Book Reviews

Nucleic Acid Targeted Drug Design. Edited by C. L. Propst (Northwestern University) and Thomas J. Perun (Abbott Laboratories). Marcel Dekker: New York. 1992. xvi + 644 pp. $165.00. ISBN 0-8247-8662-9.

As the editors note in the preface, their earlier volume on *Computer-Aided Drug Design*, published in 1989, covered only protein targets, as they deemed the technology for design of drugs using nucleic acids as targets to be too immature. However, the rapid pace of developments in the field justified publishing the volume under review in 1992. At the time of this review two years later, the rapidly moving field is the genesis of probably the biggest disappointment in this otherwise valuable volume: so much has happened since the chapters were written apparently in late 1990 and early 1991. The chapters in the current volume will nevertheless provide a reasonable underpinning for researchers who are just entering the field or for those who need to assess the research.

The volume has been organized into Methods and Applications sections, although the break is not clean. The editors do a good job in the first chapter to introduce the general subject and delimit the scope of the book. The theme of the volume is to present the pertinent methodologies and current state of knowledge in the use of nucleic acid structures as the basis for design of ligands as pharmaceutical agents. In this regard, it is commendable that, where appropriate, most authors couched their chapters in the context of the molecular biological events entailing the nucleic acids, rather than considering the problem as one of simply molecular recognition.

Methods of three-dimensional structure determination, i.e., X-ray crystallography and NMR, are discussed by A. H.-J. Wang and H. Robinson in Chapter 2. The basis of using computational methods and computer graphics for modeling DNA–ligand interactions are presented by S. N. Rao in Chapter 3, but this particular topic shows up in some of the applications chapters as well as Chapter 5, where A. J. Hopfinger, M. G. Cardozo, and Y. Kawakami describe the construction of QSARs using ligand–DNA modeling. Techniques for discerning sequence specificity in ligand binding to DNA are described by J. C. Dabrowiak, A. A. Stankus, and J. Goodisman in Chapter 4. As a model of the specificity that can be achieved, sequence-specific DNA recognition by proteins and a brief overview of DNA metabolism are given in Chapter 6 by T. Kodadek.

Chapters covering applications emphasize agents which have demonstrated groove binding, intercalation, alkylation, or cleavage of DNA. Generally the rationale—DNA structure-based—in selecting and modifying drugs to enhance specificity and potency is given. M. L. Kopka and T. A. Larsen discuss netropsins and lexitropsins (Chapter 7); W. A. Remers, M. D. Barkley, and L. H. Hurley discuss DNA adducts of tomaymycin (Chapter 8); L. A. Mitscher and L. L. Shen discuss a quinolone–DNA binding model for inhibition of DNA gyrase (Chapter 9); P. C. Dedon and I. H. Goldberg discuss neocarzinostatin and other endiynes, such as calicheamycin, as DNA-cleaving agents (Chapter 10); and M. Agbandje and R. McKenna describe applicable methods and knowledge status for several DNA-intercalating drugs (Chapter 11). The only chapter devoted to RNA as a target is Chapter 12, where J. O. Deshler and J. J. Rossi describe ribozymes and the rationale for their design to catalytically cleave a target RNA. Single-stranded RNA can also be a target for antisense oligonucleotides, as related by N. Bischofberger and R. G. Shea in Chapter 13. They also describe targeting DNA duplexes with oligonucleotides to form triple-stranded helices. Bischofberger and Shea also briefly describe the development of oligonucleotide aptamers in "irrational drug design"; large random-sequence pools of oligonucleotides are screened to see which bind to any selected target, which could be a nucleic acid, a protein, or something else; those which bind are amplified, identified, and subjected to further study.

This volume reasonably reflects where the major efforts have been expended in targeting nucleic acids for drug design. However, in that, it may have failed to provide a vision of where the field could go. The major emphasis here is on targeting double-stranded DNA. Designing drugs that bind to other natural DNA structures, such as telomeres, is ignored. There is no mention of developing small molecule ligands for RNA. While some already exist, e.g., the aminoglycosides, there is much potential for further development. Part of the reason for the slight is undoubtedly the sparse information available on RNA structures. However, an explosion of information about RNA three-dimensional structures is just starting. All evidence indicates that there will be a much greater variety of RNA than DNA structure types to target.

Readers sensitive to typographical errors will go berserk with this volume. There is on average more than one per page, with references being particularly vulnerable. Some grammatical errors also occur. Editorial work should also have caught items such as the statement in Chapter 4 that a more detailed discussion of the antitumor agent CC-1065 would be found in Chapter 8, where it was not to be found. Reproduction of some of the figures in the volume suffers. While eight figures are reproduced in color, numerous others were obviously reproduced in black and white from color graphics. Some of these are acceptable, while others range from marginally useful to completely worthless.

In spite of the negative comments made above, on balance, the quality of the authors' scholarship and the editors' perspective provided in Chapter 1 make this volume a worthwhile addition to one's library. I am sure it will not gather dust here but will be sought by students and postdocs.

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