LECTURES

PL00

LIFE ON THE EDGE: THE NATURE AND ORIGINS OF PROTEIN MISFOLDING DISEASES

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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 [C.M. Dobson, *Nature* 426, 884-890 (2003)]. 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 [D.M. Korzhnev, X. Salvatella, M. Vendruscolo, A.A. Di Nardo, A.R. Davidson, C.M. Dobson and L.E. Kay, "Low Populated Folding Intermediates of the Fyn SH3 Domain Characterized by Relaxation Dispersion NMR", **Nature 430**, 586-590 (2004)].

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 [T.P. Knowles, A.W. Fitzpatrick, S. Meehan, H.R. Mott, M. Vendruscolo, C.M. Dobson and M.E. Welland, "Role of Intermolecular Forces in Defining Material Properties of Protein Nanofibrils", **Science 318**, 1900-1903 (2007)], 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 [C.M. Dobson and F. Chiti, *Annu. Rev. Biochem.* 75, 333-366 (2006)]. 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) [L. M. Luheshi, G.G. Tartaglia, A.C. Brorsson, A.P. Pawar, I.E. Watson, F. Chiti, M. Vendruscolo, D.A. Lomas, C.M. Dobson and D.C. Crowther, "Systematic In Vivo Analysis of the Intrinsic Determinants of Amyloid-beta Pathogenicity", **PLoS Biol. 5**, e290 (2007)]. 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 behaviour [Tartaglia et al., *Trends Biochem. Soc*. 32, 204-206 (2007)], and how this concept sheds light on the origin, current proliferation and potential means of prevention of many of the diseases associated with misfolding.

PL01

CHEMICAL TOOLS FOR THE STUDY OF COMPLEX BIOLOGICAL SYSTEMS

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This presentation will discuss the design, synthesis and application of new chemical probes for studying complex biological systems. Due to the pivotal role played by of intracellular protein phosphorylation in all aspects of signal transduction, the focus of recent initiatives in the group has been on protein kinases and the phosphoprotein products of kinase-mediated phosphorylation as key targets for probe development.

In the area of kinase sensor development, novel amino acids including chelation-enhanced fluorophores, such as the sulfonamido-substituted 8-hydroxyquinoline, which is featured in the amino acid Sox, will be presented as robust building blocks for the modular assembly of selective and active chemosensors for a wide array of kinases including both Ser/Thr and Tyr kinases. In particular, recent studies on the semisynthesis and evaluation of highly selective probes for the MAP kinase ERK will be highlighted. Novel amino acids, such as DAPA and 4-DMNA, which include the environment-sensitive phthalimide and naphthalimide fluorophores will also be described together with applications in the diagnosis of peptide/protein and phosphorylation-dependent protein/protein interactions. Finally, the synthesis and application of caged phosphoamino acids, such as cpTyr, for examining phosphorylation-mediated cellular functions in living cells in real time will be highlighted.