

In Memoriam

Susan Lee Lindquist
(1949–2016)James Shorter^{1,*}

Lindquist was a visionary and pioneer who transformed our understanding of how protein folding sculpts biology, evolution, and disease. She revealed several unanticipated mechanisms by which protein folding can buffer, release, and potentiate genetic variation in response to environmental stress, thereby enabling the rapid evolution of beneficial new traits. Her discoveries provide a rich framework for innovative therapeutic interventions in several fatal diseases, including Alzheimer's disease, Parkinson's disease, and cancer.

Susan Lee Lindquist was a heroic pioneer and iconic visionary who revolutionized our understanding of how alterations in protein folding can sculpt biology, evolution, and disease [1]. Among many great achievements, perhaps the most striking was the revelation of multiple unprecedented mechanisms by which protein folding can buffer, release, and potentiate genetic variation in response to environmental stress, thereby enabling the rapid evolution of beneficial new traits [1–6]. In her wake, she leaves a rich legacy of fundamental, path-breaking discoveries and perduring insights, which provide a framework for innovating therapeutic interventions in several fatal diseases, including Alzheimer's disease, Parkinson's disease, and cancer. Among her countless honors and prestigious awards were the National Medal of Science (2009) and the Albany Prize in Medicine (2016). She was elected as a member of the National Academy of Sciences (1997) and the Royal Society (2015). Sue died of cancer on October 27 at age 67 years.

Sue was a spectacular scientist who combined a searing intellect with deep wisdom, sagacious intuition, and limitless creativity. These characteristics enabled Sue to make connections across disparate disciplines that nobody else could make. Her infectious esprit for scientific discovery was combined with disarming warmth, positivity, openness, directness, and generosity, which made her an inspirational, nurturing, and indefatigable mentor. These synergistic traits empowered extraordinarily effective collaborations between scientists from diverse backgrounds and disciplines. Indeed, researchers from diverse backgrounds – physicists, chemists, biochemists, biologists, mathematicians, and physicians – wanted to work in her laboratory. Sue wrote papers that were accessible to wide audiences and her seminars were captivating and clear. I was inspired to postdoc in her laboratory during my Ph.D. after hearing her present a seminar at The Imperial Cancer Research Fund at Lincoln's Inn Fields in London, U.K. hosted in late 1998. The pursuit of science with Sue was invariably filled with verve, courage, and good humor.

Born in Chicago in 1949, Sue was the granddaughter of Swedish and Italian immigrants. Her proud parents, Iver and Eleanor, were not college graduates, but they greatly valued education. As early as fifth grade, Sue became enthralled by the question: what is life? This passion inspired Sue to gain her B.A. in Microbiology from the University of Illinois at Urbana–Champaign (1971), where she received a National Science Foundation fellowship. Sue then earned her Ph.D. in Biology from Harvard University (1976) where she worked with Matthew Meselson. It was during her Ph.D. where Sue first became interested in how cells respond to environmental stress by expressing heat-shock proteins (Hsps).

Sue returned to her beloved Chicago for a brief postdoctoral stint with Hewson Swift

at the University of Chicago, where she would later join the faculty (1978) and rise to full professor (1988). While at the University of Chicago, Sue married Edward Buckbee and would have two wonderful daughters, Alana and Nora. She also launched a remarkable and radical series of trailblazing discoveries. These continued when Sue moved her research program to the Whitehead Institute for Biomedical Research at Massachusetts Institute of Technology (MIT), which is where I trained with Sue as a postdoctoral fellow (2002–2007). Sue would spend the rest of her career at the Whitehead Institute as Director (2001–2004), Institute Member (2001–2016), and Professor of Biology at MIT (2001–2016).

Early work from Sue's group established how Hsp expression was coordinated and regulated in response to environmental stress. She brought Flp recombinase technology to *Drosophila* for the first time [7]. Her focus shifted to define Hsp function, which yielded innumerable profound insights. Perhaps the most vivid advance concerned Hsp90, an abundant and specialized molecular chaperone with a selective clientele of metastable signal transducers that regulate a diverse array of critical biological processes [1]. She found two surprising roles for Hsp90 in evolution (Figure 1). First, Sue's group established that by folding its clients, Hsp90 maintained signaling pathways and could even buffer the effects of mutations in these pathways [2–4]. This Hsp90 buffer enabled storage of cryptic genetic variation [2–4]. Compromising Hsp90 function via environmental stress revealed this genetic variation and caused new traits to appear, which could be assimilated [2–4]. Second, Sue's group established that Hsp90 could also potentiate genetic variation, allowing new mutations to produce immediate phenotypes, which could also be assimilated [2,6]. Here, compromising Hsp90 function caused new traits to be lost [2,6]. These powerful mechanisms of evolutionary change were

