teresting research area, and some fields related to telomerase inhibition are not covered in this book. There is a certain imbalance in the dedication of seven chapters to hTERT and only two each to hTR and other telomeric components. Another shortcoming is the near total neglect of quadruplex ligands, which were initially designed as indirect telomerase inhibitors. However, recent studies have demonstrated that these compounds are more likely to interfere with telomeric functions and induce uncapping than act as true telomerase inhibitors. Therefore, such an absence is not detrimental. Finally, the index, despite being only three pages long, is sufficiently inclusive to be helpful.

Overall this book will be a useful resource for researchers performing telomerase-related experiments. Anticancer approaches directed at telomerase inhibition are varied, and the choice of a strategy depends on the goal. This book features a compendium of methods and provides the researcher with a set of practical tools, as all protocols are described in a very clear and accurate fashion. We would have appreciated additional figures to outline complex experimental procedures. As a final warning, one should keep in mind that this book is part of a "Methods" series and does not claim to be an introduction to the field for those having an academic interest in telomerase. Only two pages—in the first chapter—are actually dedicated to a description of the enzyme and its function. Excellent reviews or special issues can be found in the literature that do serve this purpose. This book constitutes an excellent choice *only* if the reader plans to perform telomerase inhibition-related experiments.

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Computational and Structural Approaches to Drug Discovery: Ligand–Protein Interactions

Edited by *Robert M. Stroud* and *Janet Finer-Moore*.

RSC Press, Cambridge 2008. xviii + 382 pp., hardcover £89.00.—ISBN 978-0-85404-365-1

Based on the substantial evolution of computational methods (bioinformatics and cheminformatics) as well as methods of structure determination (crystallography and NMR spectroscopy) during the last few decades, there has been a massive increase in the number of publications applying such methods to drug discovery. Moreover, various combinations of these methods have quickly gone beyond the level of academic exercise and have been transformed into innovative drug-producing techniques with great relevance and industrial application. The topics covered in this book comprise a historical perspective of how these methods have been developed, an assessment of their successes and failures, and prospects as to how these methods can be improved.

The editors have assembled a highly interesting team of experts from both academia and industry including many scientists who have significantly influenced and shaped the fields of research on which they report and comment in this book. In Section One, the editors themselves, together with J. Blaney, give an overview of the topic, describing "the promise and the problem". Instead of indulging themselves in praising the methods described, they assess both success and failures, and thus establish a level of open and impartial discussion that reflects the high quality and fundamental credibility of the book. Consequently, the focus on the current limitations of a given method and how they can be overcome is a strong aspect of this book. This initial overview in the first section is complemented by a retrospective given by H. Kubinyi, a medicinal chemist with decades of experience in industrial drug discovery. "The changing landscape in drug discovery" describes how new strategies and techniques have evolved and how the bottlenecks and problems have shifted accordingly. Although high initial enthusiasm for the potential of novel methods has quite often been tempered, their practical value to facilitate drug discovery becomes clear upon posing the question: "Where would we stand without them?"

Structure-based design methods are described and illustrated, as well as critically evaluated in Section Two. The successful design of purine nucleoside phosphorylase (PNP) inhibitors is presented by Y. Zhang and S. E. Ealick to exemplify the usefulness of high-resolution crystal structures in drug design. In the following chapter, A. M. Davis, S. J. Teague, and G. J. Kleywegt describe applications and limitations of X-ray crystallographic data, such as hidden uncertainties when deriving and depositing an atomic model from the electron density. This chapter is especially valuable for modelers without personal experience in crystallography and a warning for all who use crystal structure coordinates uncritically as the "ultimate truth". A fundamental problem, mentioned above, is presented in detail (Chapter 5) by D. Hamelberg and J. A. McCammon, in their discussion about bound waters: "Do they leave or stay?" They report on the usefulness of computational methods for predicting the positions of bound waters in protein cavities and discuss the impact of such bound waters on the free energy of ligand binding. More importantly, they relate this insight to strategies that try to harvest these effects in drug discovery. In Chapter 6, M. L. Verdonk and W. T. M. Mooij explicate how the steadily increasing amount of crystallographic data on protein–ligand complexes has lead to the development of knowledge-based techniques by deriving statistical preferences for the interaction between atoms or functional groups. These methods have gained importance in structure-based design by predicting "binding hotspots" or as scoring functions such as DrugScore, PMF, and ASP. The authors critically assess that these may not have been proven superior to empirical or force-field-based scoring functions in general, but they provide great potential for the implementation of tailor-made scoring functions for particular targets or target families. Con-

cluding the section of structure-based design, C. A. Schiffer discusses the identification of resilient macromolecules and how this can lead to inhibitors that are effectively robust against drug resistance. Using HIV-1 protease as an example, the author demonstrates that understanding the molecular recognition of diverse substrates can allow the design of such robust inhibitors. Thus, although an inhibitor exerts a selective pressure on a rapidly evolving target, mutations that would decrease inhibitor affinity are, at the same time, necessarily detrimental for substrate recognition.

Section Three addresses docking algorithms and their impact on drug discovery. G. L. Warren, C. E. Peishoff, and M. S. Head give an overview on the recent evaluations of docking algorithms and scoring functions. While the prediction of binding modes is rather successful with the use of modern docking algorithms, the prediction of binding affinities, and hence the ability to rank a series of compounds, suffers from a lack of suitable scoring functions. How can docking be used, especially during the early stages of the drug-discovery process? In Chapter 9, D. T. Moustakas addresses the topic of drug target selection and characterization, lead discovery, and lead optimization. Chapters 10 and 11 deal with a most challenging, yet promising topic: the flexibility of protein side chains in docking procedures. L. A. Kuhn presents in Chapter 10 various methods used for side chain flexibility modeling in docking and recent insight gained from analyzing conformational transitions between ligand-free and -bound crystal structures. A variety of approaches for handling small-scale induced fits, modest conformational changes, and main chain flexibility are illustrated, and their putative contribution to a more realistic docking scenario is evaluated. The author emphasizes that learning from nature about the types of motions that are common in proteins upon ligand binding will facilitate better docking protocols and algorithms. Analyzing the application of rotamer libraries to represent small- and medium-scale protein flexibility, in Chapter 11, A. C. Anderson outlines a number of successful studies including the discovery of MMP-1 inhibitors, thymidylate synthase inhibitors, protein tyrosine phosphatase 1B inhibitors, and more.

Section Four is all about library screening techniques. The issue to design chemically diverse libraries containing drug-like compounds is a key aspect of this section. The use of computational models to predict this drug-likeness is the topic of D. E. Clark in Chapter 12. Methods that address the prediction of physicochemical properties, such as solubility and lipophilicity, as well as the prediction of ADMET behavior such as oral bioavailability, metabolism (e.g. cytochrome P450 activity), and propensity to cause adverse effects (e.g. hERG channel blockade) can provide an "enrichment" of the desired properties. High-throughput screens are widely used these days in industrial drug discovery (Chapter 13). However, in addition to useful hits, "nuisance compounds" are also often found which exhibit unusual properties that can lead to a waste of time and money in the follow-up stages. B. K. Shoichet, B. Y. Feng, and K. E. D. Coan report their discovery of the very interesting phenomenon of inhibition by aggregation and how counter-screens can prevent the loss of significant investments into the "development" of screening artifacts. Iterative and hierarchical concepts of virtual ligand screening (VLS) have become increasingly popular in recent years. In Chapter 14, A. E. Beuscher and A. J. Olson give a short introduction to these methods and illustrate the application of diversity-based VLS using their program AutoDock. However, not only the steadily growing number of AutoDock users, but everybody interested in the field of virtual screening will benefit from the information and recommendations provided. In Chapter 15, M. Kato, S. Braun-Sand, and A. Warshel characterize the challenges and progress in calculating free energies of binding from first principles. Although a great improvement in the calculation of electrostatic contributions has been achieved, a reasonable description of the relevant binding entropy and the effect of water penetration still pose considerable challenges.

Fragment-based approaches that are situated at the interface between high-throughput screens and iterative structure-based design are discussed in Section Five. "How should a fragment library be designed and what constitutes a hit," are important questions answered by A. Ciulli, T. L. Blundell, and C. Abell (Chapter 16). They describe how fragments can be extended, linked together, or chemically self-assembled from dynamic combinatorial libraries. Furthermore, the authors present a short overview about biophysical techniques such as X-ray crystallography, NMR spectroscopy, mass spectrometry, thermal shift methods, ITC, SPR, and their applicability to ligand and particularly fragment-based screening. By comparison, a rather new strategy for structure-based drug design is disulfide tethering, which was first reported in 2000. In Chapter 17, J. A. Hardy distinguishes between native cysteine tethering, which targets a cysteine residue that occurs naturally in a specific binding or active site, and tethering of cysteines artificially created by protein engineering. Various modifications of this concept have been developed, such as cooperative, extended, or breakaway tethering. The author evaluates these as well as the role tethering can play in identifying allosteric sites as a validation tool for HTS hits or in structure determination. Undoubtedly, transforming a covalent hit into a reversibly binding noncovalent lead is a challenge of the tethering approach. Nevertheless, tethering has good potential to facilitate the drug-discovery process. Finally, Chapter 19 is dedicated to one of the major target families of drug discovery: protein kinases. The multitude of structural work performed on ligand–kinase interactions and the insight gained from it are summarized by C. Zhang and S.-H. Kim. The particularly important issue of inhibitor specificity against single targets or regions of the kinome can best be addressed by the structural understanding of the molecular recognition patterns, bioinformatics approaches based on this data, and kinome-wide assays to verify design ideas.

This book is in every respect well balanced, and a multitude of readers can therefore profit from it. It is a "rich potpourri" of modern drug-discovery techniques and contains excellent overviews and brief outlines of these methods, not omitting their limitations and challenges.

This is especially valuable for students or younger researchers developing an interest in these topics. The often critical but always very fair assessments, the personal outlooks and comments, as well as the numerous examples given are surely a positive quality of the book and should also appeal to experienced academic and industrial scientists.

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Metallochemistry of Neurodegeneration: Biological, Chemical and Genetic Aspects

By *Henryk Kozlowski*, *David R. Brown*, and *Gianni Valensin*.

RSC, Cambridge 2006. xii + 281 pp., hardcover £89.95.—ISBN 978-0-85404-360-6

The World Health Organization estimates that neurological disorders currently afflict over 1 billion people, with an estimated 24 million of those suffering from Alzheimer's disease (AD), which occurs almost exclusively in people over the age of 65. These disorders place a significant burden on the patients, their families, and the health care infrastructure. Addressing neurological disorders represents a significant emerging challenge as the world population increases in both size and age. For example, Alzheimer's Disease International projects that the number of AD cases will double every 20 years, which means that over 80 million people will suffer from the disease by 2040. Both the prevalence and severity of neurological disorders have motivated researchers to study disease pathologies and to search for therapeutic strategies. A growing body of evidence from these studies suggests a connection exists between the incidence of neurological diseases and either an imbalance in metal ion concentrations or a malfunction of a metalloenzyme.

In their new book, Kozlowski, Brown, and Valensin provide an overview of metalloneurochemistry and review some of the significant research from the field reported in the last 10–15 years. A growing number of bioinorganic chemists have recently joined the efforts of neuroscientists to study the chemistry of metals in the central nervous system (CNS) and the possible role of metals in neurological disorders. This book presents the relationship between metals and brain function from two different perspectives. First, several chapters are dedicated to four of the most prominent neurodegenerative disorders: AD, Parkinson's disease, amyotrophic lateral sclerosis, and prion diseases, and the proposed roles of various metals in these diseases. The second approach involves a survey of specific metals implicated in multiple disorders. Both the natural functions of these metals and detrimental consequences of exposure or overexposure to these metals are evaluated. Included in this overview are the clinical applications of lithium and the neurotoxicity of aluminum, which are both metals without functions in normal mammalian biology.

The most extensive discussion in the book is dedicated to copper. Mechanisms of copper homeostasis and entry into the CNS are presented in the context of widespread diseases, like AD, and also with respect to rarer disorders such as Wilson's and Menkes' diseases, which have been highlighted in recent studies of metallochaperones. The links between prion diseases such as bovine spongiform encephalopathy (mad-cow disease) and copper are analyzed with examples from genetic, biochemical, and coordination chemistry studies, providing a balanced presentation for readers with different scientific backgrounds. Although this is an instructive approach, the emphasis on copper may lead the uninitiated reader to erroneously conclude that metals such as iron, zinc, and calcium are of lesser importance in understanding neurological disorders. While it would have been impossible to provide a comprehensive picture of all the metal chemistry implicated in neurodegeneration in this book, it does provide an excellent springboard for initiating a study of the these subjects when used in conjunction with the primary literature and other books that review research at the interface of inorganic chemistry and neuroscience.

Studying the chemistry of aging and age-related diseases at the molecular level provides a promising avenue to address these issues, and the final chapter of the book examines the application of lanthanide-based MRI agents in the diagnosis and study of brain-related diseases. An increasing number of young scientists, including chemists, are choosing to focus on metalloneurochemistry because of the global health crisis associated with neurological disorders; however, finding effective therapeutics for existing neurological disorders and practicing preventative medicine remains challenging, as disease pathogenesis is not fully understood. Even with the abundance of data acquired by various methods to date, new investigators in the field can find numerous unanswered questions that cannot be studied with existing technologies. Solving many of the problems described in this book will require today's scientists to make innovations in MRI reagents, fluorescent sensors, caged complexes, pro-chelators as well as chemically modified biomolecules and new model systems to study disorders. Subsequent treatment of diseases will require similar advances in synthetic, biological, and coordination chemistry. This book conveys the urgent need for such research and development, and should motivate researchers in the field to continue to push the boundaries of metalloneurochemistry.

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Thermal Analysis of Pharmaceuticals

Edited by *Duncan Q. M. Craig* and *Mike Reading*.

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Working in the field of solid-state analysis of pharmaceuticals for many years, I accepted the invitation to review this

