NIH Award from the National Institute on Aging

Principal investigator: Richard I. Morimoto, Biochemistry/Molecular Biology/Cell Biology, Weinberg School of Arts and Sciences

- **Project:** Proteostasis Sensors to Assess the Cellular Protein-Folding Capacity
- **Start Date:** September 30, 2009
- **Total Award Amount:** $1,000,000

**How the results of this project will benefit society:**

The expression of damaged proteins is associated with hundreds of human diseases associated with aging. These include neurodegenerative diseases (Alzheimer’s disease, ALS, Huntington’s disease), diseases of the immune system and metabolism, and cancer. How protein misfolding in one compartment of the cell affects another and variability among tissues represents key questions that have not been resolved. This proposal is to develop a molecular toolbox of folding sensors that provide real-time living cell imaging to quantify the health of the proteome, the complete set of proteins expressed and modified following their expression by the genome. The tools that we develop will be made available to all other researchers upon request upon publication.

**The problem the project is trying to solve:**

The long-term health of all metazoan cells is inextricably linked to protein quality control. This is achieved by proteostasis, a complex network of molecular interactions that determines the health of the proteome. Proteostasis balances protein biosynthesis, folding, translocation, assembly/disassembly, and clearance with the challenges imposed by environmental or physiological stress that result in a flux of misfolded and damaged proteins. An imbalance in homeostasis, if left unattended, can result in severe molecular damage to the cell, dysregulation of key tissues leading to pathology, and susceptibility to diseases of aging. Adaptation and survival requires an ability to sense damaged proteins and to coordinate induction of protective stress response pathways, chaperone, and clearance networks. Despite the abundance and apparent capacity of chaperones and other components of the proteostasis network to restore folding equilibrium, the cell is poorly adapted for chronic proteotoxic stress as occurs when certain aggregation-prone proteins are expressed in metabolic disease, cancer, and neurodegenerative disease. This decline in repair activities that challenges the integrity of the proteome is influenced strongly by genes that control aging thus linking stress biology, metabolism, and protein homeostasis with the health and lifespan of the organism.

**How the project will work:**

This proposal brings together the complementary strengths of two groups, the Dillin laboratory at the Salk Institute and the Morimoto laboratory at Northwestern University to develop and test a new set of molecular tools that will report on the health of the proteome. (The Dillin and Morimoto labs will splits the total award money.) These “proteostasis sensors” are designed to provide real-time assessment of the capabilities of protein folding quality control in each compartment of the cell and to assess the consequences of protein damage, cell stress, aging, and diseases of protein conformation. These tools will be initially developed for use in C. elegans to obtain a rapid test of hypothesis and the ability to assess functional capacities using genetic approaches and then extended to mammalian tissue culture cells and eventually in transgenic mice.

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