SMALL MOLECULE THERAPY FOR GENETIC DISEASE

This book summarizes the substantial work that has been accomplished with simple molecules in the treatment of inborn errors of metabolism. These agents are discrete, often of natural origin, and provide predictable therapeutic responses. As such, they avoid many of the practical difficulties associated with gene and protein therapies.

This book will enable interested clinician/scientists and others to rapidly survey the field, thus ascertaining what has been done as well as future directions for therapeutic research. Its important introductory chapters discuss the infrastructure of the field. These chapters focus on an introduction to pharmacokinetics and pharmacodynamics, a description of the FDA Office of Orphan Products, and a summary of the operation of the National Institutes of Health Office of Rare Diseases Research. The remainder of the book is devoted to a review of small molecule therapy for genetic diseases. The book closely analyzes the cofactors used to augment the function of defective enzymes and the compounds that are able to use an alternative pathway to avoid the consequences of the metabolic block present in the patient. Among other therapies, the authors discuss the use of zinc and tetrathiomolybdate to treat Wilson disease and the use of cysteamine to treat nephropathic cystinosis.

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Small Molecule Therapy for Genetic Disease

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Preface

The problem of recognition and treatment of rare diseases has been a topic of interest since Representative Henry Waxman held hearings on this issue in 1980. Led by Representative Waxman, clinician/scientists, legislators, patient interest groups, and drug companies all participated in the formation and passage of the Orphan Drug Act of 1983 (PL 97–414). In that legislation, an orphan disease was defined as a condition that affects fewer than 200,000 Americans. In testimony during hearings while the bill was being drafted, it was learned that treatments for more than 100 rare diseases existed but were not being developed because of lack of interest by pharmaceutical companies because of the small market and thus, lack of potential profitability. The Act provided tax incentives for clinical trials of these agents, grants to assist investigators in performing the trials, and a structure at the U.S. Food and Drug Administration (FDA; The Office of Orphan Products; see Chapter 2) to help shepherd applications through the agency. The Act has been an unqualified success. In fact, President Reagan, who initially threatened to veto the legislation, later described it as “... one of the most significant and successful pieces of health care legislation during my presidency...”1,2

The topics addressed in this book are all rare diseases within the meaning of the Orphan Drug Act. The success of these therapies is recognition of the hard work expended by clinical investigators (many of whom are authors of chapters in this book) to bring successful treatment for these serious and often life-threatening conditions to new drug approval.

This book is published with several goals in mind. One is to provide a convenient repository for the substantial work that has been accomplished by individual investigators treating rare genetic disorders with simple molecules. In the current era in which macromolecular therapy is looked to as the ultimate treatment for diseases as disparate as cancer, coronary artery disease, and genetic disease, it is somewhat reassuring to realize the broad scope that small molecules have in treating many serious, life-threatening disorders across the age span. These agents are discrete, often of natural origin, and provide predictable therapeutic responses. As such, they avoid many of the practical difficulties associated with gene and protein therapies.

Another goal is to provide a handbook that will enable potential clinician/scientists and others to rapidly survey the field, thus ascertaining what has been
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done and what can yet be done. Assisting implementation of these aspects of the book are three very important chapters in Section I, Infrastructure. This section includes an introduction to pharmacokinetics and pharmacodynamics, which, although covered in the usual medical school curriculum, are often not retained in the depth needed to plan and execute a Phase I or Phase II drug trial. Readers will find definitions of terms to assist in reading the pharmacologic literature, important examples of parameters required to prepare a viable FDA New Drug Application, and substantial references to assist in further reading.

Chapter 1, on the FDA Office of Orphan Products, written by the second director of that office, Dr. Marlene Haffner, and Dr. Tan Nguyen, provides an outstanding review of the functions of that office. It behooves everyone considering undertaking a therapeutic trial for an orphan disease to read this chapter. Grants for clinical trials in rare diseases are funded by this office, and protocol assistance is provided to help otherwise naïve investigators wend their way through the new drug approval process at the FDA.

Those who wish to embark on a clinical trial of a small molecule to treat a rare disease will benefit by reading Chapter 2 on the National Institutes of Health (NIH) Office of Rare Diseases Research, written by its director, Stephen Groft, PharmD. This chapter contains substantial and varied information that will assist investigators in accessing many resources at NIH, including finding funding for clinical trials and access to specialized analytical facilities that will be useful in many of these endeavors.

The remainder of the book is devoted to a review of small molecule therapy for genetic diseases. Section II is a review of cofactors used to augment the function of deficient enzymes by increasing production of more active holoenzyme through treating the patient with that enzyme’s specific cofactor. When successful, the results are startling, as described in Chapter 4, by Dr. Kirit Pindolia and Dr. Barry Wolf, on treatment of biotin-responsive disorders.

Section III is devoted to compounds that are able to use an alternative pathway to avoid the adverse consequences of the metabolic block present in the patient. A number of ingenious molecules have been devised and approved by the FDA to treat diseases in this category.

The final section, Section IV, covers the use of metal ions to treat severe disorders including Wilson disease, which has the distinction of being one of the first approved orphan products, and Menkes disease and other acquired and inherited copper deficiency syndromes.

From the perspective of rare disease patients, a book like this can serve many purposes, including assisting them in educating their health care providers. It was well documented by the National Commission on Orphan Diseases that patients and their families must first become experts in their rare disorder and then educate their health care professional. According to a survey commissioned by the National Commission on Orphan Diseases, one-third of rare disease patients wait between one and five years to receive a correct diagnosis, and one in seven such patients waits six years or more.1 We hope this book will assist in reducing that interval. Additionally, by drawing attention to rare disorders, it is hoped that this
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book may encourage practitioners treating such patients to consult the growing number of Web-based registries that facilitate locating an appropriate clinical trial.

To the extent that this book succeeds in meeting any of these goals, the effort expended will have been justified.

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It is also critical to acknowledge the contributions of the many patients and their families whose courage to volunteer for clinical trials enables all such studies and new drug approvals. On behalf of all the authors, I salute our patients and hope that clinical trials of orphan drugs continue to improve their health and quality of life. Lastly, I thank my wife, Dr. Marijim Thoene, DMA, whose constant support inspires my efforts.

REFERENCES