PREFACE

The continuous improvement of human health and quality of life can be linked directly to the discovery, development, manufacture, and applications of pharmaceutical agents. Although many drugs for various human diseases are available, there are still numerous unmet medical needs, providing plenty of opportunities to researchers in the pharmaceutical and biotechnology industries. Drug discovery is a high-risk and potentially high-reward endeavor, costing approximately $1 billion in recent years for a new drug to reach the marketplace. Enzymes and their multiple applications play a critical role, both in vitro and in vivo, in the discovery and development process for most new therapeutic agents. To assist researchers in taking advantage of practical enzyme tools and strategies, one of the current editors coordinated the publication of a previous enzyme-based drug discovery book: *Enzyme Technologies for Pharmaceutical and Biotechnological Applications* (HA Kirst, WK Yeh, and MJ Zmjewski, eds., Marcel Dekker, New York, 2001). With respect to the field of enzymes for drug discovery, there have been significant and exciting advances in the first decade of the twenty-first century, and the current editors are pleased to produce the first in a series of three volumes on Chemical Biology of Enzymes for Biotechnology and Pharmaceutical Applications.

The three editors have a combined pharmaceutical discovery experience of over 60 years. Through several years of a highly collaborative effort, the editors anticipate providing the three unique enzyme-focused books soon: Volume I, *Enzyme Technologies: Metagenomics, Evolution, Biocatalysis, and Biosynthesis*; Volume II, *Enzyme Technologies in Drug Discovery*; and Volume III, *Design of Enzyme Inhibitors for Therapeutics*. The book chapters in each Enzyme Technologies volume, contributed by highly experienced biotechnology and pharmaceutical scientists, present many key enzyme areas that are critical for drug discovery,

development, and production. Thus, for all potential and practicing researchers, from beginners to experts, the three enzyme-based volumes are unique and informative for both training and improving enzyme skills and strategies for drug discovery, development, and manufacture.

The first volume consists of three parts: A, New Approaches to Finding and Modifying Enzymes; B, Biocatalytic Applications; and C, Biosynthetic Applications. In Part A, Moe, McMahon, and Thomas describe functional metagenomics as a technique for the discovery of novel enzymes and natural products in Chapter 1. The chapter focuses on the emerging field of metagenomics and applications for identification of novel enzymes and natural products from a full DNA content of soil-dwelling microbes. Next, in Chapter 2, Vick and Schmidt-Dannert describe directed enzyme and pathway evolution. The authors present the practical applications of directed evolution to enzymes and pathways, discuss the tolerance of enzymes for multiple mutations and the potential benefits of neutral drift and "adaptive evolution" and describe in vitro evolution of one or more metabolic functions in assembled pathways, allowing the synthesis of new isoprenoid or acetate-derived natural products. In Chapter 3, Fourage, Sonet, and colleagues discuss combining natural biodiversity and molecular-directed evolution to develop new industrial biocatalysts and drugs. The authors explore approaches to the discovery and design of biocatalysts based on the combined use of biodiversity screening and molecular-directed evolution, and the impact of these approaches in drug development. Part A is completed with Chapter 4 by Fox and Giver on the principles of enzyme optimization for the rapid creation of industrial biocatalysts. The authors discuss the critical interplay of three orthogonal aspects for efficient enzyme optimization: the fitness function, diversity generation, and the search algorithm.

In Part B, biocatalytic applications can be considered "green chemistry" for very significant economical and environmental benefits in developing and producing key pharmaceutical ingredients. Chapter 5, by Goswami, on enzyme catalysis in the synthesis of active pharmaceutical ingredients, based on the high selectivity of enzymatic transformations, provides an extensive review of specific applications of different reactions in producing active pharmaceutical ingredients and potential benefits with associated issues. Chapter 6, by Rozzell and Lalonde, deals with enzymatic processes for the production of pharmaceutical intermediates. Examples are given of ketoreductase-based methods for the production of key precursors of two blockbuster drugs (atorvastatin, trade name Lipitor, Pfizer; and montelukast, trade name Singulair, Merck), providing higher stereochemical purity of the final product and dramatic reductions in solvent use and waste. Chapter 7, by Faber, Glueck, Seisser, and Kroutil, covers novel developments employing redox enzymes. The authors provide an overview of recent developments employing enzymes in organic synthesis and focus on dehydrogenases for the reduction of sterically demanding ketones. Also covered are cloned enoate reductases from the "old yellow enzyme family" as popular catalysts for asymmetric reduction of activated alkenes.

Part C deals with applications involving the modification of enzymes and pathways for producing novel pharmaceutical intermediates and products as well as for improving yields of natural and modified products. Chapter 8, by DeSieno, Denard, and Zhao, provides an extensive overview of drug discovery and development by combinatorial biosynthesis. The chapter highlights some past accomplishments, exemplified by major efforts in polyketide synthases and nonribosomal peptide synthases, as well as recent advances in combinatorial biosynthesis, including new tools for manipulating biosynthetic pathways and an expanding list of heterologous hosts for the production of improved drugs. Chapter 9, by Baltz, Nguyen, and Alexander describes the reprogramming of daptomycin and A54145 biosynthesis to produce novel lipopeptide antibiotics. The chapter is an extensive review on applying combinatorial biosynthesis among multiple compatible hosts for generating many new derivatives of daptomycin and A54145, and some that have improved properties relative to daptomycin and A54145. Chapter 10, the final chapter, by Zhao and Liu covers pathway and enzyme engineering and applications for glycodiversification. The authors report that numerous promiscuous sugar biosynthetic enzymes and their corresponding glycosyltransferases toward alternative substrates have facilitated efforts to create novel chemical entities with altered sugar structures via pathway and enzyme engineering and thus highlight the great potential of glycodiversification as an effective strategy for development of new therapeutic agents in drug discovery.

The editors graciously acknowledge outstanding contributions by two scientific consultants to the first volume of the Enzyme Technologies series. Herb Kirst and Milt Zmijewski, co-editors of the earlier *Enzyme Technologies* book, were extremely helpful in identifying and recommending the most appropriate enzyme topics and authors for inclusion in this volume. Also, Dr. Zmijewski was involved extensively in reviewing the entire manuscript. Without their significant assistance, the content of the volume would be much less satisfactory and timely. The editors are thankful to all the authors for close and in some cases time-consuming collaboration in multiple reviews toward producing the highest-quality chapter manuscripts possible with consistent formats. The editors are pleased by the agreement, suggestions, and encouragement from the publishers to produce a truly unique and potentially highly useful Enzyme Technologies series to benefit current and future researchers for drug discovery and development.

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