SOUTHWESTERN NEWS

Media Contact: Ione Echeverria
214-648-3404
ione.echeverria@utsouthwestern.edu

## 'WILD-HARE IDEA' PAYS OFF: UT SOUTHWESTERN RESEARCHERS DEVELOP NEW ASSAY FOR PROTEIN FOLDING

DALLAS – May 10, 2001 – Physiology researchers at UT Southwestern Medical Center at Dallas have developed a new method to assess the solubility and folding of proteins, which could lead to the development of new drugs to treat folding diseases like Alzheimer's, Parkinson's, mad cow and certain forms of cancer. The new assay also could be used in future examinations of the human genome.

The research is a direct result of a program funded by Rolf and Ute Schwarz Haberecht, the "Wild-Hare Idea Program," which provides seed money for especially innovative ideas from UT Southwestern researchers that might otherwise go unfunded and undeveloped.

Last year, Dr. Christian Wigley was one of four researchers awarded a Wild-Hare grant. He proposed to develop a bio-assay to evaluate agents that can potentially block the detrimental protein aggregation that is the hallmark of diseases like Alzheimer's.

For a protein to work properly, it must find its correct three-dimensional shape in a process known as folding. Frequently, researchers find that a protein misfolds, either because of genetic mutation or environmental factors. This often results in a nonfunctional protein that sometimes forms insoluble protein aggregates within a cell. The misfolding of proteins is the molecular basis for many diseases for which treatments have proven elusive.

"The ability to screen for folding and solubility in vivo could be used to develop compounds that either promote proper folding or inhibit the toxic effects of misfolding," said Wigley, a research fellow in physiology who works with Dr. Philip Thomas, associate professor of physiology.

The assay developed by Wigley and his colleagues and described in a recent issue of *Nature Biotechnology* uses the well-known alpha-complementation system of beta-galactosidase. This enzyme can be divided into two inactive fragments which, when reunited, restores enzyme activity, producing a blue-colored product. When fused to the alpha-fragment, the solubility

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properties of a disease-related protein are reflected by beta-galactosidase activity. With such an assay in hand, "we now are positioned to rapidly screen for modulators of folding and solubility," Wigley said.

"Our assay is quite sensitive to changes at the very-low-solubility range," Wigley said. "There is very little background with very-low-solubility proteins; therefore, a small change can be seen in the assay because the signal is integrated over time."

Wigley said this new assay may prove useful in conjunction with existing folding assays because "unlike the green fluorescent protein-folding assay developed earlier, our assay is able to report very slow associative misfolding events, such as aggregation, which are characteristic of several neurodegenerative diseases."

Wigley is hopeful that the assay also may help genetic scientists with a perplexing question: With all the thousands of newly identified protein sequences to study, where do they start?

"They have all of the equipment and all of the people in place," he said. "But which mutation should they go after? Do they express and characterize a thousand different domains individually, or do they just sink en masse into an assay and look for the blue well?"

Other researchers from UT Southwestern included two students, Rhesa Stidham and Nathan Smith. Dr. John Hunt from the Department of Biological Sciences at Columbia University also participated in the research.

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