

E0079

Total Chemical Synthesis of Proteins for Crystallographic Structure Determination: Current Status, Future Promise. Stephen B.H. Kent and Duhee Bang, The Univ. of Chicago.

Modern methods have made the total chemical synthesis of proteins a practical reality. Here we describe the historical use of chemical synthesis to elucidate the original structures of the HIV-1 Protease and its complexes with substrate-derived inhibitors. We then compare and contrast the synthetic methods used in that work with the modern ligation methods that were invented subsequently: a fifty-fold improvement in yields and ease of synthesis were attained. Using modern chemical protein synthesis methods, hundreds of proteins – correctly folded and biologically active – have been made directly from predicted sequence data. Original crystal structures have been determined by X-ray crystallography and by multidimensional NMR techniques. There has also been a dramatic increase - an order of magnitude - in the size of synthetically accessible protein molecules. The principles underlying the chemical ligation approach for the total synthesis of proteins are described. Using chemistry, virtually any desired modification can be made to the protein molecule. This provides a powerful tool for the systematic dissection of the molecular basis of protein biological function. Current & future challenges & opportunities in the use of total chemical synthesis for protein structure determination will be discussed.