THE HARTWELL FOUNDATION

2006 Individual Biomedical Research Award

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Development of an *in vivo* Model of Conformational Disease for High Throughput Genetic and Drug Screens

A biochemical abnormality of alpha-1-Antitrypsin (AT) protein is a commonly inherited genetic defect and the leading cause of liver transplantation in children. The defect involves misfolding of the molecule shortly after its synthesis in the liver. Misfolding prevents the protein from normal secretion into the blood, resulting in abnormal accumulation and numerous secondary metabolic abnormalities, which lead to liver failure. Dr. Silverman proposes to study the genetic cause of this disease by utilizing a unique animal model, the microscopic roundworm, *Caenorhabditis Elegans* (C.elegans). The innovative feature of the this model system is that although the worms contain only 969 cells, most genes and fundamental cellular processes of the worm are similar to humans. The worms reproduce efficiently asexually, thus providing a readily available and uniform test population, without the need to set up crossbreeding. The use of C.elegans is also inexpensive and therefore, ideal for high-throughput screening of small-molecule drugs. Since the worm is transparent, Silverman intends to assay quickly for biological effects in the worms by means of green fluorescent reporter proteins, utilizing state-of-the-art automated image-capture and analysis software. If successful, the results of his research will make it possible to identify rapidly and efficiently the underlying genetic components that contribute to complex human disease processes involving misfolded proteins and organ damage. Potential future applications of Silverman's approach may extend to research on emphysema, Alzheimer, Parkinson, Huntington, ALS and prion diseases.