



## News Release

# UMass Amherst Researchers Win \$1.2 Million EUREKA Award to Study Disease-Related Protein Misfolding

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Contact: [Jan Lathrop](#)  
413/545-0444

**AMHERST, Mass.** - Three University of Massachusetts Amherst scientists have received a four-year, \$1.2 million EUREKA grant from the U.S. National Institutes of Health (NIH) to study folding and misfolding of secretory proteins in the cell's protein factory, the endoplasmic reticulum, where misfolding can lead to diseases such as cystic fibrosis and liver cirrhosis.

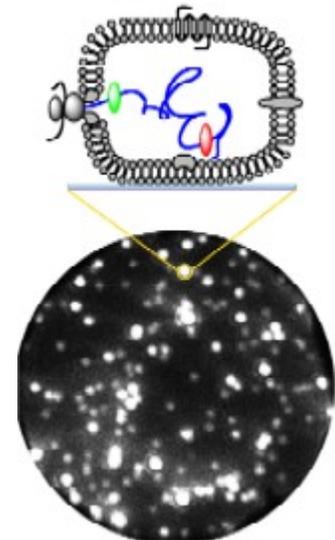
EUREKA stands for Exceptional, Unconventional Research Enabling Knowledge Acceleration. The program was created by NIH's National Institute for General Medical Sciences to support scientists who are testing new ideas in unusual ways or tackling major methodological or technical challenges. Janna Wehrle, who manages this and other protein folding grants at NIH, says, "This project represents an exceptionally bold effort to determine how proteins fold—not in a test tube but in real cells. By examining how proteins take shape in the crowded and dynamic environment where it actually occurs, this work may lead to a better understanding of how the folding process goes awry in diseases like cystic fibrosis and some forms of liver cirrhosis."

Anne Gershenson and her biochemistry and molecular biology colleagues Daniel Hebert and Lila Gierasch begin pilot studies this month using new techniques they adapted to observe how individual secretory proteins fold, not only in real cells but in real time. For this work, they will also use a powerful new super-resolution fluorescence microscope built by UMass Amherst physicist Jennifer Ross and her students. It provides a clear view of individual molecules with far more precision than was possible using traditional light microscopy.

Members of this UMass Amherst research group have been pioneers in studying proteins *in situ*, or in place, rather than in test tubes. Up to now, much valuable protein-folding research has used whole purified proteins that are forced by heating or other treatment to unfold in a test tube. Scientists then study their refolding into the three-dimensional shapes necessary to carry out the cell's tasks. But as Gershenson and Gierasch pointed out in an influential 2009 article in *Nature Chemical Biology*, "we have arrived at the post-reductionist era of biochemistry" when it is no longer enough to study isolated parts of complex networks. Rather, they say scientists must now examine proteins in their native, complicated and highly concentrated environments to truly understand the way they work.

The cell's endoplasmic reticulum is a protein-folding factory, churning out hundreds of secretory proteins to be exported from cells, as well as membrane proteins that reside on the cell surface, Gershenson explains. This factory comes complete with a large number of proteins responsible for quality control. They assist in folding and determine whether and when a protein should be exported to take up its required position. How proteins fold as they are synthesized and how quality control mechanisms affect protein folding are the focus of Gershenson and colleagues' investigation.

The UMass Amherst researchers use a technique called fluorescence resonance energy transfer, or FRET, for light-marking proteins and monitoring their folding. In it, two differently-colored fluorescent dyes that are sensitive to each other, a donor and an acceptor, are introduced into the protein chain as it is made. When these are farther apart in a not-yet-folded protein, the donor emits greener fluorescence. As the protein folds and the two dyes get closer together on the three-dimensional structure, their proximity results in emission of a redder fluorescence. Spectroscopically analyzing the fluorescence allows investigators to precisely track donor-to-acceptor distance changes.



Further, by introducing the FRET donor and acceptor molecules at slightly different parts of the protein chains in each of hundreds of experiments, Gershenson and colleagues will be able to map protein changes associated with folding *in situ*, in real time.

"Once we get the system operating with good fluorescence and we become adept at incorporating the FRET dyes, our method should prove useful to other researchers for studying a wide variety of other proteins which are involved in many other disease processes," she says. "That's the big promise of this approach, and the challenge."

Over the three years of the program, NIH has awarded 56 grants totaling \$67.4 million to support these highly innovative research projects which promise big scientific payoffs. Awards announced today total \$25.2 million to 21 institutions.

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