Susan Lindquist: Visionary scientist and peerless mentor

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The science universe is dimmer after one of our brightest stars, Susan Lee Lindquist, was taken by cancer on October 27, 2016. Sue was an innovative, creative, out-of-the-box scientific thinker. She had unique biological intuition—an instinct for both the way things worked and the right questions to ask to uncover new research insights. Her wide-ranging career began with the study of protein folding and molecular chaperones, and she went on to show that protein folding can have profound and unexpected biological effects on such diverse processes as cancer, evolution, and neurodegenerative disease. As Sue's laboratory manager, I would like to offer a ground-floor perspective on what made her an exceptional scientist, mentor, and leader. She created a harmonious, collegial environment where collaborative synergy fueled meaningful progress that will impact science for decades to come.

I still vividly remember the first time I met Sue as a prospective graduate student at the University of Chicago—she was in her office surrounded by artwork from her young children. Sue became part of my graduate student life as I rotated in her laboratory and she served as a member of my thesis committee. After graduating, I came to the Whitehead Institute, where I have been Sue's laboratory manager for almost 15 years. It is hard to overestimate what an enormous figure she has been to me. We developed a fantastic partnership and trust based on common values, instincts, and sensibilities. I am honored and privileged to have learned from her for so many years.

Scientist

Susan was born on June 5, 1949, into a middle-class family in Illinois; her parents, Iver Lindquist and Eleanor Maggio Lindquist, were first-generation immigrants. Sue was always proud of her Swedish and Italian heritages. The combination of the two contrasting cultures was reflected in her multidimensional character: an indomitable, passionate spirit balanced with cool, logical pragmatism. Though her parents highly valued education, expectations were low and barriers were high for a girl in her generation. She did not set out to be a scientist, but her natural curiosity and appetite for the big questions in life became apparent at a young age when she became enthralled after her fifth-grade teacher posed the question, "What is life?" That moment would define her scientific style, as she always kept a big-picture perspective and asked fundamental questions in her research.

Susan overcame mild dyslexia to earn a scholarship to the University of Illinois, Urbana-Champaign, where she studied microbiology. It was there she began her research career and wrote her first grant, a National Science Foundation fellowship, at the encouragement of one of her professors. Surpassing even her own expectations, she enrolled in a PhD program at Harvard University and joined the laboratory of Matthew Meselson, where she had the freedom to explore whatever interested her, a situation that suited her perfectly and that she later cultivated in her own laboratory. In the Meselson laboratory, she began her study of the heat-shock response, being the first to exploit *Drosophila melanogaster* tissue culture to study the induction of heat-shock mRNAs. Earning her PhD in 1976, she moved to the University of Chicago to do a short postdoc in the laboratory of Hewson Swift before joining the faculty there in 1978. She thrived at the University of Chicago, becoming a Howard Hughes Medical Institute Investigator and full professor in 1988 and the Albert D. Lasker Professor of Medical Sciences in 1999. In 2001, she moved her laboratory to the Whitehead Institute for Biomedical Research, where she served as director from 2001 to 2004 and was also a professor at the Massachusetts Institute of Technology until her death this past fall.

Early in her career, being a female professor in science was challenging, and she occasionally recounted stories of obstacles she faced in this male-dominated profession. She recalled writing an R01 while in her third trimester of pregnancy in her office located two floors away from the only women's restroom in the building. She had to frequently trudge up and down the steps because of her pregnancy, and, of course, trips became increasingly difficult. Early on, she just accepted things as they were and resolved to work twice as hard.

In her own laboratory, Sue shifted from examining the transcriptional response to heat stress to investigating the class of proteins that was induced: molecular chaperones. She was fascinated by the fact that, although all eukaryotic cells placed at an extreme temperature perish, those same cells survived if first exposed to an intermediate temperature. Sue's laboratory went on to show that a genetic program that responds to this and other stresses is activated in all cells. Thus, she launched her career studying heat-shock proteins whose functions made the difference between life and death after stress.

One of Sue's most important discoveries came through her work on the abundant heat-shock protein Hsp90. She shattered

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Susan Lindquist. Photo courtesy of Sam Ogden.

dogma by proposing a molecular mechanism for Hsp90 in the evolution of new traits. Like other chaperones, Hsp90 helps unstable proteins fold within the incredibly crowded environment of the cell. Uniquely, however, it has a select set of diverse, metastable "client" proteins, mostly involved in signaling and development, that require Hsp90 for normal folding and function. By nature of its activity, Hsp90 allows mutant proteins that would otherwise be unstable and degraded to fold and function in the cell. This activity allows new traits to arise and enables adaptation of populations to new environments.

Sue was surprised at how controversial these ideas were to the evolutionary biology field. After all, she was providing an experimentally testable hypothesis to support a possible mechanism for evolution. But through dogged perseverance, in a seminal series of papers, Sue and her laboratory provided evidence that Hsp90 can be both a capacitor and potentiator for genetic variation in *Drosophila*, plants, yeast, and even cavefish (Rutherford and Lindquist, 1998; Queitsch et al., 2002; Jarosz and Lindquist, 2010; Rohner et al., 2013). Always aware of the broad implications of her discoveries, Sue went on to link Hsp90 to the emergence of drug resistance in fungal pathogens as well as to cancer. Many oncogenic kinases are highly dependent on Hsp90 activity, and her work contributed to making chaperone function a therapeutic target for the treatment of human disease.

In addition, Sue's paradigm-shifting research has driven forward research in the field of prion biology. Sue came to study prions serendipitously after she found that Hsp104 is a unique chaperone and protein-remodeling factor with an ability to disentangle aggregated proteins and return them to normal function. This discovery led to a call from a colleague studying a bizarre color trait in yeast. The trait, originally described and called [*PSI+*] by Brian Cox in 1965, defied Mendelian genetics and was dominantly inherited through the cytoplasm. Her colleague found that Hsp104 profoundly influenced [*PSI+*] biology, suggesting a controversial protein conformation–based mechanism of inheritance: the prion hypothesis. This connection launched two decades of research into the rich world of prion biology. Sue's laboratory pioneered techniques and provided genetic and biochemical evidence to show that [*PSI+*] is a protein-based element of inheritance in which a metastable, self-perpetuating change in protein conformation can affect phenotype over generations.

[*PSI+*] was just the beginning. Sue's laboratory went on to discover over two dozen more prions in laboratory strains and wild yeast (Alberti et al., 2009; Halfmann et al., 2012). Typical of her optimistic nature, Sue saw the silver lining in these heritable protein aggregates that many viewed as disease mediators or mistakes of nature. She realized that because changes in protein shape are accompanied by changes in function, they could lead to a wide array of new and complex traits. Because prions are metastable and can switch over generations, Sue proposed that prions are a sophisticated "bet-hedging" device allowing cells to sample phenotypic states in a changing environment.

Motivated in part by a family friend's struggle with Huntington's disease, Sue next set her determined focus on studying protein homeostasis in human disease. Many neurodegenerative diseases are associated with the accumulation of misfolded proteins. Understanding that, as eukaryotes, yeast have more in common with humans than most other single-cell organisms, Sue reasoned that many of the problems caused by misfolded proteins and the cellular coping mechanisms in place would be universal. She made the bold move to use yeast as "living test tubes" to study the cellular basis of the toxicity caused by disease-related proteins, such as α-synuclein (Parkinson's disease) and amyloid-β (Alzheimer's disease). Sue was met with considerable pushback. Indeed, Sue even had to convince many members of her own laboratory that this was a good idea. Once again, her perseverance and instinct paid off. Using yeast for high-throughput genetic and chemical screens to identify suppressors and enhancers of the toxicity caused by these human disease proteins, followed by validation of the hits in more complex organisms and even patient-derived iPS cells, she identified pathways, genes, and compounds that modify disease pathology (Chung et al., 2013; Tardiff et al., 2013). In fact, the platform she developed became the basis for Yumanity Therapeutics, a biotechnology start-up she founded together with several members of her laboratory.

Susan's brilliant mind was truly unique. She had incredible scientific intuition and an amazing ability to see connections that others missed. She instinctively knew the key questions to ask and readily visualized the larger scientific significance. Her creativity stemmed from nonlinear thinking: her mind was a supercomputer, with many subprograms constantly running in the background. Answers would often pop out at random times, and she would be struck by a great idea or insight. What was so charming about Sue with this gifted mind is that she was the prototypical absent-minded scientist: so focused on thinking about science that she would easily get lost and forget or lose important items. We were often chasing after to her to return things accidentally left behind. However, she never forgot an experiment or result, remembering them, in detail, back to the earliest days of her laboratory. Sue was always more interested in ideas that would "change the way people think" about a field. Some of the most interesting advice I ever received from her was provided while writing a paper. She told us to read all the current literature, see what questions they are asking, and think about how our data speaks to those questions. This impact will continue in the work of her numerous trainees, many of whom run independent research laboratories around the world.

Mentor

Mentoring young scientists was one of the things that Sue most valued and enjoyed. She took such pride in the scientists she trained to do science the way she did: ethically, creatively, rigorously, challenging doctrine, and looking at problems in new ways. One reason Sue was such a great mentor is that she loved people and had an exceptional touch with them. She had an uncanny ability to understand their concerns, motivations, strengths, and weaknesses. She used that gut instinct to adjust her management style to bring out the best in each individual. A highly empathetic person, Sue was understanding and supportive when people had personal challenges or triumphs. She laughed with us and cried with us; she was quick to give a warm hug or reassuring touch. Sue was open and down to earth; she shared so much of herself, it was both disarming and welcoming. One postdoc recalled that before she joined Sue's laboratory, she had met Sue at a conference. Both needed to get back to Boston and when the train was delayed, Sue offered her a ride in her car. They spent two hours together, talking about science and life.

Sue understood the paramount importance of a collegial, open atmosphere, where laboratory members share ideas and advice in a supportive, constructive manner. She knew that a scientist who was happy would accomplish more and have the intellectual capacity to be more creative; personnel conflicts drain time, handicap communication, and limit scientific progress. Outstanding applicants were drawn by Sue's bold, creative science, clearly written papers, and alluring charisma, but most joined the laboratory for two reasons: Sue's infectious scientific enthusiasm and the friendly, collegial, collaborative atmosphere in the laboratory. Sue worked hard to cultivate a nurturing environment. She set a strong positive tone for the laboratory. She was always cheerful and encouraging, and she never lost her temper. She had a wonderful way of looking at the world: a pragmatic realism, balanced with a joyful optimism and knowledge that something good was always around the corner; you just had to keep working at it. Lab members came away from meetings with her feeling invigorated and enthused about their projects. She encouraged and sponsored frequent social events, knowing that they ease social tensions and spark pivotal connections and collaborations. Furthermore, she actively discouraged competition within the laboratory and helped prevent it by giving people projects with unique, broad questions that were well delineated from others. Importantly, if a conflict arose, she would address it head-on. She would not tolerate squabbling or egos preventing scientific progress. Finally, Sue had a strong sense of fairness and justice. She was ethical and could be counted on to resolve disputes, leaving each person's dignity whole. It was reassuring that Sue was always the mature adult and the final word.

A unique aspect of Sue's mentorship was the great care she took teaching people to write and communicate clearly. Sue was a gifted communicator with an ability to render complicated concepts accessible to all. Each manuscript was a labor of love, where every word was painstakingly debated and carefully chosen. One laboratory member recalls Sue pondering for 10 minutes about whether "cannot" should be one word or two in a particular context. Papers were written and rewritten many times, often with additional experiments performed to shore up conclusions and close loop holes in logic. Sue wrote and edited the manuscripts in many, long one-on-one sessions with the author, talking through each section and, interestingly, always starting at the abstract. Though frustrating at times, laboratory members invariably said it was an amazing and illuminating experience. They saw Sue's thought and writing process, and, as a result, they learned to be better communicators of science. If Sue felt a trainee's writing needed improving (which she always did), she would hand him or her a copy of Strunk and White's Elements of Style—sometimes more than once. Laboratory members had a tongue-in-cheek competition for who could acquire more copies of the revered writing guide.

Leader

As her stellar career progressed, Sue was widely recognized for the breadth and significance of her scientific achievement. She was elected to the National Academy of Sciences, the National Academy of Medicine, and the British Royal Society and was honored with many awards, including the Presidential National Medal of Science, the E.B. Wilson Award, the Otto Warburg Prize, and, most recently, the Albany Prize, which she heart-breakingly accepted from her hospital room.

Sue's confidence grew over the years, from that time when she was a junior professor who did not call attention to herself and quietly suffered with a terrible chair that gave her major back problems. She no longer accepted things as they were and was ready to jump into action when she saw an injustice. When Sue became director of the Whitehead Institute, she found that postdoc salaries were very low and many trainees were struggling, especially those with families. She increased the salaries and installed incentives for those who obtained fellowships, actions that have led Whitehead to be ranked by *The Scientist* as the No. 1 place in the country to do a postdoc for many years since then.

Sue led by example, never expecting anyone to work harder than she did. We marveled at her energy level: back-to-back meetings all day long, dinner, and then email late into the night. She cared deeply about her reputation and was, at her core, a people pleaser. She was an outstanding role model and advocate for women in science, acknowledging how hard it is to balance work and family life, but providing a shining example that it can be done.

Sue's family was key to her success in science and in life. Her charming, cultured husband Edward has a calm, dignified demeanor and was a perfect equalizer to Sue's hectic, overcommitted world. They shared a love of dancing, literature, theater, and ballet. Her lovely, intelligent, spirited daughters, Nora and Alana, provided welcome joy and respite from the stresses of grant writing and paper rejections. Her face glowed when she spoke of them; indeed, her family was a major source of her creativity and energy.

Susan Lindquist was larger than life. She was so strong and fiercely determined that it is hard for many of us to accept she is gone. That is why I am choosing not to think of her as gone. She and her indomitable spirit will be with us always in her discoveries and in the future work done by the many privileged enough to have known her. Together, it is our job to make sure that her impact on science and the world will endure.

References

Alberti, S., R. Halfmann, O. King, A. Kapila, and S. Lindquist. 2009. A systematic survey identifies prions and illuminates sequence features of prionogenic proteins. *Cell.* 137:146–158. http://dx.doi.org/10.1016/j.cell.2009.02.044

Chung, C.Y., V. Khurana, P.K. Auluck, D.F. Tardiff, J.R. Mazzulli, F. Soldner, V. Baru, Y. Lou, Y. Freyzon, S. Cho, et al. 2013. Identification and rescue of I-synuclein toxicity in Parkinson patient-derived neurons. *Science.* 342:983–987. http://dx.doi.org/10.1126/science.1245296

Halfmann, R., D.F. Jarosz, S.K. Jones, A. Chang, A.K. Lancaster, and S. Lindquist. 2012. Prions are a common mechanism for phenotypic inheritance in wild yeasts. *Nature.* 482:363–368. http://dx.doi.org/10.1038/nature10875

Jarosz, D.F., and S. Lindquist. 2010. Hsp90 and environmental stress transform the adaptive value of natural genetic variation. *Science.* 330:1820–1824. http://dx.doi.org/10.1126/science.1195487

Queitsch, C., T.A. Sangster, and S. Lindquist. 2002. Hsp90 as a capacitor of phenotypic variation. *Nature.* 417:618–624. http://dx.doi.org/10.1038/nature749

Rohner, N., D.F. Jarosz, J.E. Kowalko, M. Yoshizawa, W.R. Jeffery, R.L. Borowsky, S. Lindquist, and C.J. Tabin. 2013. Cryptic variation in morphological evolution: HSP90 as a capacitor for loss of eyes in cavefish. *Science.* 342:1372–1375. http://dx.doi.org/10.1126/science.1240276

Rutherford, S.L., and S. Lindquist. 1998. Hsp90 as a capacitor for morphological evolution. *Nature.* 396:336–342. http://dx.doi.org/10.1038/24550

Tardiff, D.F., N.T. Jui, V. Khurana, M.A. Tambe, M.L. Thompson, C.Y. Chung, H.B. Kamadurai, H.T. Kim, A.K. Lancaster, K.A. Caldwell, et al. 2013. Yeast reveal a "druggable" Rsp5/Nedd4 network that ameliorates I-synuclein toxicity in neurons. *Science.* 342:979–983. http://dx.doi.org/10.1126/science.1245321