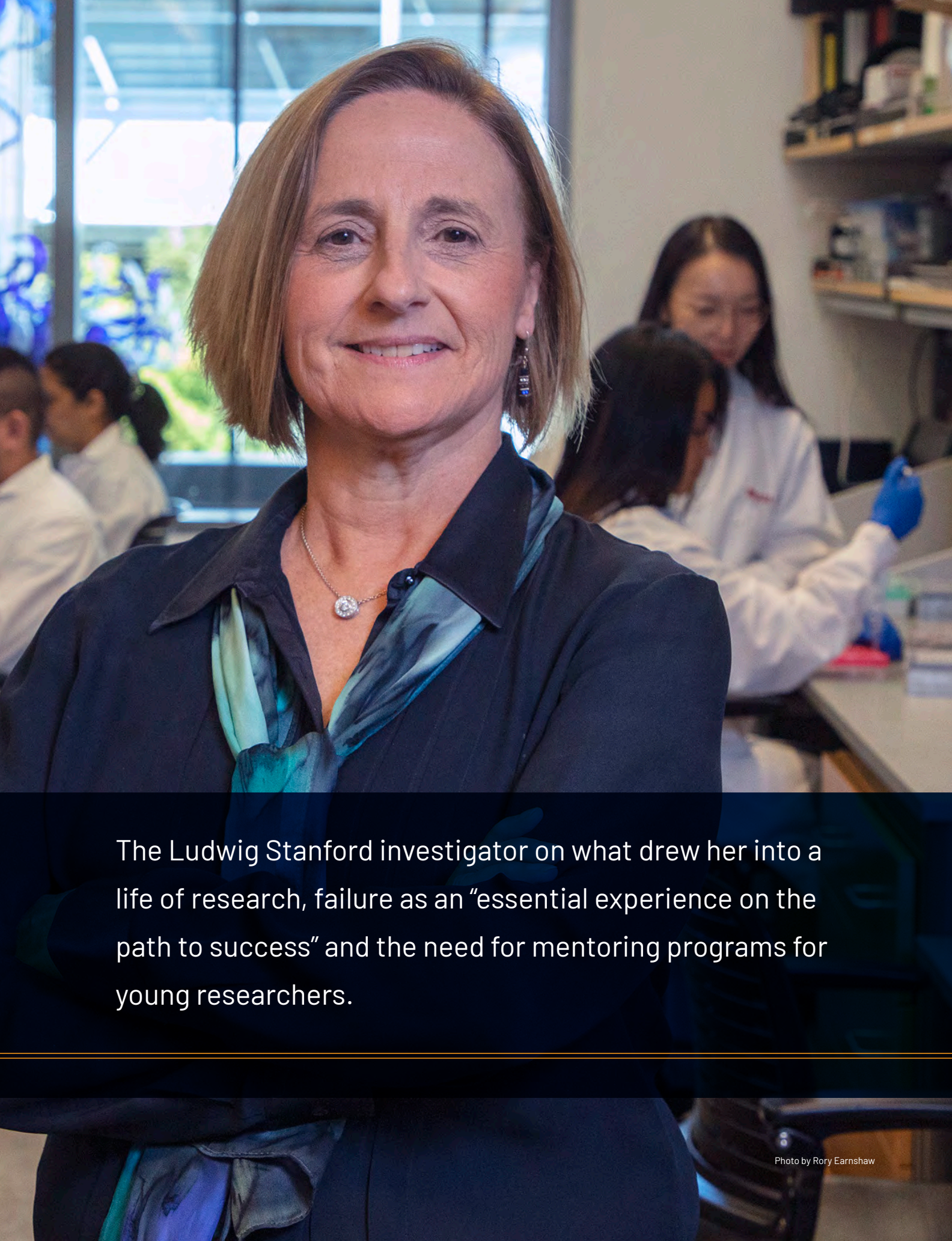
Crystal MACKALL



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

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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."

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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.”