Susan Lee Lindquist

(1949–2016)

Biologist who found unexpected power in protein folding.

CEAL CAPISTRANO

Susan Lee Lindquist revealed the profound ramifications of a process that most scientists had overlooked: protein folding. Through elegant experiments in yeast, plants, flies and human cells, Lindquist demonstrated how this process by which proteins adopt their proper shapes fuels evolution. It can buffer the effects of genetic variation, allow new traits to emerge and enable the rapid evolution of new adaptations. Her insights have paved the way for innovative strategies to treat diseases including Alzheimer's, Parkinson's and cancer.

Lindquist was a visionary who connected concepts across disparate disciplines. When her bold ideas were met with doubt, she persevered, gathering evidence until she changed biological thinking. Her positivity and love for discovery were infectious.

Lindquist, who died from cancer on 27 October, was born in Chicago, Illinois, in 1949. Early on, she became enthralled by a teacher's question: what is life? In search of answers, she studied microbiology at the University of Illinois Urbana–Champaign. She earned her PhD in molecular and cellular biology from Harvard University in Cambridge, Massachusetts, in 1976.

It was at Harvard that she began studying how cells respond to heat and other stresses by producing heat-shock proteins (Hsps). After a brief postdoc at the University of Chicago, she joined the faculty there in 1978 and became a full professor in 1988. In 2001, she moved to the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology in Cambridge. She served as its director until 2004, and as a professor of biology from 2001 until her death.

Lindquist focused on Hsp90. This abundant protein acts as a molecular chaperone, helping to fold many proteins important for cell signalling. She identified two surprising roles for Hsp90 in evolution. First, she found that Hsp90 could protect cell-signalling pathways from the effects of mutations in other proteins. If Hsp90 function was compromised by environmental stress, genetic variants would fold differently and new traits would appear rapidly. Her striking experiments in plants, for example, revealed that inhibiting Hsp90 function could yield some beneficial phenotypes, including altered growth of stems and roots, and increased resistance to herbivores.

Second, Lindquist established that Hsp90 can allow mutations that would otherwise result in an unstable protein to produce a functioning protein with a new phenotype. Both roles expand the repertoire of traits that can be selected through evolution. Lindquist demonstrated that these powerful mechanisms are probably universal across eukaryotes.

Lindquist also shattered dogma about misfolded proteins associated with disease. She discovered that Hsp104 could wrest clumps of misfolded proteins apart and return them to their functional form. This finding led her to study prions. These infectious proteins cause normally folded proteins to assume self-replicating conformations that cause fatal neurodegenerative disorders such as Creutzfeldt–Jakob disease and scrapie.

She was fond of saying that prions transmit perduring molecular memories. At a time when prions were deemed merely disease-causing villains, she established that they can also confer beneficial functions, including antibiotic resistance and improved metabolism. Indeed, Lindquist helped to reveal how prions may function in long-term memories by stimulating translation at synapses.

Beginning in the 1990s, Lindquist championed yeast as a model to probe both cancer and neurodegeneration. Sceptics questioned (and still do) why anyone would try to study a brain disease in yeast. Undaunted, she developed a series of yeast models that express each of the major human neurodegenerative disease proteins. As in the brain, these proteins formed aggregates and were toxic in yeast. She identified yeast genes that reduced the toxicity of protein misfolding connected to Parkinson's disease and established that these same genes are protective in mice and rats.

She co-founded two Cambridge companies, FoldRx Pharmaceuticals (acquired by Pfizer in 2010) and Yumanity Therapeutics to uncover therapies for neurodegenerative diseases caused by protein misfolding. Her use of yeast in drug screening is now accepted practice.

Researchers from diverse backgrounds — from physicists to physicians — wanted to work in Lindquist's lab. Both of us pursued postdocs at the Whitehead after being inspired by seminars she gave at our graduate institutions. One of us (J.S.) moved from the United Kingdom to the United States and the other (A.D.G.) shifted discipline to work with her.

Sue believed that scientists had a moral obligation to address important societal problems. In her papers, she used language that was accessible to wide audiences. She was a nurturing mentor, inviting group members to her house on weekends to write manuscripts. We were fortunate to get to know her in this personal setting, interacting with her wonderful daughters and husband, and learning that it was possible to be a world-class scientist and have a family. Her unwavering commitment to promoting women in science is memorialized by the Whitehead Institute Fund to Encourage Women in Science.

Somehow, Sue found time in her unrelenting schedule to sit on the grass and watch her students and postdocs play soccer on Friday afternoons in Cambridge — always there to cheer us on. The world feels smaller without her. ■

James Shorter *is associate professor of biochemistry and biophysics at the University of Pennsylvania, Philadelphia, Pennsylvania, USA.* **Aaron D. Gitler** *is associate professor of genetics at Stanford University, Stanford, California, USA. Both worked with Susan Lindquist in the 2000s as postdocs at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts.*
e-mails: jshorter@mail.med.upenn.edu, agitler@stanford.edu

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