

Never Give Up



COMMUNITY

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Kendra Frederick, Ruth Scherz-Shouval and Gabriela Caraveo Piso

Three Whitehead Institute postdocs are leaving this fall for tenure-track positions at leading institutions. Common among them is remarkable drive and talent. But they also share the same leader – Susan Lindquist, a brilliant investigator and mentor who encourages her postdocs to aim high and never give up.

At a time when tenure-track positions in academia are scarce, and a gender disparity lingers when it comes to academic appointments,

three women – Kendra Frederick, Gabriela Caraveo Piso and Ruth Scherz-Shouval – all postdocs in the lab of Susan Lindquist– will leave Whitehead this fall for faculty positions at leading research universities or institutes. Each admits that being responsible for her own lab is intimidating – “Having a baby wasn’t as scary,” says Gabriela – but it’s also exhilarating knowing that they will soon have the opportunity to build something. And they’re all eager to pay Susan’s mentorship forward.

When Kendra Frederick came to Whitehead in 2007 to study how physiological environments influence protein folding, she was impressed with Susan’s openness to bold paths and emerging technologies “Susan gives you an opportunity to choose the projects you want to pursue, no matter the obstacles,” says Kendra. “Once you figure out what path you want to pursue, she’s a ferocious ally in helping you get what you need.” Kendra worked with Robert Griffin’s group at MIT and the Francis Bitter Magnet Lab to develop a technology to study protein folding events, particularly ones involved in neurodegenerative diseases.

“It’s a very big, very empty lab,” says Kendra in regards to the Assistant Professor position she was offered at the Department of Biophysics at University of Texas Southwestern Medical Center (UTSW). But she’s ready to continue her research independently, saying she was well-trained. Using methods she learned in Susan’s lab, including yeast genetics, Kendra will focus her academic work on the dynamic process of protein folding within complex environments, especially those that promote human disease. She’s also a CPRIT (Cancer Prevention and Research Institute of Texas) Scholar, which will help fund the purchase a high field magnet capable of dynamic nuclear polarization, making UTSW the fourth installation site in the country to own such a tool.

Gabriela Caraveo Piso joined the Lindquist lab the same year as Kendra. The lab was using yeast to model neurological diseases, an unconventional approach at the time, but Gabriela saw the potential. “It was a crazy idea until Susan proved the value,” she says. Gabriela tried several projects before focusing on what started as a “pet project” during her doctoral studies – the signaling behavior of calcium, which is elevated in a group of neurological diseases known as synucleinopathies. In the brain, calcium levels can rise in response to high levels

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of the protein alpha-synuclein. Gabriela was able to study calcium's behavior in a yeast model where alpha-synuclein level could be manipulated. "I didn't think it was going to be anything, but after the work published it just got bigger and bigger," she notes.

At a conference, Gabriela met David Yue, a Johns Hopkins University scientist, who showed interest in her poster. The unexpected meeting evolved into a fruitful collaboration. Gabriela says collaboration is the Lindquist lab's secret sauce. Operations as large as Susan's have their advantages – often more funds to do high-risk research or buy new technologies – but the cost can be that members, even subgroups, can work as silos. "Susan makes an effort to recruit people who are highly collaborative," she says. Gabriela spent years working with her collaborators, using an FDA approved drug (tacrolimus, which is used for organ transplantation surgeries) to lower the activation of calcineurin, a protein that is heightened with alpha-synuclein accumulation. Whether it's neurons in culture or animal models of Parkinson's disease, reducing the activity of calcineurin with tacrolimus eliminates the toxic effects of alpha-synuclein.

To support this work, the Lindquist lab received a significant charitable contribution from a donor with a personal connection to Parkinson's. After encouraging *in vivo* data, the donor then supported a second phase of research. "If the results of the second phase are as positive as we think they will be," she says, "we'll have strong grounds for a clinical trial." Gabriela admits that most basic scientists don't get many opportunities to translate their research, and she is deeply grateful for the philanthropic support that has accelerated her work. She believes donors can have an enormous impact on a field by supporting research like hers that has translational potential.

As for the future, Gabriela's pet project will serve as the foundation for her appointment as an Assistant Professor in the Neurology Department at Northwestern University. Gabriela says the fact that two of her female colleagues also received academic appointments signals a shift to an era "when hiring is based on intellectual capacity, not gender." And the jobs are well-deserved, she says, noting how hard they all worked in their postdoc years. "It's intimidating to have my own lab, where you're responsible for other people's success, but I'm excited to train others and continue my research."

Within the context of the lab's protein-folding focus is a vibrant group determined to elucidate the role that the transcription factor *Heat Shock Factor 1* (HSF1) plays in cancer. When Ruth Scherz-Shouval arrived five years ago from Israel, postdocs in the lab were investigating HSF1 in this realm, but no one was focused on how the "tumor microenvironment" – a complex milieu of immune cells, fibroblasts and blood vessels – influences tumor growth. It became Ruth's niche.

HSF1 regulates the cell's response to high temperatures, the so-called "heat shock response." It was known that HSF1 is important in cancer – low levels make cells resistant to the growth of tumors. She says, "Basically, if you don't have HSF1, you are much less likely to get cancer." After five years of research, Ruth revealed that HSF1 helps recruit normal cells into the tumor microenvironment. The field is wide open, however, with many unanswered questions. Ruth will continue to study how normal cells are recruited and reprogrammed in the tumor microenvironment when she begins her tenure-track position this fall in the Department of Biological Chemistry at the Weizmann Institute of Science. Ruth notes that many female grad students don't pursue a postdoc because they don't think they eventually could run their own lab. "I think having a female mentor like Susan helped prove that it is possible."

All three postdocs speak of Susan's mentorship in the highest regard. Ruth knew she would run her own lab one day, so she watched the ways Susan communicates and manages people, knowing she would have to do the same. Susan has two children, so Ruth paid particularly close attention to how her mentor led her lab while juggling the demands of family. "It made me confident that I could balance all the things that are important to me while running my own lab," Ruth says, adding that although Susan expects results, if research is progressing, postdocs can have a life outside the walls of Whitehead. Ruth came to the lab with two children and had another baby during her postdoc. She says some lab heads might not have been entirely comfortable with that.

Perhaps the greatest gift that Susan instilled each postdoc was the self-reliance to head a lab. Susan gives postdocs the freedom to run their projects autonomously, and postdocs also write their own grants. But when they need guidance, Susan is always available. "Sue is great at seeing the right path," says Ruth. "She knows what's important and the best way to go."

All three postdocs also acknowledge Whitehead Institute's uniquely cozy, collaborative environment. "Everyone passes each other in the elevator, which made me comfortable approaching faculty members for advice," says Ruth.

At Whitehead, postdocs are also deeply appreciated members of the research enterprise. They get the credit and respect they deserve, enjoying social perks such as beer hours and forums, while benefiting from generous workplace offerings, including childcare resources and above-average salaries. Both of Kendra's children were born during her postdoc, and she helped pay for preschool with a childcare scholarship. Ruth says the salary was important for her family, especially as they moved from Israel. Whitehead also makes it convenient for postdocs to engage in public outreach. For years, Kendra mentored undergraduate students through the MIT Undergraduate Research Opportunities Program (UROP) and participated in a variety of public programs at Whitehead.

Of course, science isn't an easy road to travel. Experiments fail, grants and papers are rejected, but Ruth says she loves the freedom. "I get to work with great people and am paid to ask questions I'm curious about," she notes. And if one can persist through the dark days, science has its rewards. An experiment works. A prediction bears fruit. Papers publish. For Susan, there's the added joy of seeing her postdocs accept appointments at leading research institutions around the world.

Ruth also keeps in mind that she may one day make a real difference in patients'. "Solving basic biology problems lays the foundation for cures," she says. "You're a small piece of a large community, but your contributions are meaningful."

As for advice to postdocs dreaming of academic positions, Kendra tells scientists, especially women, "No one will give you something you don't ask for. Whether it's an opinion on an application or resources for your research, figure out what you need and then ask for it."

All three postdocs will soon be asked to fill empty rooms with talented scientists asking important questions. In times such as these, Gabriela is reminded of Susan's advice during a difficult review process: "She told me that upsetting reviewers is often a sign of the work's importance. Never give up. If your work is solid, keep fighting."

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