About the Editors

Hendrik Gert Kruger

Gert Kruger graduated from Potchefstroom University, South Africa, in 1996 under the supervision of Frans (FJC) Martins and Attie (AM) Viljoen. His PhD lineage is traced back to Rudolf Criegee (Wutzburg) via Johan Dekker (Karlsruhe). The Dekkers introduced cage chemistry to South Africa, which Kruger actively pursues at the University of Kwazulu-Natal. He is also combining the pentacycloundecane cage with peptides as potential HIV protease inhibitors and anti-tuberculosis agents (see <http://cpru.ukzn.ac.za>).

Fernando Albericio

Until very recently, Fernando Albericio held various appointments: Professor at the University of Barcelona, Group Leader at the Institute for Research in Biomedicine-Barcelona, and Research Professor at the University of KwaZulu-Natal in Durban, South Africa. In March 2014, he was appointed by President Rafael Correa of Ecuador as the Inaugural Rector of Yachay Tech, a new Ecuadorian university. His major research interests cover practically all aspects of peptide synthesis (new reactions, building blocks, coupling reagents, solid phase supports, protecting groups, and linkers) and combinatorial chemistry methodologies, as well as synthesis of peptides and small molecules with therapeutic activities. Furthermore, his group is also involved in developing new systems for drug delivery and strategies for diagnostics as well. In Ecuador, he is running a program of Biodiversity based Medicinal Chemistry. He has published over 750 papers, filled more than 55 patents, and has co-authored four books. He has also edited several scientific journal issues and acted in the editorial board of several others. Recently, he has been honored with a Doctorate Honoris Causa by the Universidad de Buenos Aires (Argentina), Vincent du Vigneaud award by the American Peptide Society, A-rating by the National Research Foundation (South Africa), the Research Medal of the Royal Society of Chemistry (Spain), and was nominated as a Member of the European Academy of Sciences and Arts.

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Foreword

Advances in the discovery and development of peptide therapeutics

Hendrik Gert Kruger &
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We are celebrating the anniversaries of two seminal papers that changed the field of therapeutic peptides, namely 50 years of the solid-phase synthesis of a tetrapeptide by Bruce Merrifield and 20 years of the synthesis of a protein using chemical native ligation by Steve Kent and coworkers. Interestingly, the two approaches are interconnected, since the unprotected peptides used in the chemical ligation method were/are prepared by the solid-phase strategy. Taking advantage of these and other findings, and as a result of great efforts of a large number of colleagues, peptides now provide the basis of a large number of active pharmaceutical ingredients used in major fields of medicine. In this regard, the relevance of peptides is reflected in the following: in the 1980s, only 29 peptide-based compounds were in clinical phases for just five indications, while this year (2014) more than 130 peptides are being tested in clinical trials for 18 different therapeutic applications. The renaissance of peptides as drugs is exemplified by the fact that, in addition to many new biotech companies, the so-called large pharmaceutical corporations are rebuilding their peptide units, which in some cases were erroneously dismantled in the 1990s.

This book comprises 12 compelling chapters written by scientists actively involved in the respective fields of research. The philosophy of this book is to focus on the latest developments and also to point out the most likely future directions of each specific field. As far as possible, the authors have provided

references to review papers in the field, thus allowing novice researchers to trace the history of the developments that have taken place.

The book kicks off with the latest developments in peptide drug discovery, demonstrating that peptide drugs cover the space between small molecules and proteins. Given the nearly twofold likelihood of success of peptides over small-molecule drugs in clinical trials (the most expensive part of drug development), peptide drugs are becoming a focal point of research interest. Methods to overcome former difficulties with peptide drugs are presented.

Chapter 2 addresses the latest technologies used for peptide synthesis. In this regard, the field of peptide synthesis has matured, bringing about constant advances in amidation strategies, efficiency, practical aspects, yield and scalability, thus opening up new opportunities for peptide synthesis. Several examples of recent achievements and interesting evolutions are highlighted in this chapter.

Chapter 3 considers peptide manufacturing, mainly in two categories, namely small-scale production and large-scale production by commercial companies. Small-scale production typically uses highly automated equipment and generalized protocols with little or no process development. These products are generally sold for research purposes. All aspects of peptide manufacturing, including process development, resin amino acids, coupling reagents, solvents, cleavage and purification, are discussed.

The next part of the book, Chapters 4–12, covers key aspects of the therapeutic applications of peptides. In addition to their use as active drugs, the successes and new developments of cancer-targeting peptides are highlighted in Chapter 4. Conjugation of carrier peptides with drug molecules or imaging agents and their applications in cancer treatment and diagnostics are presented. Chapter 5 is then devoted to peptide cancer vaccines and immunotherapy.

Chapter 6 focuses on antimicrobial peptides, which typically exert a biological mode of action via membrane disruption. Applications such as antiparasitic, antiviral, antifungal and anticancer agents are presented. Moving to Chapter 7, attention is turned to peptides used to combat metabolic diseases, such as obesity and Type 2 diabetes, both of which result from lifestyle changes of modern society.

Chapter 8 deals with the application of peptides for the treatment of CNS disorders, such as Alzheimer's, Huntington's and Parkinson's disease, and amyotrophic lateral sclerosis. Less than 2% of small drugs penetrate the blood–brain barrier. Peptides have an advantage over small molecules in this regard, but improved *in vivo* stability requires further development of delivery systems and formulations. Two related chapters then follow. Chapter 9 is dedicated to the latest developments in peptide drug formulations

and the second to peptide delivery. The stability of peptides is a major concern for formulations. Traditionally, peptide drugs have largely been administered intravenously because they are seldom stable enough for oral delivery. Formulation research now shows progress in alternative administration routes, such as pulmonary, oral, oromucosal and uptake through nasal channels. Chapter 10 focuses largely on the latest developments in oral delivery of peptides by means of smart polymers, among others.

Chapter 11 covers the applications of peptides as theranostic agents. These compounds can be used *in vivo* for therapeutic and diagnostic purposes. Examples involve peptides targeting somatostatin receptors (SSTR1–SSTR5), gastrin/cholecystokinin receptors and gastrin-releasing peptide/Bombesin receptors. In most cases, radioactive agents are complexed to these peptides via linkage to a suitable ligand.

While each of the aforementioned chapters ends with a section devoted to future developments, the final chapter concludes by addressing the outlook for peptide therapeutics. In this regard, the authors demonstrate that pharmaceutical companies are showing renewed interest in this field, as reflected by 70 peptides currently approved as therapeutic agents. They highlight the advantages of peptides (selectivity and general lack of toxicity), which bolster their further development. However, the resurgence of interest has also been fuelled both by the failure of peptidomimetics to live up to their promise and by technological advances in the field of peptide science. The current status of peptide therapeutics and of peptides in the pipeline is disclosed. This part is followed by a description of the ongoing challenges, opportunities and new directions for the development of novel peptide therapeutics. Finally, the authors draw attention to potential hurdles along the way and to some exciting bright spots on the horizon.

From the synthetic perspective, current methods allow the preparation of almost any small to medium-sized peptide and a large number of proteins by chemical ligation. The coming years are expected to witness the development of new synthetic methods in aqueous environments, possibly following prebiotic chemistry.

The contributions of this book, together with the opinions of other analysts, reinforce the notion that therapeutic peptides can look forward to a golden era. Most pharmaceutical companies have in the pipeline peptides designed under totally new scientific paradigms, such as stapled and other cyclic peptides, cyclotides and lasso peptides. The maturation of these new topological concepts should allow for a new generation of novel peptide-based drugs.

Finally, and as mentioned in the last chapter by Manning, Verlander and coworkers, the development of the so-called small molecules as drugs originated predominately in pharmaceutical companies, while in the case of

peptides the collaboration between academia and the industry has very often been the starting point for several peptide drugs now on the market. In our view, these strong academic/industrial collaborations will lead to an increasing portfolio of peptide-based drugs.

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