

Preface

Site-specific mutagenesis of DNA, developed some 30 years ago, has proved to be one of the most important advances in biology. By allowing the site-specific replacement of any amino acid in a protein with one of the other nineteen amino acids, it ushered in the new era of “Protein Engineering”. The field of protein engineering has, however, evolved rapidly since then and the last fifteen years have witnessed remarkable advances through the use of new chemical, biochemical and molecular biological tools towards the synthesis and manipulation of proteins. The chapters included in this book reflect the rapid evolution of protein engineering and its many applications in basic research, biotechnology, material sciences and therapy. It is our hope that this book will provide the reader with an introduction to state-of-the-art concepts and methods and will be of use to anyone interested in the study of proteins, in academia as well as in industry.

Beginning with studies of enzyme mechanisms involving hybrid proteins generated by domain swapping (chapter by Goodey and Benkovic), the next two chapters (by Merkel et al. and Imperiali and Vogel Taylor) describe the ligation of chemically or biologically synthesized peptides to generate proteins carrying a variety of post-translational modifications and their use as biological probes. The following chapter (by van Kasteren et al.) reviews novel methods for chemical modification of amino acid side chains of proteins for the generation of mimics of post-translational modifications. The next several chapters cover different strategies towards expansion of the genetic code and the synthesis, *in vivo* and *in vitro*, of proteins carrying a variety of unnatural amino acids. These strategies involve mis-aminoacylated transfer RNAs generated either through chemical synthesis or enzymatic mis-aminoacylation. The unnatural amino acids include those that are photoactivatable or fluorescent, those that carry heavy atoms such as iodine, chemically reactive groups such as keto- or azido- groups, spectroscopic probes, or those that mimic phosphoamino acids. The potential applications of this newly emerging technology towards studies of proteins and the generation of proteins carrying novel chemical, physical and biological properties are virtually unlimited. One of these chapters (the one by Dougherty) focuses on applications of unnatural amino acid mutagenesis

to the study of receptors and channel proteins of the central nervous system. Another chapter (the one by Hecht) includes modification of ribosomal RNA for the synthesis of proteins carrying D-amino acids *in vitro*. Two other chapters (by Hirao et al. and Leconte and Romesberg) discuss the use of new DNA and RNA base pair systems for expansion of the genetic code through expansion of the genetic alphabet. One of these chapters (the one by Leconte and Romesberg) also includes a discussion of directed evolution for the identification of DNA polymerases proficient in the use of unnatural base pairs in DNA synthesis. The final chapter (by Slusky et al.) deals with the important topic of membrane proteins, including a discussion of computational concepts for the design of peptide inhibitors to probe protein-protein interactions in membrane proteins.

The chapters are written by experts who have contributed much to the areas covered. It was a pleasure working with these colleagues and we thank them for their suggestions, their infinite patience and most importantly for their contributions to this book. We also thank Prof. Hans J. Gross and Ursula Gramm, Life Science Editor at Springer-Verlag, for their continuous support throughout the development of this project.

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