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Advanced Functional Materials Series

斜丛书 丛书主编 师昌绪

Bioinspired and Biomimetic Polymer Systems for Drug and Gene Delivery

生物启发与仿生型高分子药物及基因递送系统

Edited by Zhongwei Gu

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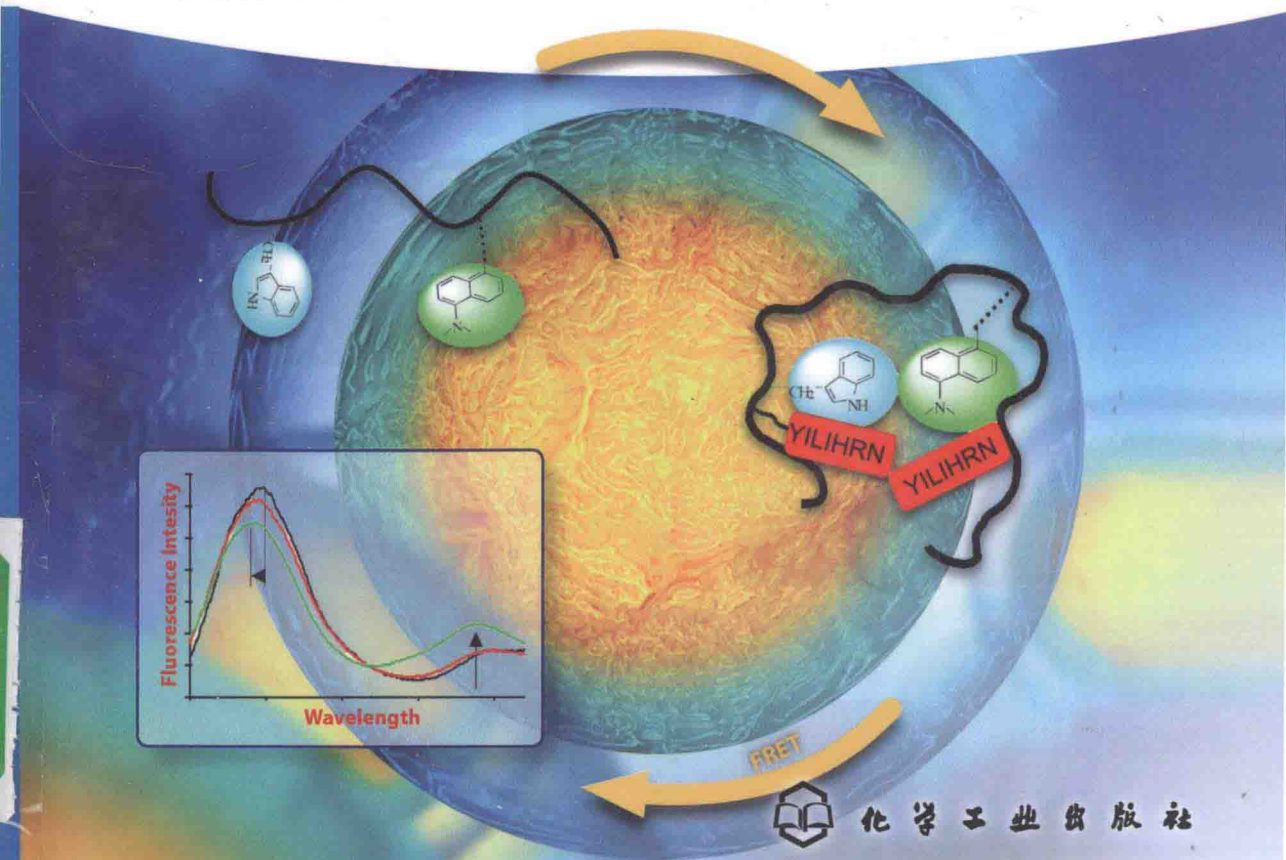

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·北京·

近年来，生物活性物质控释系统的研究主要集中于：时控型药物控释系统；自调节药物控释系统；靶向药物控释系统；组织/细胞微环境响应性药物控释系统以及核酸类药物递送系统。受自然界启发，如何运用仿生的方法构建和优化药物、蛋白质和基因的递送系统已是一个新兴的发展方向和趋势，它是涉及生物学、材料学、化学、物理学、药学、工程学等学科的多学科交叉研究领域。

本书汇聚了包括美国工程院院士在内的多名国内外药物控释系统研究领域的著名科学家近年来的最新研究工作。作为国际上第一本生物启发和仿生高分子的药物及基因递送系统的专著，本书不仅报道了药物递送领域的最新进展和未来发展方向，还分别从材料与细胞相互作用、载体材料的组织/细胞微环境响应性设计、控释系统在体内环境下生物活性物质的高效释放及有效表达等不同的角度对药物递送系统的未来发展方向进行了新的诠释和展望，充分体现了前瞻性和新颖性，是该领域一部难得的、非常有价值的专著。

本书可供从事生物工程、纳米技术及材料领域的高校、科研院所、公司企业的相关研究人员使用。同时可作为生物医学工程、高分子科学及相关交叉学科的研究生及本科生教学参考书。

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Foreword

In recent years, the rapid development of polymer science and advances in modern medicine, pharmacy, biology, and engineering have fostered the emergence of a new field focused on the theory and technology underlying drug delivery. This inter-disciplinary field is called drug delivery systems (DDS). It shows great promise and has become a hotspot in biomedical material research, especially in biomedical polymers.

The successful development of advanced, efficient DDS depends on the design and construction of the materials and micro devices involved. The research frontier focuses mainly on targeted delivery, especially cell and molecular targeting, and on controlled release stimulated by the tissue or cellular microenvironment. The complex *in vivo* physiological and pathological environment often obscures the effects of active targeting. In this way, producing a highly efficient system capable of active targeting *in vivo* is the key to improving the efficacy of DDS. Drug release systems capable of biological sensing are called bioinspired and biomimetic delivery systems. They automatically adjust the drug release in response to external stimuli, such as changes in temperature, pH, magnetic fields, ultrasound, and electric fields. They have received a considerable amount of attention from researchers and pharmaceutical companies worldwide. Drug release systems that can be switched on and off via self-feedback upon changes in the chemical or physical signals given off by a lesion or intelligent carrier have drawn particular interest. Systems that can undergo rapid stimuli-responsive controlled release under *in vivo* microenvironment conditions would be far more useful to actual clinical treatment regimens.

This book embodies the wisdom and achievements of renowned experts and research teams in this field from China, the United States, Germany, Japan, and Korea. The discussion provided herein covers the most important, active, and cutting-edge parts of this field, reflecting the latest developments and trends in DDS research. The chief editor, Professor Zhongwei Gu, studied under the pioneer biomedical polymers in China – Professor Xin-De Feng (Academician of Chinese Academy of Sciences). Gu entered this field in the 1970s and has become a well-known professor of polymer biomaterials in China. It is our hope that this book will promote scientific research and biomedical applications in the vibrant and

exciting area. Young academics and professionals interested in DDS may also benefit from this treatise.

We would like to thank all our editors for their hard work and dedication. We would also like to thank John Wiley & Sons Publishing Company and Chemical Industry Press for their forward-looking strategic vision and the timely publication of this book.

August 2014

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Preface

The rapid development of biomedical materials science and engineering and advances in modern medicine, pharmacy, biology, and engineering have made the great promise of advanced drug delivery systems (DDS) increasingly clear. These DDS systems are made of carrier materials and drugs, including peptides, proteins, antigens, and nucleic acid drugs, allowing the controlled release of active agents. The advanced DDS systems would not only be a revolutionary change from the traditional mode of drug delivery but may also facilitate the development of currently infeasible approaches to the treatment of cancer, cardiovascular disease, AIDS, congenital genetic defects, and other diseases. It has also greatly promoted the development of molecular diagnostic medicine, which may facilitate the early diagnosis and exploration of the pathogenesis and development of disease and the resultant pathological and physiological changes. With the continuous development of new materials and new technologies and urgent clinical needs, the production of carrier materials and the drug controlled-release/delivery system has become an important part of the entire pharmaceutical industry, and is growing to be the most promising sunrise industry, bringing tremendous and far-reaching impact on the global pharmaceutical industry. The forces driving its rapid growth are as follows: First, the research and development of carrier materials capable of restoring and improving the body's physiological functions and delivery systems capable of releasing them in a controlled manner are the main direction of contemporary biomedical material research. Second, diseases that are currently difficult to cure may become treatable or easier to detect early. This may involve a significant reduction in health care costs. Third, drug delivery systems capable of controlled release have several advantages over current systems. They tend to last longer, deliver their payload more efficiently in terms of time, and are less toxic to the patient. This also improves the bioavailability of drugs, especially peptide, protein, and nucleic acid drugs. Fourth, these systems are conducive to the development of new drugs. They can reduce costs, shorten development cycles, and provide a quicker return on investment than conventional drug development.

The designs and preparation techniques of carrier materials and micro-systems are the key to the development of the advanced, efficient drug controlled-release/delivery system and the theranostic micro devices. The cutting-edge areas and future trends of this field mainly include the following aspects.

The first aspect is the intelligent/microenvironment-triggered (stimulus-responsive) DDS. Such systems use the material's ability to detect changes in pH, redox, other chemical signals, temperature, optics, magnetic fields, electrical signals, mechanical signals, other physical signals, and enzymes, receptors, and other biological signals to facilitate responsive drug release. It may be the most promising and the most valuable DDS with the greatest prospect in clinical applications in the ᵗ21st century. The key technology in this field is to improve the sensitivity of the material and the DDS, in order to achieve rapid response *in vivo*.

The second aspect is the targeted DDS itself, which includes passive and active targeting. Passive targeted DDS cannot recognize the target cells, instead relying on the size effect to reach the target site. For example, a drug carrier system that is 20–200 nm in size triggers an enhanced permeability and retention (EPR) effect based on the defects (holes) in the blood vessels of the tumor tissues, thereby causing efficient local accumulation of drugs. Precise control of the particle size, sufficiently narrow size distribution, and increase in the circulation time *in vivo* are crucial to passive targeting. Active targeted DDS introduces a targeting group capable of recognizing the target tissue, target cells, or even target molecules. The ability to recognize the cells or molecules of a specific tissue or organ is highly relevant to material preparation. The advantages of this type of DDS are its high selectivity and reduced side effects to normal tissues and organs, which would be very valuable in the treatment of common multiple malignancies.

The third aspect is self-regulated DDS. The system must mimic the complex biochemical processes *in vivo* and release the drug in accordance with the body's needs, rather than at a stable, predetermined speed. The release mechanisms involve the microporous or bulk diffusion of the polymer reservoir or the enzymatic degradation on the surface of the polymer matrix.

The fourth aspect is time control. To achieve constant speed, zero-order release of the drug is the main direction. The chemical structure, composition, and degradation properties of the material and its capacity for drug penetration and diffusion are key to achieving constant release. Transdermal drug delivery avoids the first-pass effect and gastrointestinal damage because it does not require that the drug pass through the liver. This makes it more practical for patients requiring long-term continuous administration. It is also highly efficient and may reduce the rate of side effects. In addition, the source of the drug, usually a patch, can be removed at any time. The core issues in transdermal drug delivery are producing a polymer film capable of drug transmission, which involves the principles of pharmacodynamics and pharmacokinetics.

This book covers bioinspired and polymer nano drug delivery systems. It is published jointly by John Wiley Publishing Company and China Chemical Industry Press. Its goal is to review relevant progress and the future direction

of development in order to promote the development of this field, the clinical application of nano drug delivery systems, and improvements in medicine. To this end, internationally renowned experts in this field co-authored the book with different styles and from different perspectives. The book consists of 12 chapters, mainly including backbone-degradable high molecular weight (second-generation) water-soluble polymer-anticancer drug conjugates, and a new paradigm of drug-free macromolecular therapeutics; nano-targeting drug delivery systems based on peptide dendrimers; nano composite colloidal systems with multiple functions including targeting, stimulus-responsive controlled release, and sensing; multifunctional polymeric micelles that can break various physiological barriers for targeted delivery; biomimetic polymer used for *in vivo* drug delivery; nanoparticle-based proteins such as gelatin, human serum albumin, collagen, silk protein, casein protein, and elastin-like polypeptides; polymer carriers for gene delivery system and their functional modifications; pH-sensitive nano drug delivery systems for targeted cancer therapy and biological imaging; drug/gene nano delivery system capable of charge flipping; nano drug carrier systems using phenylboronic acid-based glucose-responsive polymeric materials and their gels, micelles, and vesicles; nano delivery systems for cancer treatment co-carrying drugs and siRNA and activated by extracellular pH; and pH, heat, and biological molecule or light-sensitive stimuli-responsive DDS. This book covers the design principles, research and development technologies, and application prospects of advanced and efficient polymer nano DDS, and rather comprehensively discusses the outstanding progresses and future trends of the field. This forward-looking, novel treatise on polymer nano DDS is unique and extremely valuable, and I believe that it will be welcomed by readers. In particular, young scholars interested in the field of polymer nano drug delivery systems will learn a great deal from this book, and may be inspired to carry on their own research.

I would like to thank all the editors and contributing authors for their time and expertise. I am especially grateful to Dr. Gang Wu from the China Chemical Industry Press and Dr. Esakki Rahini from the John Wiley Publishing Company for their contributions to the publishing of this book. I thank Professor Bin He, Professor Yao Wu, and everyone else who have helped. I would also like to sincerely thank Professor Renxi Zhuo of the Chinese Academy of Science, a pioneer and esteemed leader in the field of polymer chemistry and drug delivery systems, for writing the preface for this book and for his guidance and support.

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