Susan Lindquist

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Susan Lindquist received her PhD in Biology from Harvard in 1976 and was a postdoctoral fellow of the American Cancer Society. She is a member, and former Director, of the Whitehead Institute for Biomedical Research. She is also a Professor at the Massachusetts Institute of Technology and an investigator in the Howard Hughes Medical Institute.

Lindquist is an expert in protein folding, studying the biological phenomena that influence the different shapes that proteins take. Her groundbreaking work has shown how changes in protein conformation affect processes such as stress tolerance, neurodegenerative disease and heredity, and has highlighted the importance of molecular chaperones, proteins whose function is to assist other proteins in achieving proper folding. Her group has pioneered the use of yeast as a discovery platform for new chemical and genetic therapies for neurological conditions such as Parkinson's and Huntington's diseases. She has used a yeast model that recapitulates many of the cell biological consequences of Parkinson's disease to discover several genes that may underlie an important mechanism of neurodegeneration in that condition.

Previously she was the Albert D. Lasker Professor in the Department of Molecular and Cellular Biology at the University of Chicago. She was elected to the National Academy of Sciences in 1997 and the Institute of Medicine in 2006. Lindquist's honors also include the Dickson Prize in Medicine, the Sigma Xi William Procter Prize for Scientific Achievement, designation by *Scientific American* as one of the top 50 leaders in business, policy, and research for 2006, the 2007 Nevada Medal for Scientific Achievement, and being named to "The Harvard 100: Most Influential Alumni" for 2007 by *02138 Magazine*.

Prion Proteins: Surprising Conformations and Surprising Functions

The protein concentration in the average cell is upwards of 300 mg/ml. This does not make for an ideal protein-folding environment, yet problems in protein folding are deeply rooted in biology. When proteins misfold, they are usually degraded by vigilant cellular quality-control mechanisms. However, some misfolded proteins persist in their altered shapes. In mammalian prion diseases, misfolded forms convert other proteins to the

same deadly forms and are transmitted between organisms, leading to devastating neurodegenerative diseases, such as “mad cow”. In yeast, however, prions are not toxic, but can actually provide mechanisms for protein-based inheritance, molecular memory, and the uncovering of helpful new phenotypes. For example, the yeast prion [PSI+] is formed from an inactive, misfolded translation-termination factor, Sup35. Its altered conformation is passed from mother cells to daughters, acting as a “seed” to perpetuate the prion state. Transmission of misfolded Sup35 results in the heritable suppression of nonsense mutations in specific markers. Thus, [PSI+] uncovers previously hidden genetic variation in a stepwise fashion by turning on the expression of previously silent regions of the genome. It provides a plausible mechanism for surviving fluctuating environments and fueling the pace of evolutionary change. Together with Eric Kandel and Kausik Si, we have also found that a regulatory protein that plays an important role in synaptic plasticity behaves as a prion in yeast. Cytoplasmic polyAdenylation element binding protein, CPEB, maintains synapses by promoting the local translation of mRNAs. We postulate that the self-perpetuating folding of the prion domain acts as a molecular memory: by concentrating and organizing the RNA-binding domain of CPEB the prion form functions cooperatively in translation and its activities are restricted to particular synapses due to its size. Based on the handful of known yeast prions, we predicted sequences that could be responsible for prion-like amyloid folding (prion domains) and identified new candidate yeast prions. Our screen identified 22 new candidate prions, whose protein-folding properties and cellular functions we have characterized using a combination of genetic and biochemical techniques. Several of the candidates are capable of self-perpetuating prion aggregation. Thus yeast prions have provided evidence for the surprising possibility that amyloid protein folds can serve as the basis for memory and inheritance.