Trends in Biochemical Sciences

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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

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Figure 1. Susan Lindquist Reflecting on Her Discoveries with Hsp90 and Evolution at the Whitehead in 2006. Photo credit, Justin Knight.

found to operate in diverse model organisms and are likely ubiquitous in eukaryotes [1].

In another seminal advance, Sue shattered the dogma that protein aggregates were intractable structures. Sue's group discovered that Hsp104 possessed a powerful protein-disaggregase activity capable of dissolving protein aggregates and restoring previously aggregated proteins to native form and function [8,9]. These transformative findings led Sue into the field of yeast prions, which are tightly regulated by Hsp104 [10]. Prions are infectious proteins that can adopt self-perpetuating conformations, which cause debilitating neurodegenerative disease in humans [11]. Sue's group enabled us to understand how yeast prions assemble and are regulated by Hsp104 [10]. Importantly, Sue's group established that yeast deploy a variety of prions for beneficial purposes, including the rapid evolution of beneficial and heritable new traits in response to environmental stress [12]. Sue made us view prions in a new light. They were no longer merely villains that cause disease [11]. They had been captured during evolution for beneficial purposes [11]. Thus, prions were recast as adaptive conduits of memory and inheritance [10–12].

In more recent years, Sue focused on tackling two major barriers that prevent us from living longer, more fulfilling lives: neurodegenerative disease and cancer. Sue championed yeast as a powerful model to study neurodegenerative disease reasoning that protein misfolding is a universal problem and that profound insights could likely be obtained from our most powerful yet humble model organism [13]. This endeavor may have seemed like a gamble, but Sue was dauntless, and importantly, she was right. Yeast models have now enabled the discovery of genetic and small-molecule modifiers that rescue animal models of disease [13]. I strongly suspect that these findings will lead to urgently needed therapeutics. Indeed, these profound discoveries led Sue to co-found FoldRx (acquired by Pfizer) and Yumanity Therapeutics. Sue's group would also make stunning insights into Hsp90, heat-shock factor 1, and transcriptional responses in cancer, which also inspire hope for therapeutics [14,15].

We are massively diminished by Sue's death. Sue strongly believed that scientists had a binding moral obligation to serve society and solve important conundrums that would have global, wide-reaching consequences. Importantly, Sue was not only a great scientist. She was a wonderful person. She would invite group members to her house to work on manuscripts at the weekend, and here you could really get to know Sue and meet her family. In my view, it would be in this setting where the most insightful writing would happen. Although exceptionally busy with numerous responsibilities, Sue would somehow find time to sit on the grass near the goal and watch her students and postdocs play soccer on Friday afternoons in East Cambridge – always there to cheer us on.

The world feels horribly smaller without Sue. Her startlingly prescient insights and her sage advice have empowered so many in science and beyond. She will be remembered long into the future for her game-changing, visionary science, as well as the many wonderful and talented scientists she nurtured and trained. It was a great privilege to know her and to pursue science with her.

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References

1. Lindquist, S. (2009) Protein folding sculpting evolutionary change. *Cold Spring Harb. Symp. Quant. Biol.* 74, 103–108
2. Jarosz, D.F. and Lindquist, S. (2010) Hsp90 and environmental stress transform the adaptive value of natural genetic variation. *Science* 330, 1820–1824
3. Queitsch, C. *et al.* (2002) Hsp90 as a capacitor of phenotypic variation. *Nature* 417, 618–624
4. Rutherford, S.L. and Lindquist, S. (1998) Hsp90 as a capacitor for morphological evolution. *Nature* 396, 336–342
5. True, H.L. and Lindquist, S.L. (2000) A yeast prion provides a mechanism for genetic variation and phenotypic diversity. *Nature* 407, 477–483
6. Cowen, L.E. and Lindquist, S. (2005) Hsp90 potentiates the rapid evolution of new traits: drug resistance in diverse fungi. *Science* 309, 2185–2189
7. Golic, K.G. and Lindquist, S. (1989) The FLP recombinase of yeast catalyzes site-specific recombination in the *Drosophila* genome. *Cell* 59, 499–509
8. Parsell, D.A. *et al.* (1994) Protein disaggregation mediated by heat-shock protein Hsp104. *Nature* 372, 475–478
9. Glover, J.R. and Lindquist, S. (1998) Hsp104, Hsp70, and Hsp40: a novel chaperone system that rescues previously aggregated proteins. *Cell* 94, 73–82
10. Shorter, J. and Lindquist, S. (2005) Prions as adaptive conduits of memory and inheritance. *Nat. Rev. Genet.* 6, 435–450
11. Lindquist, S. (1997) Mad cows meet psi-chotic yeast: the expansion of the prion hypothesis. *Cell* 89, 495–498
12. Newby, G.A. and Lindquist, S. (2013) Blessings in disguise: biological benefits of prion-like mechanisms. *Trends Cell Biol.* 23, 251–259
13. Khurana, V. *et al.* (2015) Toward stem cell-based phenotypic screens for neurodegenerative diseases. *Nat. Rev. Neurol.* 11, 339–350
14. Scherz-Shouval, R. *et al.* (2014) The reprogramming of tumor stroma by HSF1 is a potent enabler of malignancy. *Cell* 158, 564–578
15. Whitesell, L. and Lindquist, S.L. (2005) HSP90 and the chaperoning of cancer. *Nat. Rev. Cancer* 5, 761–772