Present Research

One of the essential characteristics of living systems is the ability of their molecular components to self-assemble into functional structures. Equally important, however, is the way in which the processes leading to this organization are balanced within the cellular environment through the mechanism of homeostasis. My research focuses on proteins, since these are the molecules that enable, regulate and control all the chemical processes on which life depends. In order to function the large majority of proteins need to fold into a specific three-dimensional structure. The wide variety of highly specific structures that results from protein folding, and which serves to bring functional groups into close proximity, has enabled living systems to develop astonishing diversity and selectivity in their underlying chemical processes by using a common set of just twenty building blocks, the amino acids.

Most of my research activity focuses on the prediction of the mechanisms of protein folding and aggregation through a combination of *in vivo*, *in vitro* and *in silico* studies.

I have recently observed a remarkable anti-correlation between the expression levels of human genes *in vivo* and the aggregation rates of the corresponding proteins measured *in vitro* (1). A simple principle lies behind this link that arises from an evolutionary pressure acting to decrease the risk of aggregation in highly crowded cellular compartments. *La raison d'être* for this evolutionary pressure is that failure of proteins to fold correctly can give rise to cellular malfunctions and diseases. It is important to stress that the ability to form aggregates is not only restricted to proteins whose deposition is associated with specific diseases, but represents a generic property of polypeptide chains (2). In fact, the transition of normally soluble proteins to insoluble aggregates does not only imply a loss of biological activity, but results in production of species that are inherently toxic to cells, even when they are not associated with any known diseases. Even though the propensity to form insoluble aggregates varies from one system to another, I was able to predict the kinetics of aggregation using an algorithm that was derived from the analysis of relevant physico-chemical properties of protein sequences (3).

Predictions of aggregation propensities

One of the main causes of incorrect protein folding *in vivo* is cell stress, which may be caused by heat shock, nutrient depletion, or other *stimuli*. Production of inactive proteins not only represents an energetic drain and a metabolic load for the cell but also result in accumulations that can ultimately cause structural strains. Misfolded proteins that escape the *quality-control mechanisms* of the cell often lead to the impairment of relevant biological processes and affect the viability of the organism. Protein aggregation has been associated with more than 30 diseases and in particular amyloid fibrils have been found involved in a number of pathologies including *Alzheimer's,*

Parkinson's, Huntington's, prion disease, and type II diabetes. Alzheimer's disease is the most common of a number of neurodegenerative disorders (including Parkinson's and Huntington's diseases) that are sometimes described as 'protein misfolding' diseases. The hallmark of all these conditions is the accumulation of microscopic thread-like assemblies of proteins, known as amyloid fibrils, into deposits such as the amyloid plaques of *Alzheimer's* disease and the *Lewy bodies* of *Parkinson's* disease.

Predictions of protein toxicity

It has been shown that the aggregation of proteins into these fibrils can be highly toxic to cells and it likely to be the key event in the development of this type of neurodegenerative diseases (4). Although a small number of cases are attributable to a specific genetic mutation, the fundamental reason for the aggregation that results in Alzheimer's disease remains unknown. In the group of Prof C. M. Dobson, and Dr M. Vendruscolo we have carried out experiments *in vitro* to determine the factors that cause the aggregation of proteins into amyloid fibrils. Moreover, I have developed a mathematical description of the effect of each of these factors and from this approach. My equation predicts with remarkable success (80% or better) the rate at which a protein will aggregate under laboratory conditions (Figure 1)(2). In particular, I have found that the propensity to form short fibrils (or *protofibrils*) strongly correlates with toxicity in living organisms (4).

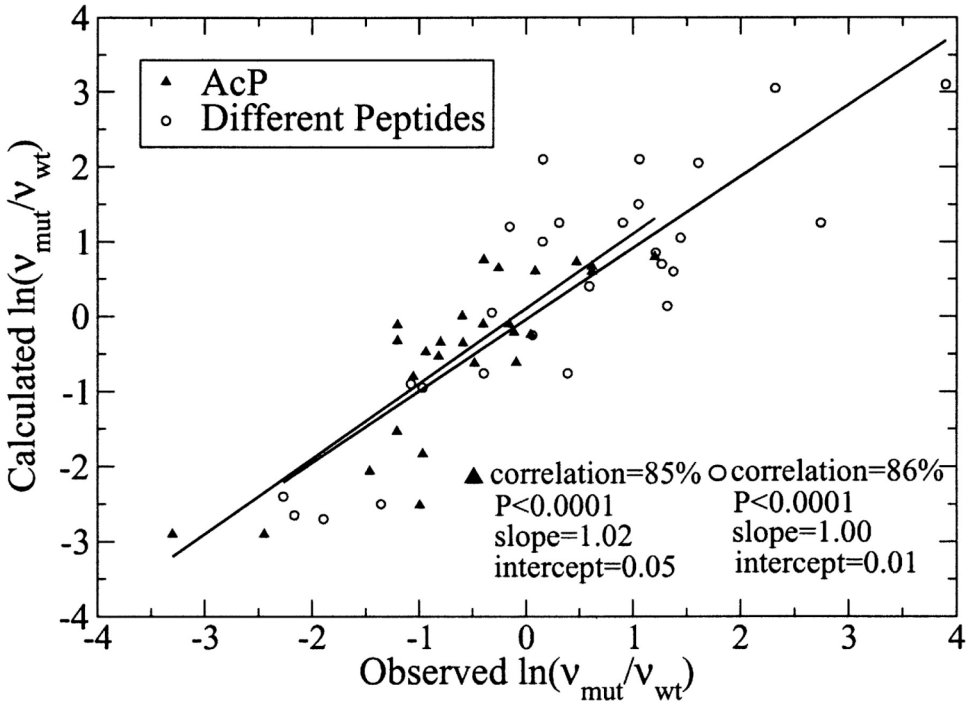

Figure 1. Calculated vs. observed changes in aggregation rate upon mutation: AcP protein (28 triangles) and heterogeneous groups of peptide and protein systems, including islet amyloid polypeptide, prion peptides, alpha -synuclein, amyloid beta-peptides, leucine-rich repeat and some model peptides (27 circles)(2).

References

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4) Luheshi LM, Tartaglia GG, Brorsson AC, Pawar AP, Watson IE, Chiti F, Vendruscolo M, Lomas DA, Dobson CM, Crowther DC Systematic In Vivo Analysis of the Intrinsic Determinants of Amyloid beta Pathogenicity Plos Biology November 2007 I Volume 5 I