Book Reviews

Enzyme Technologies for Pharmaceutical and Biotechnological Applications. Edited by Herbert A. Kirst, Wu-Kuang Yeh, and Milton J. Zmijewski, Jr. (Eli Lilly and Company). Marcel Dekker, Inc., New York, NY. 2001. xv + 611 pp. 15 × 22.5 cm. $195.00. ISBN 0-8247-0549-1.

The publisher advertises *Enzyme Technologies for Pharmaceutical and Biotechnological Applications* with claims that it is a "state-of-the-art reference" that "provides a comprehensive review of enzymatic functions in human and animal health−covering basic principles and applications in antibiotic biosynthesis, biocatalysis, and screening and assay optimization, as well as new and emerging technologies in the biotechnological industries". Although the editors are quite well-known and respected, my first thoughts were that the publisher's claims were likely to be rather exaggerated, to say the least. It did not take more than a few minutes of browsing, however, before I was marking pages and noting references. Indeed, after a deeper review of its contents, my opinion is that *Enzyme Technologies for Pharmaceutical and Biotechnological Applications* actually lives up to the publisher's bold claims.

There are more than fifty contributing authors to this volume. Although an overwhelming number of these authors hail directly from the scientific staff of Eli Lilly & Company, the breadth of topics, methods, and emerging technologies presented in the text are wide-ranging and complete. In fact, the book could be viewed as a testament to the company's devotion to a diverse biotechnological research effort.

Enzyme Technologies for Pharmaceutical and Biotechnological Applications is divided into four major sections, the first titled "Biosynthesis". This section includes five chapters, including γ-(L-α-Aminoadipyl)-L-Cysteinyl-D-Valine Synthetase as a Model Tripeptide Synthetase; Metabolic Engineering for Cephalosporin C Yield Improvement and Production of Intermediates; Bioconversion of Penicillins to Cephalosporins; Direct Fermentative Production of Acyltylosins by Genetically Engineered Strains of *Streptomyces fradiae*; and Engineering *Streptomyces avermitilis* for the Production of Novel Avermectins: Mutant Design and Titer Improvement. The second section is titled "Biocatalysis", with four chapters, including Biocatalytic Syntheses of Chiral Intermediates for Antihypertensive Drugs; Cloning, Structure, and Activity of Ketone Reductases from Baker's Yeast; Cross-Linked Enzyme Crystals: Biocatalysts for the Organic Chemist; and Enzymatic Deacylation of Echinocandins and Related Antifungal Agents. The third section, "Screening/Optimization" is composed of seven chapters, including Roles of Enzymes in Antibacterial Drug Discovery; Penicillin-Binding Proteins as Antimicrobial Targets: Expression, Purification, and Assay Technologies; Development of a High-Throughput Screen for *Streptococcus pneumoniae* UDP-*N*-Acetylmuramoyl-Alanine: D-Glutamate Ligase (MurD) for the Identification of MurD Inhibitors; Purification and Assay Development for Human Rhinovirus Proteases; Screening for Parasiticides Using Recombinant Microorganisms; Screening for Inhibitors of Lipid Metabolism; and Design and Development of a Selective Assay System for the Phospholipase A2 Superfamily. The fourth and final section, "Emerging Technologies", includes the following eight chapters: Understanding and Exploiting Bacterial Polyketide Synthases; Polyketide Synthases: Analysis and Use in Synthesis; Enzymatic Synthesis of Fungal *N*-Methylated Cyclopeptides and Depsipeptides; New Strategies for Target Identification, Validation, and Use of Enzymes in High-Throughput Screening; Use of Genomics for Enzyme-Based Drug Discovery; Assigning Precise Function to Genes; Redesigning Binding and Catalytic Specificities of Enzymes; and Proteomics: Chromatographic Fractionation Prior to Two-Dimensional Polyacrylamide Gel Electrophoresis for Enrichment of Low-Abundance Proteins to Facilitate Identification by Mass Spectrometric Methods.

Each chapter is well referenced, and *Enzyme Technologies for Pharmaceutical and Biotechnological Applications* also includes a thorough and comprehensive index. The editors have done an excellent job of compiling 24 diverse chapters for industrial and research scientists with interests in adopting and maximizing enzyme technologies for pharmaceutical discovery, development, and manufacturing. In addition, the volume is a welcome addition to the graduate student reading list and is useful for the preparation of undergraduate class notes.

Like a majority of the scientific references marketed today, *Enzyme Technologies for Pharmaceutical and Biotechnological Applications* is not inexpensive, but prospective purchasers can take heart in the knowledge that this is a text that is likely to become a well-worn reference, rather than a bookshelf showpiece.

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Natural Compounds in Cancer Therapy: Promising Nontoxic Antitumor Agents from Plants and Other Natural Sources. John Boik (University of Texas). Oregon Medical Press, Princeton, MN. 2001. viii + 521 pp. 21.5 × 27.5 cm. $32.00. ISBN 0-9648280-1-4.

The noted cancer pharmacologist and physician Dr. Michael Kastan of St. Jude Children's Hospital in Memphis is often quoted as saying, "Cancerous cells develop and grow under conditions so unpleasant that any self-respecting normal cell would commit suicide [undergo apoptosis]." Dr. Kastan's argument, increasingly embraced by others involved in anticancer drug development, is that we should be identifying compounds that target the survival factors that cancerous cells adopt to grow under hypoxia, acidic pH, and glycolytic metabolism. In John Boik's book he refers to these adaptive properties as "do not die" signals.

Boik, known previously for his book "*Cancer and Natural Medicine*", makes a persuasive argument in his new book that 38 known natural products (some herbal extracts and others as their isolated active principles) not only have the ability to target these survival factors but can do so with a greater therapeutic index than most cytotoxic agents currently employed in cancer chemotherapy. For example, modern cancer chemotherapy often employs combinations of three, four, and five cytotoxic and/or growth modifying agents. These combinations are chosen to hit multiple targets to maximize tumor cell kill and minimize the emergence of resistance to any one class of agents. However, the number of drugs employed in these combinations is invariably limited by additive and/or cumulative adverse effects on host tissues (e.g., myelosuppression). With his argument and solid data to support his hypothesis, Boik proposes that combinations of 15 to 18 of these natural products (including flavonoids, curcumin, melatonin, vitamins E and C) might serve to retard or kill a variety of neoplasms before approaching this dose-limiting host toxicity threshold.

The author spends the majority of the first 12 chapters describing the tremendous progress made in understanding the molecular and cell biology of cancer and the specific defects peculiar to individual tumor types. While these chapters seem to be written primarily for the advanced lay reader, I was taken on several occasions with how Boik caught some key references that have even escaped my attention as a cancer pharmacologist. Hence, the two introductory parts of the book will be well-received by a large majority of readers. Boik then does an admirable job in Chapters 13 to 22 of exhaustively reviewing the in vitro, preclinical, and clinical data on these 38 natural agents and their effects on cell growth, transcription factors, apoptotic mediators, and determinants of tumor invasion and metastasis. Unlike many "natural medicine" books I have seen, Boik is extremely careful in differentiating between the validity and limits of extrapolating in vitro and animal study results. In fact, the strength of this book as a research tool is derived from how Boik has taken a methodical approach (using some models employed by NCI's Developmental Therapeutics Program) to setting the stage for dosing in potential clinical studies using predictive computer modeling for parameters such as oral bioavailability and oral lowest-observable-adverse-effects-level
(LOAEL) in scaling results obtained from published rodent studies. The appendices detailing the rationale and methodology for these calculations should be required reading for anyone involved in experimental chemotherapy, regardless of the source of their compound of interest.

There are only minor shortcomings to the book. For example, I would not have chosen the subtitle to refer to these promising new natural products as "nontoxic" since toxicity is relative to a compound's therapeutic index. Chemical structures are also compiled in a separate appendix rather than shown in the area of discussion. And quite obviously, Boik could have expanded his discussion of natural products currently employed as cancer chemotherapeutics because these represent the shoulders upon which his hypotheses stand. Finally, while doing an admirable job in Chapter 23 of discussing the potential role and controversy of using conventional chemotherapy and radiotherapy with natural compounds (primarily antioxidants possessing other growth-modifying effects), Boik may have underestimated the potential for antagonism of known chemotherapeutic regimens by the addition of any of the 38 compounds he describes. Indeed, it is provocative that high doses of vitamin E synergize with the antitumor action of doxorubicin and 5-fluorouracil in human colon carcinoma xenografts of SCID mice. [Chinery, R.; Brockman, J. A.; Peeler, M. O.; Shyr, Y.; Beauchamp, R. D.; Coffey, R. J. *Nature* (*Med*.) **1997**, *3*, 1233−1241]. In his defense, the combination of "natural" and conventional chemotherapy remains controversial among holistic and allopathic physicians alike. Even the nation's most respected integrative oncology practitioners such as Jeremy Geffen, M.D. and Dan Labriola, N.D. feel that it is premature to combine antioxidants with conventional chemotherapy until further work is done. Nonetheless, Boik provides us with substantial intellectual fodder for these future studies.

Most importantly, Boik points out that there is little economic incentive for the intense study of these agents when compared with the development of patentable, prescription chemotherapeutics. In his informative and provocative book, Boik clearly indicates that it is only through the efforts of dedicated scientists supported by NIH funding (from NCCAM and NCI) and private foundations that the most important work can be done to maximize the utility of low-toxicity natural products as combination agents and adjuncts to cancer chemotherapy.

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Medicinal Chemistry into the Millennium. Edited by W. M. Campbell and I. S. Blagbrough (University of Bath, U.K.). Royal Society of Chemistry, Cambridge, U.K. 2001. x + 397 pp. 15 × 23 cm. £69.50. ISBN 0-85404-769-7.

This volume contains essays representing presentations made at the European Federation of Medicinal Chemistry Symposium held in Edinburgh on September 6−11, 1998. The chapters are organized into 10 major topic areas divided into 30 essays: new technologies in drug discovery, ion channels, glycine antagonists, seven-transmembranal receptors, growth factors, intracellular signaling, protease inhibition, glycochemistry and glycobiology, nitric oxide synthase inhibition, and predicting drug metabolism and pharmacokinetics. As such, the book is not a comprehensive treatment of contemporary medicinal chemistry, as one might have thought from the title, but does however treat, on the whole successfully, the recent state of the art on a variety of actively pursued topics. The print and the drawings are a bit small but are easily readable, the plastic cover is durable, and the paper is adequate for the purpose. The chapters are authored by well-known scientists active in the fields being discussed. Most of the authors have made a commendable effort to treat their topics in the context of the state of the art without overemphasizing their own contributions, so these chapters will likely remain timely for a somewhat longer period than the usual

collection of essays coming out of a meeting. This reviewer found much interesting detail present in these essays, for it is not possible to be abreast with all the literature in our ever-expanding field. This book can be recommended in particular for those wishing to get up to speed on contemporary topic areas involving literature that they do not ordinarily read or for those who wish to get a feeling for the views of opinion leaders on these topics. The references include citations extending mostly into 1997 with a sprinkling into 1998, but the book itself lacks an index. The price of the book will make it more suitable for libraries than for individuals to possess.

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