

THE
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LECTURE SERIES

SUSAN LINDQUIST, PH.D.

FROM YEAST TO HUMAN STEM CELLS:
A POWERFUL DISCOVERY PLATFORM FOR
COMBATting NEURODEGENERATIVE DISEASES

NOVEMBER 19, 2015

4:00 P.M.

208 LIGHT HALL

THE
Flexner
DISCOVERY
LECTURE SERIES

Upcoming Discovery Lecture:

JOE G. N. "SKIP" GARCIA, M.D.

University of Arizona

Dec. 10, 2015

208 Light Hall / 4:00 P.M.

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FROM YEAST TO HUMAN STEM CELLS: A POWERFUL DISCOVERY PLATFORM FOR COMBATTING NEURODEGENERATIVE DISEASES

Many neurodegenerative diseases (NDs) result from problems in basic protein folding and share the occurrence of complexes of misfolded, aggregated proteins in affected neurons. Parkinson's disease (PD) involves alpha-synuclein (α -syn) and Alzheimer's disease (AD) involves A β and tau. Biological processes maintaining protein homeostasis within cells are highly conserved from yeast to human allowing us to develop models for the pathologies caused by these ND-associated proteins by expressing the human proteins in yeast. This causes yeast to grow more slowly. Yeast offer a well-defined genetic toolbox easily manipulated to identify biochemical processes disrupted by each ND-associated protein. Through genetics, we can discover genes that modify the pathologies caused by each protein. In addition, these yeast can be grown in the presence of thousands of compounds (high throughput screening) to identify compounds alleviating toxicity. Each yeast model exhibits a specific mechanism of cellular toxicity and yields a discovery platform directly relevant to the human disease associated with that protein.

Our screens of α -syn-expressing yeast identified genes and compounds that alleviated toxicity. These findings were validated when the same genes and compounds rescued dopaminergic neurons in other organisms as well as cortical human neurons differentiated from PD patient-derived induced pluripotent stem cells. Our screens of yeast suffering A β -induced toxicity revealed additional genes that are risk factors for AD in humans and compounds that specifically rescue neurons from A β -induced toxicity. Combining these discovery platforms with state-of-the-art chemical genetics screens allowed identification of compounds with high therapeutic potential as well as insight into how these compounds work to alleviate toxicity.



SUSAN LINDQUIST, PH.D.

2014 VANDERBILT PRIZE WINNER

PROFESSOR OF BIOLOGY, MIT

INVESTIGATOR, HHMI

MEMBER, INSTITUTE OF MEDICINE

MEMBER, NATIONAL ACADEMY OF SCIENCES

Susan Lindquist received her PhD in Biology from Harvard University in 1976. She was an American Cancer Society Post-doctoral Fellow at University of Chicago before joining the faculty there in 1977 and becoming the Albert D. Lasker Professor of Medical Sciences in the Department of Molecular Genetics and Cell Biology and a Howard Hughes Medical Institute Investigator. In 2001 she moved to the Whitehead Institute for Biomedical Research in Cambridge, MA, where she was the Director from 2001-2004. She is currently a member of the Whitehead, Professor of Biology at MIT and an HHMI Investigator. Dr. Lindquist works on protein folding in problems as diverse as evolution, malignancy, drug resistance and neurodegenerative disease. Her studies of protein folding have demonstrated that alternative protein conformations and aggregations can have profound and unexpected biological influences, providing insights in fields as wide-ranging as human disease, evolution and biomaterials. She is on the Board of Directors of Johnson & Johnson and co-founded two biotech companies - FoldRx, developing therapies for diseases of protein misfolding and amyloidosis and Yumanity, identifying and developing therapies for neurodegenerative diseases caused by protein misfolding.

Her honors include membership in the National Academy of Sciences, the National Academy of Medicine (IOM) and the Royal Society. She has been awarded the Dickson Prize in Medicine, the Otto-Warburg Prize, the Genetics Society of America Medal, the FASEB Excellence in Science Award, the Max Delbrück Medal, the Mendel Medal, the E.B. Wilson Medal, a Vallee Professorship and the Vanderbilt Prize. In 2009 she was the recipient of the President's National Medal of Science.
