Main Lectures

ML–20.01 CRYSTALLOGRAPHY IN BIOTECHNOLOGY. Tom L Blundell, ICRF Unit of Structural Molecular Biology, Department of Crystallography, Birkbeck College, University of London, Malet Street, London WC1E 7HF

Proteins are (1) targets for many drugs and pesticides which are important in modern medicine and agriculture, (2) useful therapeutic agents for a wide range of diseases, (3) important in stereospecific syntheses in the chemical industry and (4) widely used in processing of complex substrates in the food industry. In each improved protein design is an objective, and for this knowledge of the three-dimensional structures is a central prerequisite. X-ray crystallography has provided this information and now plays a central role in biotechnological programmes.

All design processes involving proteins can be described as engineering and design cycles. The protein engineering cycle involves the introduction of amino acid replacements, insertions or deletions on the basis of a known three-dimensional structure. The mutant proteins are expressed and characterised biochemically and structurally, and this new structural information provides the basis of a further cycle in the design process. For herbicide and drug design knowledge of a complex is required and very often the modification is made by chemical methods rather than by genetic engineering. In a similar way vaccine design may be carried out by automated peptide synthesis or by recombinant techniques.

The lecture will describe the application of these design cycles to specific examples:

1. Engineering new proteolytic enzymes for the food industry.
2. The design of antihypertensive agents as inhibitors of renin.
3. The design of chimaeric neurotrophic factors based on the structure of nerve growth factor.
4. The design of agents to decrease amyloidosis by interfering with the binding of serum amyloid P-component to amyloid fibres.

A major theme in the lecture will be learning about design processes from the evolution of three-dimensional structures, both with respect to families of proteins and with respect to natural mutations that lead to disease states. In the latter case the example of porphobilinogen deaminase in acute intermittent porphyria will be discussed.

