2008 Ada Doisy Lectures in Biochemistry—Abstracts

2 p.m., Thursday, April 10

"Life on the Edge: The Nature and Origins of Protein Misfolding Diseases"

Christopher M. Dobson
University of Cambridge, Department of Chemistry

Natural proteins are a highly select group of molecules, and their properties have a number of very special characteristics when compared to random sequences of amino acids, one of which is the ability to fold to unique and often highly intricate structures [1]. This characteristic has enabled biological systems to generate a vast range of functions and an astonishing degree of specificity in their chemical processes. Great progress has been made recently in defining the conceptual basis and fundamental principles that underlie the folding of natural proteins. Of particular significance have been approaches that bring together biochemical and biophysical experiments with computer simulations to define the characteristics of the ensembles of protein structures that are populated *in vitro* at different stages of the folding process of individual proteins [2]. In addition, the roles of a wide variety of cellular processes associated with the folding of proteins *in vivo* are being unravelled, leading to an increasingly detailed understanding of the life cycles of proteins from their synthesis and degradation.

Because proteins are involved in every chemical process taking place within living systems, the failure of proteins to fold, or to remain correctly folded, can give rise to serious cellular malfunctions that frequently lead to disease. One particularly important group of such diseases is associated with the aggregation of misfolded proteins into remarkable thread-like structures known as amyloid fibrils [3], and includes disorders ranging from Alzheimer's disease to late-onset diabetes, conditions that are becoming increasingly common in our aging populations. The manner in which the normal soluble forms of peptides and proteins can convert into these pathogenic amyloid structures is being uncovered by a wide variety of *in vitro* experimental studies along with theoretical simulations and bioinformatics studies [4]. As with folding, these studies are increasingly being linked to events occurring *in vivo* using a variety of strategies. Of particular interest are experiments an simulations designed to link the principles of misfolding and aggregation to the effects of such processes in model organisms such as *Drosophila* (the fruit fly) [5]. This talk will draw together some of the ideas that are emerging from recent work in our laboratory including evidence for the extremely narrow boundary between normal and aberrant behavior [6], and how this concept sheds light on the origin, current proliferation and potential means of prevention of many of the diseases associated with misfolding.

1. Dobson, *Nature* 426, 884-890 (2003)
2. Korzhnev et al., *Nature* 430, 586-590 (2004)
3. Knowles et al., *Science* 318, 1900-1903 (2007)
4. Dobson and Chiti, *Annu. Rev. Biochem.* 75, 333-366 (2006)
5. Luheshi et al., *PLoS Biol.* 5, e290 (2007)
6. Tartaglia et al., *Trends Biochem. Soc*. 32, 204-206 (2007)

12 p.m., Friday, April 11

"Novel Enzymes, Rapid Structure Determination, and an On-line Computer Game"

David A. Baker
University of Washington, Department of Biochemistry

I will describe the design of novel enzyme activities from scratch using new computational protein design methods. I will also describe recent advances in protein structure prediction which make possible, in favorable cases, the prediction of unknown structures with near atomic accuracy. Finally, I will describe an on-line protein folding and design game for both research and science education. Please try it out—Instructions for playing the game can be obtained from John Eargle (eargle@uiuc.edu)—and the winner will be recognized during my talk.