me, yes, there were some challenges around being taken seriously in leadership settings and also access to roles as a leader," she says.

"One of the reasons I chose Stanford was the number of women in leadership roles in Stanford Medicine," Mackall says. "Even today, Stanford is an outlier. The leadership at Stanford is pretty balanced as far as gender goes."

Photo by Rory Earnshaw

> “If you aren’t failing, you are not shooting high enough. I continue to fail not infrequently in my career. I get papers rejected. I get grants rejected I get experiments that don’t work.”

FAILING WITH GUSTO

One of the things that Mackall tries to impart to the trainees on her team is the importance of self confidence in science. “Failure is an essential experience on the path to success,” Mackall says. “If you aren’t failing, you are not shooting high enough. I continue to fail not infrequently in my career. I get papers rejected. I get grants rejected. I get experiments that don’t work.”

Mackall suspects today’s generation has more anxiety than perhaps her generation did and that women feel this anxiety more than men. “Women look at the power structure of science and they don’t see themselves there, and therefore feel like outsiders,” Mackall says. “But it’s not just women. It’s people of color, it’s ethnic minorities, it’s people who come from the working class, or disadvantaged backgrounds or sexual minorities.”

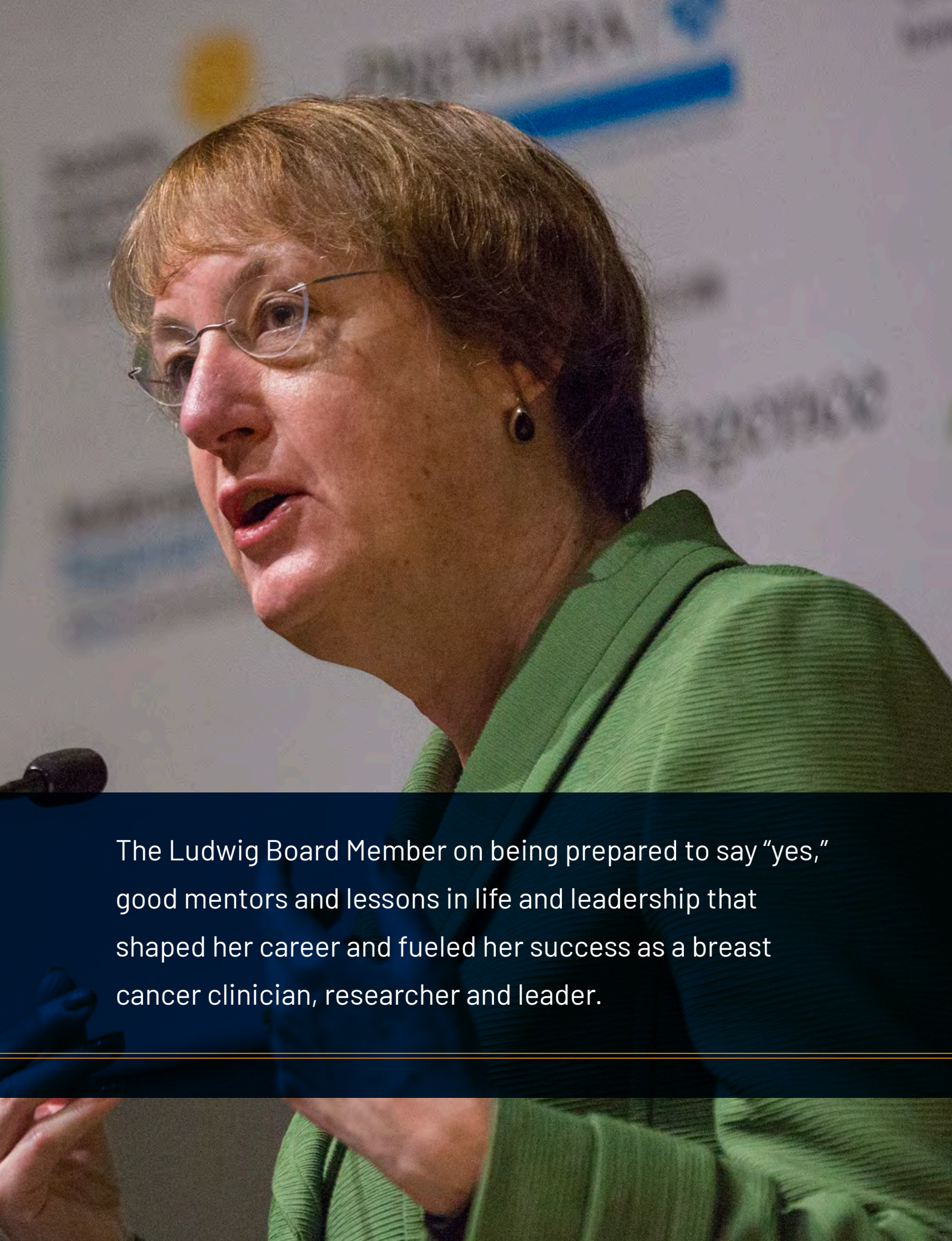
To help address this, Mackall openly talks to her trainees about her own history of failures and how she overcame her anxieties. “I really want people to know that many of the people who they look at today as successful at one time felt exactly like they do,” she says. “And that the most important issue that has to be addressed is believing in yourself and giving yourself enough of a chance to succeed.” Mackall, for example, remembers being afraid to ask questions in meetings during her early years at NCI. “But I would. I would gird myself, I would do my deep breathing, and I would stand up to the microphone and ask that question,” Mackall says. “And the more I did it, and the more I was successful, the more confidence I had.”

She was also encouraged by the questions she saw her colleagues asking. “The questions these world class scientists were asking were the same questions I had. And sometimes I had better questions. I could keep up with them intellectually.”

Organizations like Ludwig can play an important role in helping boost the self-esteem of young scientists, Mackall says. “I think that mentoring programs are incredibly valuable to young people today,” she adds. “It wouldn’t have to be particularly expensive or particularly large, but Ludwig has brilliant scientists. Leveraging that resource to support women and other individuals who are at risk of falling out of the conduit to success could be pretty impactful.”

Nancy DAVIDSON

Photo courtesy of Fred Hutchinson Cancer Center



The Ludwig Board Member on being prepared to say “yes,” good mentors and lessons in life and leadership that shaped her career and fueled her success as a breast cancer clinician, researcher and leader.

When Ludwig Board Member Nancy Davidson opened her first laboratory at Johns Hopkins University in 1987, she set her sights on exploring apoptosis, or programmed cell death, and its potential induction as a treatment for breast cancer.

Her lab—in a converted supermarket in East Baltimore where the future Co-directors of Ludwig Johns Hopkins, Bert Vogelstein and Ken Kinzler, were at the time transforming our understanding of cancer genetics—achieved notable successes. It showed, for example, that withdrawing estrogen could induce apoptosis in certain breast cancer cells.

But then Davidson attended a talk by Stephen Baylin, who is today a Ludwig professor at Johns Hopkins and a visiting professor at the Ludwig Oxford Branch, and was then helping to pioneer the study of cancer epigenetics in that same converted supermarket. Listening to Baylin speak, it occurred to her that the epigenetic gene silencing he described might account for the loss of estrogen receptor expression in some breast cancers, and she asked him if he'd be interested in testing that hypothesis. In a series of studies conducted over the next few years, the pair would go on to show that this is indeed the case.

Those studies set Davidson down a three-decade path of discovery that has illuminated the role of epigenetics in breast cancer. Now the Executive Vice President of Clinical Affairs and Director of the Clinical Research Division at the Fred Hutchinson Cancer Center and Chief of the Division of Medical Oncology at the University of Washington, Davidson has sought to apply those findings to the treatment of the disease, evaluating epigenetic modifiers as therapeutic agents in clinical trials. In addition, her collaborative clinical studies on the use of endocrine therapy for the treatment of hormone-responsive breast cancer in premenopausal women have helped to alter medical practice, as have her collaborations exploring the combination of chemotherapy and targeted therapy for HER2-positive breast cancers. Davidson has also co-led clinical studies that have illuminated the role of obesity and race in therapeutic outcomes in early stages of the disease.

Beyond her work as a scientist and clinician—with more than 400 papers to her name—Davidson is a prominent leader in her profession. She is one of only seven people, and two women, to have been elected president of both the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO).

FINDING A PASSION

Davidson was born in Colorado, moved to Maryland with her geologist parents when she was a teenager and attended Wellesley College, in Massachusetts. Majoring in biology in college, Davidson took a part time job at a lab focused on liver cancer research. It was there that she met her future husband Thomas Kensler, working with him on his research exploring the mechanism of a carcinogen in liver cancer. The experience piqued her interest in biology and the possibility of a science-related career.

After her first year at Harvard Medical School,

Davidson accepted a job offer to work in a breast cancer research laboratory at the National Cancer Institute (NCI) headed by the prominent physician-researcher Marc Lippman. "I thought, 'Wow, this is what I want to do,'" Davidson recalls. "'I can see where this is going to take me. I see the lab, I see the clinic, I see how they're connected. That's where I want to be.'" After earning her MD, Davidson completed an internship in internal medicine at the University of Pennsylvania, where she met an up-and-coming oncologist named John Glick, who would become a lifelong mentor. She then transferred for her residency to Johns Hopkins University.

Davidson next took a fellowship at the National Cancer Institute in nearby Bethesda to continue her work with Lippman. Her work there led to a job offer from Martin Abeloff at Johns Hopkins, where she opened her first laboratory and rose to become a tenured professor, director of the breast cancer program at the Johns Hopkins Oncology Center and holder of the Breast Cancer Research Chair at the university's School of Medicine.

That was when Davidson became intrigued by the idea of using hormone therapies to treat premenopausal women with early hormone-responsive breast cancer. "The dogma at the time was that young women need chemotherapy, period," explains Davidson. "We came to realize that this might not apply to all young women with breast cancer." About a year after the birth of her second child, Davidson got approval in 1988 for a major clinical trial to test that proposition. "We reported the results at ASCO the year my second child graduated from high school—17 years after the trial's conception."

The results showed that adding tamoxifen to chemotherapy after surgery dramatically extended time to relapse and disease-free survival, changing how breast cancer is treated in a large subset of premenopausal patients. Based on this study and others,

Photo courtesy of Fred Hutchinson Cancer Center

> "Saying yes is extremely important. You have to be in a position to get the invitations to lead, but then you have to be prepared to accept them. I tell people to seize the day!"

Photo courtesy of Fred Hutchinson Cancer Center

Nancy Davidson introduces Washington Governor Jay Inslee, right, during a signing ceremony at the Fred Hutchinson Cancer Research Center for a new state law raising the age at which someone can buy tobacco or vaping products to 21.

Davidson would quite literally help rewrite the ASCO treatment guidelines for such cases.

As her research proceeded apace, Davidson also became increasingly involved in ASCO. "I had received one of my first grants from them, so I was very, very loyal to the society," says Davidson. She eventually joined the Board of the organization, encouraged by her mentor, Glick. "He called me up and wouldn't get off the phone until I said yes, I would run. And I won." This subsequently led to her election to serve as ASCO president. After her tenure as ASCO president, Davidson accepted a job as director of the University of Pittsburgh's Hillman Cancer Center in 2009 and then, in 2016, moved to the prestigious Fred Hutchinson Cancer Center in Seattle, Washington, directing its Clinical Research Division and serving as head of medical oncology at the University of Washington. In 2015, she became president-elect of the AACR, completing her term in 2018.

INGREDIENTS OF SUCCESS

Davidson's passion for her work has sustained her through the ups and many downs of scientific research—and she urges young researchers to make sure they love what they choose to study. But taking the helm did not always come naturally to Davidson. Her NCI mentor Lippman, she recalls, gave her some advice that helped her cultivate the confidence required for leadership. "He said, 'You're quiet, reserved, you always sit in the back of the seminar room. Why don't you move a little farther forward?' And then

he said, 'You ought to try to ask a question after every seminar.' It was very good advice."

Such mentors, Davidson notes, have played a critical role in advancing her career. Some, like Baylin, helped shape her scientific focus, while others, like Abeloff, guided her clinical career; others, like Glick, pushed her to seize opportunities, or advised her on administration and leadership. "There were no women mentors," she observes. "All white men. And when our trainees hear that, they're like, 'What? How can that be?' But that was the fact of the matter then. I think the good news is, if people are worried that their mentors have to look just like them, I'm here to say they don't." They may simply share your interests, she says.

> "There were no women mentors. ... But that was the fact of the matter then. I think the good news is, if people are worried that their mentors have to look just like them, I'm here to say they don't."

But mentors can only help those who are willing to help themselves. "Saying yes is extremely important," Davidson says. "You have to be in a position to get the invitations to lead, but then you have to be prepared to accept them. I tell people to seize the day!"

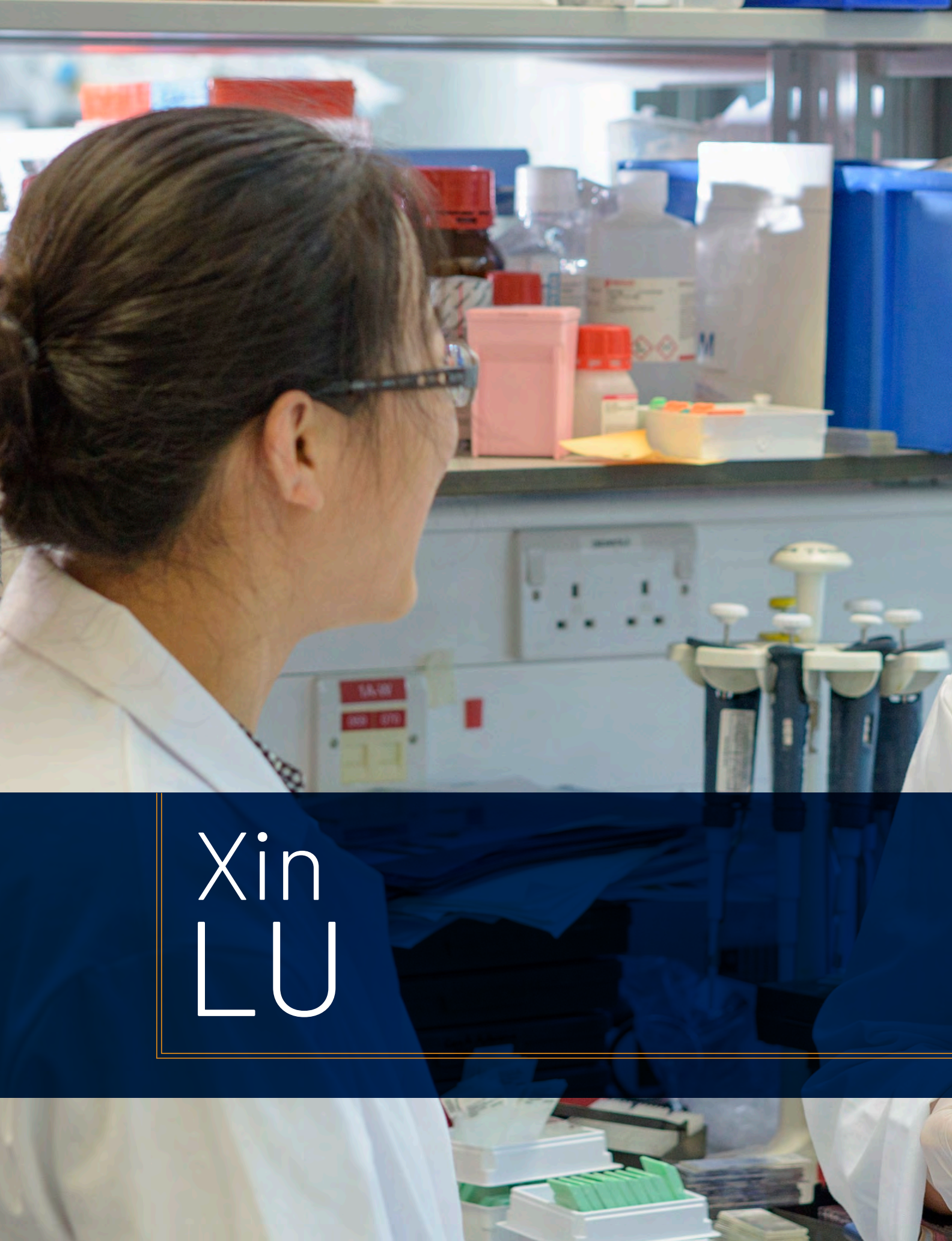
It also helps, she stresses, to know when to pivot and switch paths—in your research as much as your career. When the results of a roughly decade-long effort to use autologous bone marrow transplantation to treat advanced breast cancer came up negative in 2000, for example, Davidson promptly dropped the project, shutting it down within a week. "You have to know when to hold and when to fold," she says.

Finally, Davidson says, having a happy personal life has been a top priority of hers and one she recommends to others. She did not, for example, delay having children. Fortunately, her boss at Johns Hopkins was understanding and gave her all the time she needed for maternity and infant care. But she was lucky. "There were no duty hour restrictions when I was a resident," she says. "There certainly are now. There was no maternity leave. There is now. There's a lot more attention to parental leave. Those things have changed and all for the better."

Institutional support for childcare could certainly improve further, Davidson says. But such measures would have to be instituted equitably. There are multiple paths to having a family, including adoption, and many people with jobs are also caring for elderly parents and need just as much support. Further, legal requirements may vary from place to place for global organizations like Ludwig Cancer Research.

She and Kensler, for their part, were mutually supportive, taking turns tending to their children and their careers—and even collaborating on a few studies over the years. When he was off in China conducting research on liver cancer and its prevention, as he sometimes was for months at a time, Davidson took care of the kids. Later, they prioritized her career, after she took the job at Pittsburgh and became president of ASCO. A shared passion for cancer research also enriched their relationship.

"When I think about the best decisions I made in my life, the first was my husband, the second was having kids, and the third was my career," she says. "I think those are things that people need to keep in mind."



Xin LU

The Ludwig Oxford Director on the improbable start of her career, its steep trajectory, the mentors who helped make it possible and the lessons she learned on persistence and scientific freedom that she passes on to trainees.

Photo by Monty Rakusen

When Xin Lu first arrived in London, it was only supposed to be for a year.

The plan was for her to complete her scientific apprenticeship and then return home, to China, where she was a research assistant at a cancer institute in Beijing.

"It was not planned for me to stay in the UK until now," says Lu, who is the director of the Ludwig Institute for Cancer Research Oxford Branch.

Lu's supervisor and former graduate advisor, Min Wu, had encouraged members of his group to apprentice in labs across Europe and the U.S.—a fairly radical concept in China at the time. "Many supervisors wouldn't encourage people to do that. You don't want to lose them after so much training. But he recognized the importance of science outside of China and encouraged us to go," says Lu, who is best known for her identification of the ASPP family of proteins and characterization of their role in regulating the tumor suppressor gene p53, which is mutated in a wide range of cancers. Defects in ASPPs also cause developmental diseases including brain abnormalities and sudden cardiac death.

The bewildering plane ride from Beijing to London, which lasted almost 24 hours and included layovers in three countries, was Lu's first ever flight. When the plane finally landed at Heathrow Airport, Lu felt like she had been dropped on a new planet. Her English vocabulary was so limited that it took her two hours to buy toothpaste. And all the scientists around her seemed to be so much more accomplished.

Yet despite the challenges, Lu decided to stay, and she applied for a PhD student opening in Birgit Lane's lab at University College London. By then, Lu recalls, her

Xin Lu with Min Wu in 1987.

command of English had improved, but not by much. Her opening line at her PhD interview was "'I am from China, and my (scientific) background is very bad, but I would like to do a PhD with you.'"

Lane did accept Lu into her lab, though, and would prove to be a supportive mentor. She helped select the research questions Lu would investigate, but then gave her the freedom to establish her own scientific approach. This scientific freedom continued to be encouraged when Lu did her postdoctoral work with Sir David Lane—one of the discoverers of p53—who was then at Dundee University in Scotland and was, more recently, scientific director of the Ludwig Institute for Cancer Research.

Xin Lu with "the three most important mentors in my scientific career." From left, Sir David Lane, Birgit Lane and Min Wu.

> "I don't think it's women specific, but I do think women have a tendency to more self-doubt and I think more of them may lack confidence compared to men."

Lu says that when she first joined Birgit Lane's lab, everything was so new that she didn't realize at first how rare it was at the time for females to be PIs. She saw nothing amiss because in China, she grew up with the Communist slogan, "women hold up half the sky."

Gender equality was also the norm at home, where both Lu's parents were doctors and Lu's mother was a professor as well. Her graduate advisor's lab in China contained a roughly even mix of men and women scientists, and there were more women than men in her lab during her PhD and an even mix of men and women scientists in the lab where she did her postdoctoral research.

Photo by Paul Wilkinson

Lu just thought that's the way it should be. "It never entered into my mind that men and women are different," she says. "You have to remember also that my English was pretty limited. It would take a few years before I sensed a difference."

It was only after she was leading her own research group that she began noticing that she was sometimes treated differently—like the company representatives who dropped by her lab to sell their wares and who would speak to her male students instead of her. "It makes you wonder, 'why did they have that reaction?'" she says. "Well, I'm a short, Chinese woman. They probably just never expected me to be the supervisor."

ON THE CUTTING EDGE

Lu grew up in Guiyang, China, in the late sixties and early seventies, during the Cultural Revolution. When Chairman Mao issued a call for the "Down to the Countryside Movement" that required young students from the city to be sent to the countryside to live, Lu knew she would never survive the intensive agricultural labor. So, she learned to play the violin, practicing every day for three hours in the hope that she could make a living as a musician.

When schools and universities that had been closed during the Cultural Revolution reopened, Lu changed course. She took the university entrance exam and was admitted

to Sichuan University, where she specialized in biochemistry—a subject she chose in part to avoid going into medicine like both of her parents. But she realized she really loved the discipline. "It was during the era when biochemistry was still quite new in China. It was considered cutting edge," Lu says.

After completing her undergraduate education, Lu enrolled in a graduate program at the Cancer Institute, Peking Union Medical College & Chinese Academy of Medical Sciences, under the tutelage of cancer geneticist Min Wu. After receiving her master's degree, Lu stayed on in Wu's lab as a research assistant, where she worked for one year until her formative trip to the UK to learn about science beyond China.

FOSTERING SCIENTIFIC FREEDOM

Lu's group at Ludwig's Oxford Branch is focused on identifying molecular mechanisms that control cellular plasticity and suppress tumor growth.

In her own lab, Lu says, she tries to follow the examples set by her former mentors. As she said in a recent interview she gave to The FEBS Journal, "I give my lab members the freedom to develop the direction of their research projects, which is a vital skill for an independent research career."

This approach requires a certain degree of self-confidence on the part of the student or postdoc—a confidence that comes more naturally to some than to others. "I don't think it's women-specific," Lu says, "but I do think women have a tendency to more self-doubt and I think more of them may lack confidence compared to men."

Lu, who is today also a professor of cancer biology at the University of Oxford, acknowledges she didn't have that confidence when she started out. "I never thought I was good enough to do a PhD, let alone do a postdoc, let alone what I'm doing now," she says. "But I just kept going."

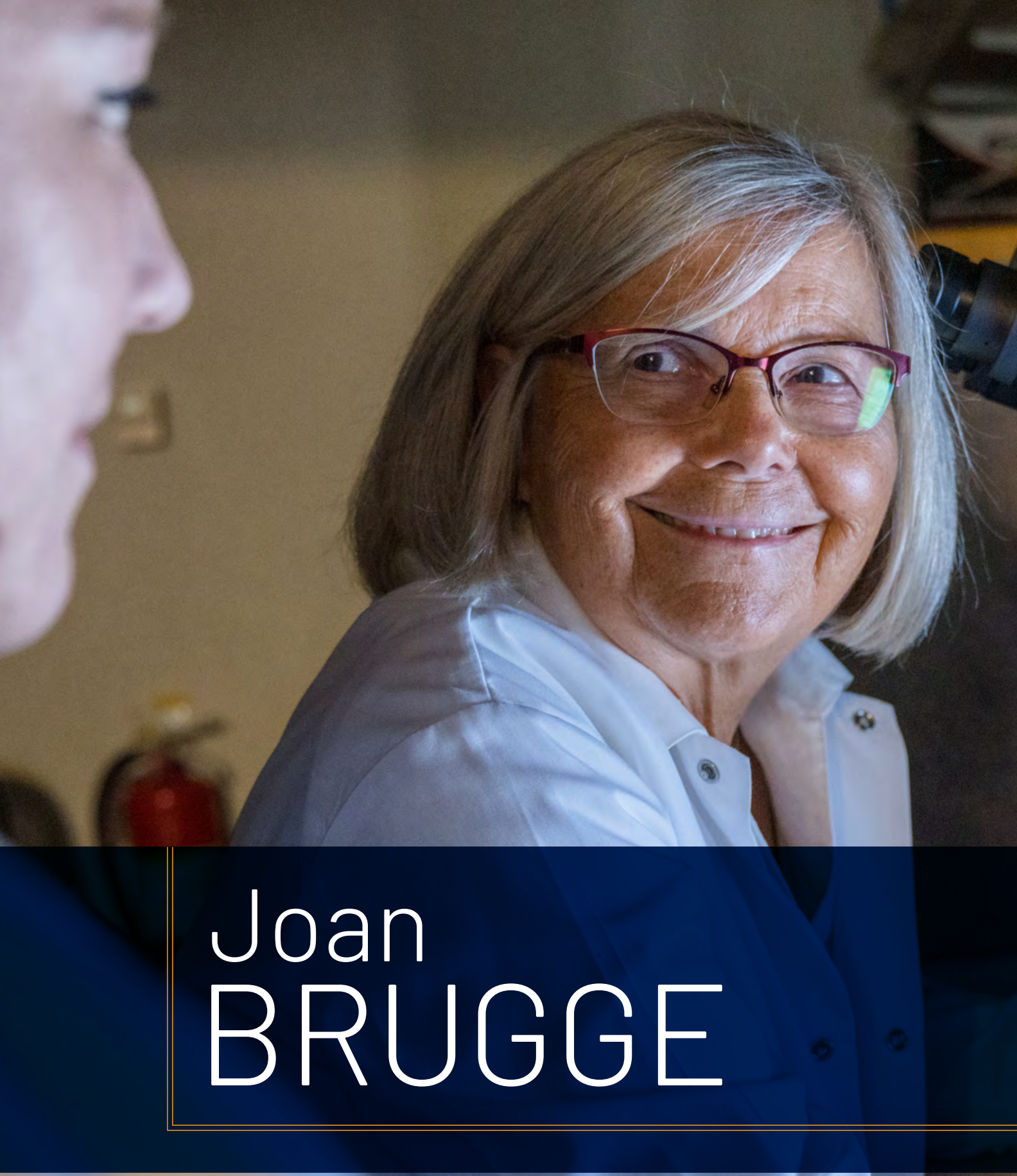
> "I never thought I was good enough to do a PhD, let alone do a postdoc, let alone what I'm doing now. But I just kept going."

That's why the advice she always gives to new students is to never give up, reminding them that persistence and optimism are essential ingredients of a successful research career and citing herself as an illustration that opportunity exists for each one of them in their chosen fields of research.

Lu says she did have to deal with some of the challenges faced by the current generation of young scientists, such as searching for reliable daycare. However, "I think each parent should take 50% of the family responsibilities," says Lu, who has two daughters. "But in a lot of societies, that's not the case. Men are not supposed to do it. It's a woman's job. And that is a problem. Luckily, my husband did a lot more childcare when our children were really young. Without that support, I don't think I could have done it."

There were times during her career, Lu says, when she felt guilty that she couldn't be more of a traditional mother. "Like they'll have cake days, and you're supposed to bake the cake and take it to school, but I had no time to do it. So, we'd always go to the supermarket to buy something," Lu says.

But in hindsight, Lu thinks witnessing that may have been a good experience for her daughters, who are now both adults. "Reflecting back, they actually think it was a pretty good way of seeing how things can be done," Lu says. "And they're proud of me for what I was able to do."



Joan BRUGGE

Photo by Sam Ogden

The Ludwig Harvard Co-director on the risky moves she made over the course of her career, the challenges of balancing lab and family and the rewards of creating a model for collaborative science at the Ludwig Harvard Center.

Joan Brugge was 25 and finishing her PhD at Baylor College of Medicine in Texas when she began worrying that she wouldn't be able to excel as a scientist while simultaneously being a good mother and wife.

So, she decided she would complete a postdoc to hone her skills, but then seek a job as a research associate in someone else's lab instead of trying to start her own. "I was concerned that I wouldn't be able to handle the responsibilities of being a lab director and faculty member without it significantly compromising my ability to be a good mother and wife," Brugge recalls.

Aware of Brugge's concerns, her graduate advisor and role model Janet Butel pleaded with her to reconsider. As a young assistant professor who ran a rigorous lab investigating tumor viruses while raising two young kids, Butel had shown Brugge that it is possible to have a family and still be a successful scientist. Brugge just didn't think it was feasible for her. It would take several years—and a breakthrough scientific discovery made during her postdoctoral studies—to convince her otherwise.

That breakthrough was her identification of the Src protein, which is encoded by the Rous sarcoma virus and turns healthy cells cancerous. On the foundations of that discovery, Brugge went on to elucidate many basic mechanisms of cancer initiation, progression and resistance to therapy. After an interlude at a biotechnology company in the early 1990s, she returned to academia to take a new approach to studying cancer, developing three-dimensional cell culture models to better capture cellular evolution and behavior in tumors. Brugge, who is today co-director of the Ludwig Center at Harvard and professor of cell biology at Harvard Medical School, has used these sophisticated culture systems to make notable discoveries on the cellular heterogeneity of tumors and contribute to new strategies to treat the stubborn problem of drug resistance.

Her other passion is leading, in partnership with George Demetri, the Ludwig Center at Harvard, which the pair structured to encourage a highly collaborative and multidisciplinary approach to cancer research. "George and I wanted to harness the enormous expertise and brilliant minds within the Harvard community to collaborate to break through the enormous barriers to highly effective cancer therapies," says Brugge. "We built a community of investigators who are dedicated to this goal and recognize the value of collaboration. After six years, weekly interactions have led not only to many productive collaborations, but also an enormous expansion of our understanding about aspects of cancer outside our own areas of expertise."

A BEACON

The daughter of a paper salesman and a homemaker in Cincinnati, Ohio, Brugge was drawn to science and mathematics as a child. But she didn't even consider a career in either field until she got to college. "I had absolutely no role models to be inspired by," Brugge says. "At the time, the career options I was aware of were teaching or nursing. For young women in my generation, those were the opportunities."

Brugge was a sophomore at Northwestern University studying to be a high school

Joan Brugge, left, at her PhD hooding ceremony with her mentor, Janet Butel.

> “It is not uncommon in academics, for women especially, to be overly conscientious in contributing to the welfare of others and their institution, their department, their scientific community.”

math teacher when her younger sister was diagnosed with glioblastoma. She coped by reading everything she could find about cancer. “I wanted to understand how someone so young could develop cancer. Everybody I knew of who had cancer was older,” Brugge says.

Her readings focused on the accumulating evidence that viruses can cause cancer, and she was intrigued by both the hypothesis and the methods of its examination. “I was exposed for the first time to how experimental science was carried out—forming hypotheses, designing experiments, interpreting them, refining hypotheses,” Brugge recalls. “I was totally fascinated and just couldn’t get enough of it.”

Hooked, Brugge changed her major from mathematics to biology. “My sister’s diagnosis and then death has really been the beacon for my interest in and devotion to cancer,” Brugge says. “It’s kept me on the track of doing something about it after seeing what she went through.”

A SLICE TO CELEBRATE

Brugge was well into her postdoc at the University of Colorado when she isolated the viral and cellular forms of the Src protein. The discovery marked a major advance in cancer research: it was the first retroviral oncogene product ever identified and her discovery laid the foundation for understanding how an oncogene could transform a normal cell into a tumor cell. Brugge was so excited she wanted to celebrate with champagne. But Ray Erikson, her advisor, urged caution. The

Joan Brugge with postdoctoral fellow Carman Li.

Photo by Sam Ogden

finding had to be confirmed, he said. Brugge settled for a commemorative pie.

By the time confirmation arrived, Brugge realized that aiming no higher than research associate would no longer suffice. "I wanted to have my own lab and be able to pursue this," she says.

It also helped that her son Shawn, who was a year and a half when she was ready to start her search for an independent faculty position, was thriving in his new daycare. "We had a great situation where a family took care of Shawn because they wanted a playmate for their youngest daughter," Brugge explains.

Even though there are more daycare options available to young researchers today, Brugge still sees members of her own lab struggling with finding childcare. "A postdoc in my lab, who's pregnant and at the time was due in a few months, told me recently that she's on the waiting list for five places," Brugge says.

In this regard, societal and cultural norms tend to put more pressure on women scientists than on their male colleagues, Brugge notes. "When a child is sick, women, still more so than men, are seen as the go-to caregivers. For couples, it's usually the woman who feels the sense of responsibility to take over under those circumstances. Part of it is society—I think it's not as acceptable for a man to say, 'My son's sick,' or, 'My daughter's sick. I can't come in.'"

CHANGING COURSE

Brugge's postdoc was followed by faculty positions at the State University of New York at Stony Brook and the University of Pennsylvania. But while Brugge found running her own lab at UPenn fulfilling, she soon felt she was being pulled in too many directions. "They hadn't hired a senior person in 20 years, and there was a new dean, and he wanted to revitalize," she recalls. "I was asked to get involved with

everything, and it felt like 80% of me was in 1% parcels all over the place."

This was one factor in her decision, in 1992, to accept a position as the scientific director at ARIAD, a startup focused on structure-based drug design. Another was the opportunity to apply her skills to research that might benefit patients. After five years in industry, however, Brugge missed being more directly involved in research, so when a faculty position at Harvard Medical School became available, she accepted.

Brugge used the return to academia to shift her lab's focus away from tumor viruses and the SRC gene. "It's funny because people say to me, 'Weren't you scared to do that?'" Brugge says. "It just seemed like a really interesting thing to do. In retrospect, I see that it was risky, but I wasn't even thinking about that."

Brugge's group began using a three-dimensional cell culture system that more closely resembles the structures of normal tissue and the distorted microenvironment of tumors to better study the initiation of cancer. "Up until that time, most of the studies in tumorigenesis were performed using fibroblasts cultured as a monolayer," Brugge explains. "But most tumors are derived from epithelial cells, which were more difficult to culture. So, we decided to work on epithelial cells."

OBITUARY EXERCISE

At Harvard, Brugge found herself struggling with balancing the demands of personal life and research. Brugge suspects this is a challenge that especially affects women.

"It is not uncommon in academics, for women especially, to be overly conscientious in contributing to the welfare of others and their institution, their department, their scientific community. I was not able to control this well and in addition, I was somewhat off-the-scale in my scientific curiosity and tended to take on too many projects," Brugge says.

Fortunately, a friend who witnessed Brugge struggling intervened and introduced her to a professional coach who taught her the importance of prioritizing her time and the need to say "no."

For example, the coach had Brugge write out how she wanted her obituary to read. "It included descriptions of my contributions to cancer research, leadership and mentoring and other elements related to family. Then she says 'If you want to accomplish these things, you have to stick to your priorities. You can't let what you're doing for others interfere with your ability to achieve your own goals and make a difference.'"

It's a lesson Brugge tries to impart to others whenever she can, often using the same obituary exercise she was asked to perform. "Whenever I do a mentoring talk anywhere, especially with junior faculty, I talk about it," Brugge says. "What I suggest to them is that they choose two important activities that they really want to do as service to their department and institution, then talk with their chair about it and use that as the reason for saying no to other things."

It's also important, especially for young women scientists, not to compare themselves to their senior role models, Brugge says. "I think one of the most significant factors leading to women dropping out at the postdoc stage is this. They look at more senior women and say, 'I just can't do that, and I don't want to do it. I don't want to sacrifice my family time for this.'"

Brugge advises young researchers to instead look at people who are on the next rung of the career ladder from themselves. "If you're a postdoc, look at the junior faculty. If you're junior faculty, look at the next rung, because you have to take baby steps. This is a job you grow into."

LUDWIGCANCERRESEARCH.ORG

600 Third Avenue, 32nd Floor
New York, NY 10016

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