Successful Drug Discovery

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Volume 4

Edited by
János Fischer,
Christian Klein,
Wayne E. Childers

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Editors

János Fischer
Richter Co., Plc.
Gyömröi ut 19/21
1103 Budapest
Hungary

Christian Klein
Roche Innovation Center Zürich
Cancer Immunotherapy Division
Wagistrasse 10
8952 Schlieren
Switzerland

Wayne E. Childers
Temple University School of Pharmacy
Moulder Ctr. for Drug Discovery Res.
3307 N Broad Street
Philadelphia, PA 19140
United States

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Chemistry and Human Health Division
PO Box 13757
Research Triangle Park, NC 2770-3757
USA

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Preface

The fourth volume of *Successful Drug Discovery* continues to follow the structure of the previous volumes, consisting of three parts: General Aspects, Drug Class Studies, and Case Studies. The book series focuses on new discoveries of small-molecule drugs and biologics.

The editors thank the advisory board members: Magid Abou-Gharbia (Temple University, USA), Jagath R. Junutula (Cellerant Therapeutics, Inc., USA), Kazumi Kondo (Otsuka), John A. Lowe (JL3Pharma LLC, USA), and Gerd Schnorrenberg (Boehringer Ingelheim, Germany), and the following reviewers who helped both the authors and the editors: Jonathan Baell, Gabriele Costantino, György Domány, John M. Beals, Stephen Hauser, Jagath R. Junutula, Béla Kiss, Paul Leeson, Gábor Mező, Tomi Sawyer, Malcolm Stevens, Michael Wagner, Peng Wu. Special thanks are due to Juergen Stohner for his review from the viewpoints of the IUPAC Interdivisional Committee on Terminology, Nomenclature and Symbols (ICTNS).

Part I: General Aspects

John P. Mayer and coworkers give a comprehensive survey on the recent progress in peptide therapeutics. Remarkable achievements in various therapeutic fields and several orally administered peptides are summarized in this chapter.

Andreas Ritzén and coworker investigate the physicochemical parameters of recently approved drugs. A significant fraction of non-CNS oral drugs violate two or more of the Lipinski parameters.

Part II: Drug Class Studies

Nicolas Joubert and coworkers give an overview on antibody–drug conjugates in cancer-targeted chemotherapy. Over the last decade, they have been improved by the choice of better drugs, linkers, and mAb targets.

Wayne E. Childers and coworkers evaluate three decades in the discovery of D_2 partial agonist drugs. Progress has been made in treating the negative and cognitive symptoms of schizophrenia.

Part III: Case Studies

Derek Maclean and coworker report on the discovery of *etelcalcetide*, which affords a suitable therapy for hemodialysis patients with secondary hyperparathyroidism.

Akihiko Tsuruoka and coworkers describe how *lenvatinib mesylate* was discovered to give a new drug for the treatment of differentiated thyroid cancer.

Andrew C. Chan and coworkers describe the discovery and development of *ocrelizumab*, which represents a new generation of anti-CD20 mAb for the treatment of multiple sclerosis.

Bernard T. Golding has prepared a chapter on the discovery and development of *rucaparib*, a new PARP-1 inhibitor anticancer drug for the treatment of ovarian cancer. It also represents an example of a good cooperation of academia and industry.

Wayne J. Fairbrother and coworkers describe how venetoclax, a selective antagonist of B cell lymphoma 2 (Bcl-2), was discovered for the treatment of leukemia.

The editor and authors thank Wiley-VCH, and personally Dr. Frank Weinreich for the excellent cooperation.

Budapest — *János Fischer*
Philadelphia — *Wayne E. Childers*
Zurich — *Christian Klein*
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Part I

General Aspects

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Trends in Peptide Therapeutics

Florence M. Brunel[1], Fa Liu[2], and John P. Mayer[3]

[1] *Novo-Nordisk Research Center, 5225 Exploration Dr., Indianapolis, IN, 46241, USA*
[2] *Novo-Nordisk Research Center, 530 Fairview Avenue North, Seattle, WA, 98109, USA*
[3] *University of Colorado, MCD Biology, 1945 Colorado Avenue, Boulder, CO, 80309, USA*

1.1 Introduction

The growing importance of peptide drugs within the pharmacopoeia has become evident over the past several decades. Among the factors that have contributed to this trend is the recognition that peptide ligands regulate a multitude of physiological pathways and are often suitable for therapeutic applications, in either their native or modified form. In addition, certain attributes that are unique to peptides, such as their high selectivity, potency, and lack of toxicity, have ultimately become appreciated. The alternative means of drugging peptide receptors through target-directed screening or rational design of orally available small molecules have, with few exceptions, proved unproductive. Mimicking the activity of a peptide agonist is highly challenging, particularly in the case of Class II G-protein-coupled receptor (GPCR) targets. Successful examples have typically involved receptor antagonists such as neurokinin, angiotensin, endothelin, and orexin. These lessons have increasingly led drug discovery scientists to consider peptides as legitimate drug candidates, rather than leads or proof-of-concept models for small-molecule programs. Peptide medicinal chemists have also had to confront and overcome shortcomings such as rapid metabolism, clearance, production costs, and limited alternative delivery options. In the present chapter, we highlight the role of peptides in therapeutic areas such as metabolic disease, where peptides have been well established, as well as in areas where their impact has been minor, but now rapidly expanding. We also emphasize examples where time-extension strategies and alternative delivery routes have helped establish and strengthen the position of peptide drugs in competitive markets. Finally, we explore two novel trends in peptide drug discovery, macrocyclic and cell-penetrating peptides, both of which may expand future opportunities for peptide therapeutics.

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1.2 Peptides in Metabolic Diseases

The global epidemic of type 2 diabetes and obesity continues unabated, impacting quality of life, life expectancy, and economic well-being. Health-care organizations have devoted enormous resources toward the treatment of metabolic diseases, often dramatically improving patient outcomes [1]. Perhaps more than in any other therapeutic area, peptides have had a unique and indispensable role in treating type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) as well as obesity. This section will provide an overview of approved insulin, GLP-1 (glucagon-like peptide-1), and glucagon peptide drugs as well as those in late-stage clinical development.

1.2.1 Insulins

Insulin, which was discovered by Banting and Best in 1921, became commercially available only one year after its discovery (Figure 1.1) [2]. In spite of its miraculous potential, the short duration of action of early insulin preparations (four to six hours) required multiple daily injections and prompted the search for longer acting formulations. The first of these, insulin neutral protamine Hagedorn (NPH), developed in the 1940s, consisted of an insulin suspension complexed with protamine, a cationic protein isolated from fish sperm. The slow disassociation of the NPH complex delayed absorption from the injection site, prolonging insulin action to a range of 12 to 18 hours [3]. Insulin Lente, introduced in the 1950s, involved a neutral pH suspension of insulin formulated with excess zinc, which extended the duration of action to 24 hours and beyond [3]. Between the 1920s and the early 1980s, commercial insulin production relied on extraction of pancreatic glands from cows and pigs. The advent of biotechnology enabled the production of rDNA-derived human insulin in the early 1980s in sufficient quantity to satisfy the needs of the diabetic population, gradually

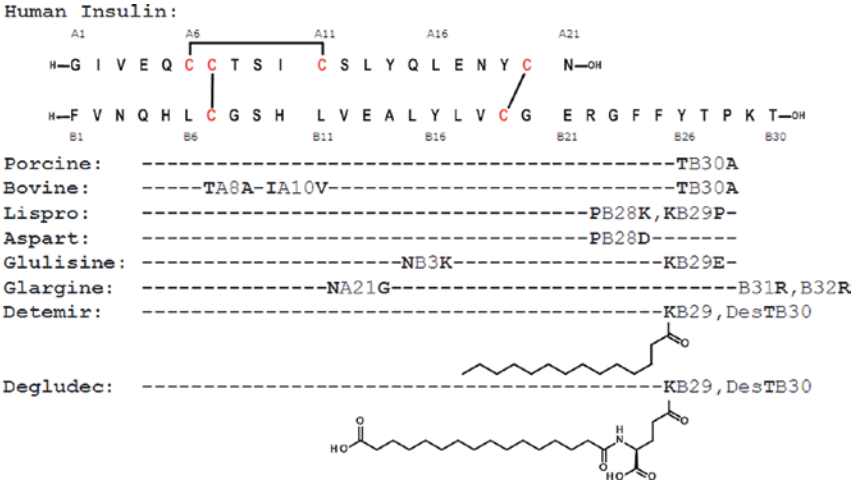

Figure 1.1 Sequences of human, porcine, bovine, and the commercially key insulin analogs.