ASCB PROFILE

Susan Lindquist

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It takes Susan Lindquist twenty-five minutes to get to her lab at the Whitehead Institute in Cambridge, and even though by Boston standards, it's an easy commute, she finds it an intolerable waste of time, twenty minutes longer than Lindquist's old commute to the University of Chicago. "I have two children who are absolutely the joy of my life and I can still say that even though they are teenagers now," Lindquist declares. "But having children and having a career meant that I had to give up other outside interests. It meant I had to arrange my life so that I wasn't wasting a lot of time going back and forth. In Chicago, I lived five minutes from my lab. It meant my kids lived in an apartment and not out in the suburbs, but they saw more of me because I was right there."

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Lindquist continues, "I do a lot of talks about 'women in science' and gender issues [around family] because I am seeing so many young women who are terribly fearful. But there are ways to arrange things so you can have a career and have children. Any career in science can be difficult, but there's actually some synergy in having children. There's the tremendous emotional support, but children also have a way of forcing you to change your thought processes. I would get lab stuff all balled up in my mind and then the kids would make me drop it. There's a real value in that. I think it refreshes your mind and frees up your creativity for when you go back."

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This December, Susan Lindquist will need some of that time for a trip to Washington where she will accept the ASCB Women in Cell Biology 2004 Senior Career Award at the ASCB's Annual Meeting. Former ASCB President Elaine Fuchs, who helped nominate Lindquist for the award, says Lindquist is a role model and a pioneering researcher in the study of protein conformation. "Susan Lindquist's focus on protein folding mechanisms has led to paradigm-shifting discoveries in stress tolerance, gene regulation, evolution, and human protein folding disease, and has now reached into the realm of biophysics," says Fuchs.

The Senior WICB Career award is given each year to "a woman or a man whose outstanding scientific achievements are coupled with a long-standing record of support for women in science." According to Fuchs, "Susan is a remarkable leader, a brilliant scientist, a tremendous mentor and colleague, a strong supporter of women and a compassionate mother of two teenaged girls. And she manages to accomplish far more within a 24-hour period than virtually anyone I know."

Lindquist's research took off with a bang with her pioneering molecular analysis of the heat shock response in *Drosophila* cell lines while she was still a graduate student under Matthew Meselson at Harvard. She continued at the University of Chicago as a post-doc with Hewson Swift and then as a junior faculty member, discovering how various heat shock proteins marshal the cell's response to toxic stress and protein misfolding. The revelation that heat shock proteins can buffer genetic variations, allowing them to accumulate silently and emerge only under stress, has had major implications for oncogenesis and for evolutionary biology. It offered an alternative mechanism that could explain how organisms could evolve quickly in the face of sudden environmental change or how cancer cells can transform so rapidly into more virulent versions of themselves.

Lindquist's work with heat shock proteins led her towards what was then a biological heresy—the idea that a protein alone could be used as a non-genetic carrier of inheritance. The controversy went public in 1992 when Stanley Prusiner at UC San Francisco suggested that a "prion," a misfolded protein, was the non-genetic, non-bacterial transmissible infectious agent for Creutzfeld-Jacob (Mad Cow) disease (he later won the Nobel Prize for the discovery). This "protein-only" hypothesis was highly controversial, says Jeff Kelly, a protein chemist at the Salk Institute. "I think it's fair to say that in the early '90s, most people thought that protein folding wasn't all that important. It's now becoming increasingly clear that assessing folding efficiency and being able to degrade things that aren't properly folded is very important in normal physiology and in pathology. Susan has had a lot to do with that change."

According to Fuchs, "Susan Lindquist and her lab provided the first biochemical evidence that certain genetic traits are transmitted entirely by self-perpetuating changes in protein folding, without changes in DNA and RNA."

"Susan has a grasp of science at the 100,000-foot-level," says Kelly. "She can appreciate so many aspects of a problem—the chemistry, the cell biology, the animal model—that she's able to think about them all in a big way. How is it that the process of prion aggregation leads to pathology? Why is that protein synthesis is required for long-term memory? Susan's specialty is working on those kind of large problems."

Like the hero of a Saul Bellow novel, Susan Lindquist is "an American, Chicago-born," even if her parents were from different worlds. "Both my parents were first-generation Americans, extremely smart but mostly self-educated," says Lindquist. "My mom's parents were from Italy and my dad's were from Sweden. They met in Chicago. Sometimes people say that I have an unusual ability to work with people from wildly different backgrounds. That's my early training. My mom was a stereotypical Italian and my dad was a stereotypical Swede. And the relations on both sides were the same way."

Growing up amidst this cultural contrast gave Lindquist her love for vivid family life. Her love of science, though, is harder to explain. "I've just always had this abiding interest in nature," she says. "I remember when I was a little, I had no interest in playing with dolls. I liked to go round the neighborhood collecting things—berries, dirt, insects—and then I would mix them all together to see what would happen."

The accomplished mud-pie chemist moved from the city to the suburb of Park Ridge, Illinois, when she was 12. She earned a full scholarship to the University of Illinois, Champaign-Urbana. There her social life blossomed. "In high school, I was shy and rather socially immature," she recalls, "but when I got to college, I was suddenly living with all these great new girl friends and all these boys were asking me out. Quite frankly, I had a blast."

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Meantime, her academics were another story, she confesses. "But I mostly got As and Bs." The As were in science classes where the work was challenging. The Bs were in everything else, once she discovered that a one-night cram session was all she needed to pass. To cover her living expenses, Lindquist waited tables part-time at the Pancake House, at a "Polynesian" restaurant and, for one memorable summer, in a cocktail lounge. "Now that was an education," Lindquist recalls. Among other things, cocktail waitressing taught her to be more serious about finding a sit-down profession.

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Back at school, two "wonderful" professors, Sam Kaplan and Jan Drake, noticed Lindquist's new focus. Drake invited her to do an undergraduate research project in his lab. "The experiment didn't work out," Lindquist recalls, "but it got me all fired up about working at the bench." Drake also suggested that she consider graduate school. In the spring of 1971, Lindquist found herself standing in front of a mailbox with two acceptance postcards in hand and not knowing which to return. Harvard beat out MIT then, but MIT managed to grab her later.

"The two most valuable things that Lindquist taught (were) how to practice high-quality science, and how to write it up clearly."

Lindquist, who was an HHMI investigator in Chicago for thirteen years before serving as Director of MIT's Whitehead Institute from 2001-2004, has broadened her scientific interests. She has proposed a new hypothesis to explain mammalian prion protein toxicity, developed a yeast model for Parkinson's, and formed a small biotech with Kelly called Fold Rx to explore the pharmacological possibilities of folded proteins. She worked with physicist Heinrich Jaeger to produce the first protein-based nano wires and with neurobiologist and Nobel Laureate Eric Kandel on the role of self-perpetuating prions in long-term memory formation.

Lindquist's family remains her anchor. Eleanora is 17 and a senior at Brookline High School. Alana is 15 and a sophomore. Nora is, according to her mother, a talented writer. She talks about writing novels, although Lindquist now wonders if sports writing might be a better fit. Since the family's move to Boston, Nora has become a "fanatical" Red Sox fan and a knowledgeable one, her mother says. "I've had colleagues come over for dinner, people who've been Red Sox fans for 30 years, and Nora will talk with them about the pitching rotation and stuff like that. They tell me, 'Wow, she really knows her stuff.'" Alana is musical, a singer with a wonderful voice, says Lindquist, but also a natural born entrepreneur. "We go into a restaurant or a store and Alana will look around and start telling me things she would change."

Their father and Lindquist's husband is Edward Buckbee, a teacher of French medieval literature when they met but now a development officer for non-profits. Buckbee is a humanist, a wise man and an unwavering believer in the value of her research, according to Lindquist. He's also a nifty dancer, she says. They are devotees of the Argentine tango, which, Lindquist hastens to point out, is very different from the stylized tango you see in ballroom competition. In Chicago, they belonged to a tango club and went dancing every week. Unfortunately, the move to Boston coincided with a dreary round of back trouble for Lindquist. But after a two-year hiatus, she says she's better and ready to tango again.

Susan Lindquist was a fabulous mentor, says Tom McGarry, who was in her Chicago lab as an MD/PhD student from 1982-'86. "Her lab was really starting to grow then, but Susan wasn't stuffy or hard to approach," says McGarry, who remains in Chicago, at Northwestern. At the time, McGarry says he didn't recognize the two most valuable things that Lindquist taught him—how to practice high-quality science, and how to write it up clearly. "It wasn't until I left Susan's lab that I realized that not every lab had such high standards, either in their science or in their writing." ■