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Obituary

Susan Lee Lindquist (1949–2016)—pioneer in the study of cellular protein folding and disease

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Susan Lee Lindquist. With permission from Ceal Capistrano/Whitehead Institute.

The scientific community is deeply saddened by the passing of Susan Lee Lindquist, Professor of Biology at MIT and a Howard Hughes Medical Institute Investigator, on October 27 after a year-long battle with cancer. Her nearly 40-year career was distinguished by groundbreaking research in cell biology and genetics, and by an extraordinary passion for nurturing and mentoring the next generation of biologists.

An inspiring and courageous innovator, Susan Lindquist has tackled and resolved a remarkable variety of difficult problems, ranging from delineating cellular responses to stress, prion-based inheritance, and the role of protein misfolding in disease to uncovering genetic variation in evolution. Her interdisciplinary vision has empowered her to devise entirely new experimental approaches and create novel conceptual frameworks in several fields.

Susan Lindquist's work began with pioneering studies of the heat-shock response, a homeostatic mechanism to protect cells from protein folding problems during heat exposure and a variety of other stresses. As a graduate student of Matthew Meselson at Harvard in the 1970s, she launched, on her own initiative, an investigation of the heat-shock response, using it as a model to understand eukaryotic gene regulation. She discovered that the heat-shock response, previously only known from *Drosophila* salivary glands, also occurred in tissue culture cells, demonstrating its generality and making it tractable to molecular analysis. She then revealed that the response was governed by a combination of translational and transcriptional mechanisms. Thanks in large part to her work—and complemented by seminal contributions of Pelham, Lis, Morimoto, and Wu—the heat-shock response provides perhaps the most beautiful and complete example of eukaryotic gene regulation documented to date.

After exploiting this system to produce groundbreaking work on eukaryotic gene expression, Susan studied the function of the stress response and of two of its individual proteins, Hsp90 and Hsp104. These investigations, carried out during her 23-year tenure at the University of Chicago, led to completely unexpected results. Using yeast as a model, her laboratory found that Hsp90 was essential for normal growth, while Hsp104 was the single most critical factor for surviving extreme stress. In collaboration with Keith Yamamoto, she established in the early 1990s that Hsp90 was required for the maturation of the steroid hormone receptors and oncogenic tyrosine kinases. Using a combination of genetic and biochemical approaches, she demonstrated that Hsp104 promotes survival after heat stress by disaggregating damaged proteins and restoring them to normal function. To do so, Hsp104 couples its own conformational changes, driven by highly coordinated successive rounds of ATP hydrolysis, to work on bound substrates. The functional analysis of Hsp104 gave rise to another, most remarkable discovery: In collaboration with Chernoff and Liebman, Susan established that Hsp104 regulates the propagation of a mysterious cytoplasmically inherited genetic factor known as [PSI^+]. Taken together with the fact that Hsp104 is a protein remodeling factor, this finding provided a strong genetic argument in support of Reed Wickner's proposal that [PSI^+] is a protein-based genetic element—a prion. Susan established that the protein suspected of being a prion, Sup35, underwent a self-perpetuating change in state that was inherited through the cytoplasmic transmission of protein aggregates from mother cells to their daughters. Remarkably, once the protein has switched states,

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from random coil to amyloid filament, it can rapidly catalyze the conformational conversion of soluble protein. This established the fundamental biochemical mechanism for prion conversion that is not only the basis of human prion disease but is also of broad potential biological significance. Indeed, collaborating with the laboratory of Eric Kandel, Susan established in 2003 a remarkable new concept in learning and memory. They found that a protein known as CPEB, which plays a key role in the maintenance of synapses in metazoan brains, has a prion-like ability to sustain itself in an altered self-perpetuating conformation.

The role of Hsp90 in the maturation of steroid receptors and tryosine kinases placed the protein in a unique position to couple environmental contingency with evolutionary change. In the mid-1990s, Susan made the stunning discovery in *Drosophila* that Hsp90 buffers naturally occurring genetic variation. The presence of Hsp90 allows flies to accumulate a multitude of mutations by keeping them in a silent state. Under stress, the effects of the variation are exposed creating new traits, and the variation can therefore be enriched by selective breeding. Once the mutations have been sufficiently enriched, the phenotypes are retained, even when the environment has returned to normal. Subsequently, the Lindquist laboratory extended this novel concept to *Arabidopsis*, demonstrating that Hsp90's capacity to buffer and release genetic variation is conserved across enormous evolutionary distances. They also showed that drug resistance in pathogenic fungi develops in an Hsp90-dependent mechanism.

In 2001, Susan moved to the Whitehead Institute in Cambridge, serving as its Director until 2004. During more recent years, much of her research focused on understanding the role of molecular chaperones and stress response pathways in neurodegenerative diseases and in cancer. Using yeast as a "living test tube", they recapitulated the protein folding transitions involved in the pathogenic aggregation of alpha-synuclein in Parkinson's disease, huntingtin in Huntington's chorea and PrP in prion disease, and through ingenious genetic screens deciphered key cellular pathways that are impaired by the aggregation process. Reconnecting with her very early work on the heat-shock response, she discovered that heat-shock transcription factor, HSF1, also drives a transcriptional program distinct from heat shock to support the progression of highly malignant human cancers. The insights gained from these studies inform on new therapeutic strategies for neurodegeneration and cancer. Indeed, not only was Susan's advice sought by major pharmaceutical companies, as a biomedical entrepreneur she co-founded FoldRx Pharmaceuticals and founded Yumanity Therapeutics and REVOLUTION Medicines.

It is impossible to imagine a more fulfilled and productive scientific career than that of Susan Lindquist. But Susan had many other qualities that make losing her so much harder. She was an outstanding communicator and science advocate. Her infectious enthusiasm for science always helped to create an atmosphere of open and friendly exchange at conferences. Furthering excellence in science and providing support for young scientists was of great importance to her. She was highly regarded as a passionate mentor and a role model for women in science. She leaves a legacy of students and postdocs who went on to successful careers. Her views of our profession and of its significance for humanity are wonderfully summarized in a statement she made on the occasion of the 50th anniversary of ASCB (http://www.molbiolcell.org/content/21/22/3804.long). I highly recommend reading it, especially to the young.

Susan Lindquist received many prestigious awards and honors, including the President's National Medal of Science—the highest scientific honor bestowed by the United States—as well as the Dickson Prize in Medicine, the Otto-Warburg Medal, the FASEB Excellence in Science Award, the Max Delbrück Medal, the E.B. Wilson Medal, a Vallee Visiting Professorship, the Vanderbilt Prize for Women's Excellence in Science and Mentorship, and the Albany Prize. She was a member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the British Royal Society.

In Susan Lindquist we are losing not only a towering figure of basic biomedical research, but also a wonderful human being. I will never forget her warmhearted friendship, her youthful enthusiasm and her great sense of humor. Susan is survived by her husband, Edward Buckbee, and her two daughters, Alana Buckbee and Nora Buckbee. She will live on in our memories and through her extraordinary achievements.