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Protein Pharmacokinetics and Metabolism

Edited by
Bobbe L. Ferraiolo,
Marjorie A. Mohler,
and
Carol A. Gloff

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Edited by

Bobbe L. Ferraiolo
R. W. Johnson Pharmaceutical Research Institute
Spring House, Pennsylvania

Marjorie A. Mohler
Genentech, Inc.
South San Francisco, California

and

Carol A. Gloff
Alkermes, Inc.
Cambridge, Massachusetts

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Contributors

Robert A. Baughman, Jr. • Research and Development, Emisphere Technologies, Hawthorne, New York 10532

Gerhard Baumann • Center for Endocrinology, Metabolism, and Nutrition, Department of Medicine, Northwestern University Medical School, Chicago, Illinois 60611

Jennifer E. Cook • Department of Safety Evaluation, Genentech, Inc., South San Francisco, California 94080

Paul A. Cossum • Department of Preclinical Development, Isis Pharmaceuticals, Carlsbad, California 92008

Bobbe L. Ferraiolo • R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477

Carol A. Gloff • Alkermes, Inc., Cambridge, Massachusetts 02139

Marjorie A. Mohler • Department of Safety Evaluation, Genentech, Inc., South San Francisco, California 94080

Jerome A. Moore • Department of Safety Evaluation, Genentech, Inc., South San Francisco, California 94080; *present address:* Celtrix Pharmaceuticals, Santa Clara, California 95052

John B. Stoudemire • Cytel Corporation, San Diego, California 92121

John M. Trang • Department of Pharmaceutical Sciences, Samford University Pharmacokinetics Center, School of Pharmacy, Samford University, Birmingham, Alabama 35229

Robert J. Wills • R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869

Peter K. Working • Department of Pharmacology and Toxicology, Liposome Technology, Inc., Menlo Park, California 94025

Victor J. Wroblewski • Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285

Preface to the Series

A major challenge confronting pharmaceutical scientists in the future will be to design successful dosage forms for the next generation of drugs. Many of these drugs will be complex polymers of amino acids (e.g., peptides, proteins), nucleosides (e.g., antisense molecules), carbohydrates (e.g., polysaccharides), or complex lipids.

Through rational drug design, synthetic medicinal chemists are preparing very potent and very specific peptides and antisense drug candidates. These molecules are being developed with molecular characteristics that permit optimal interaction with the specific macromolecules (e.g., receptors, enzymes, RNA, DNA) that mediate their therapeutic effects. However, rational drug design does not necessarily mean rational drug delivery, which strives to incorporate into a molecule the molecular properties necessary for optimal transfer between the point of administration and the pharmacological target site in the body.

Like rational drug design, molecular biology is having a significant impact on the pharmaceutical industry. For the first time, it is possible to produce large quantities of highly pure proteins, polysaccharides, and lipids for possible pharmaceutical applications. The design of successful dosage forms for these complex biotechnology products represents a major challenge to pharmaceutical scientists.

Development of an acceptable drug dosage form is a complex process requiring strong interactions between scientists from many different divisions in a pharmaceutical company, including discovery, development, and manufacturing. The series editor, the editors of the individual volumes, and the publisher hope that this new series will be particularly helpful to scientists in the development areas of a pharmaceutical company (e.g., drug metabolism, toxicology, pharmacokinetics and pharmacodynamics, drug delivery, preformulation, formulation, and physical and analytical chemistry). In ad-

dition, we hope this series will help to build bridges between the development scientists and scientists in discovery (e.g., medicinal chemistry, pharmacology, immunology, cell biology, molecular biology) and in manufacturing (e.g., process chemistry, engineering). The design of successful dosage forms for the next generation of drugs will require not only a high level of expertise by individual scientists, but also a high degree of interaction between scientists in these different divisions of a pharmaceutical company.

Finally, everyone involved with this series hopes that these volumes will also be useful to the educators who are training the next generation of pharmaceutical scientists. In addition to having a high level of expertise in their respective disciplines, these young scientists will need to have the scientific skills necessary to communicate with their peers in other scientific disciplines.

RONALD T. BORCHARDT
Series Editor

Preface

Investigation of the pharmacokinetics and metabolism of human proteins has escalated over the last two decades because of the use of recombinant human proteins as therapeutic agents. In addition, the development and improvement of analytical techniques enabling the detection of minute quantities of proteins in biological matrices have aided this process.

In assembling this volume, we sought to provide a state-of-the-art assessment of the pharmacokinetics and metabolism of protein therapeutics through complete reviews of selected examples. A comprehensive review of all protein therapeutics was not attempted; the majority of the therapeutic protein classes and crucial scientific issues have been addressed, however. Therefore, we are confident that this volume will provide a useful reference for scientists in this field.

The volume has been divided into two general parts. The first part (Chapters 1–3) is composed of general reviews of topics of importance in pharmacokinetic/metabolism studies of proteins: goals and analytical methodologies, effects of binding proteins, and effects of antibody induction, respectively. The second part (Chapters 4–8) consists of specific, detailed reviews by therapeutic protein class: growth factors and hormones, cytokines, cardiovascular proteins, hematopoietic proteins, and antibodies, respectively.

The editors are grateful to the contributors for the patience, personal sacrifice and perseverance required to complete this volume.

BOBBE L. FERRAIOLO
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Chapter 1

Goals and Analytical Methodologies for Protein Disposition Studies

Bobbe L. Ferraiolo and Marjorie A. Mohler

1. INTRODUCTION

This chapter will present an overview of the goals of protein disposition studies and some of the analytical tools used to achieve those goals. The examples cited in the goals portion of this chapter will be briefly presented since these will be explored in greater depth in the ensuing chapters. Analytical issues are of major concern in protein disposition studies since many of the standard protein analysis methods do not individually provide a positive identification of the analyte. The question of which existing methodologies and analytical technologies are most productive will be addressed.

2. GOALS OF PROTEIN DISPOSITION STUDIES

The questions that need to be addressed in protein disposition studies are the same as those that are addressed for conventional drugs (Table I).

Bobbe L. Ferraiolo • R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477. *Marjorie A. Mohler* • Department of Safety Evaluation, Genentech, Inc., South San Francisco, California 94080.

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