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DENDRIMER-BASED DRUG DELIVERY SYSTEMS

From Theory to Practice

EDITED BY
YIYUN CHENG
FOREWORD BY DONALD A. TOMALIA

WILEY

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From Theory to Practice

Edited by

YIYUN CHENG
East China Normal University
Shanghai, P.R. China

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FOREWORD

History has shown that seminal discoveries of the first three major traditional polymer architectures; namely: (I) linear, (II) cross-linked, and (III) branched architectures were in all cases followed by predictable patterns of intense international scientific and commercial activity. Unarguably, these activities were fueled by the emergence of unprecedented new architecturally derived properties and possibilities. Many of these architecturally driven properties have provided the basis for new scientific principles, applications, and commercial products which have served to enrich the human condition. Meanwhile, the past three decades since the discovery of the fourth major polymeric architecture; namely: "dendritic polymers/dendrimers" has proven to be no exception. Consistent with past patterns, a fivefold increase in literature publications (i.e., $>15{,}000$) has been documented for the past decade (2000–2011) compared to the first two decades since the discovery of this new architectural class. Furthermore, a recent survey has predicted extraordinary demand for nanomedicine derived products to grow over 17% per year through 2014 to an estimated market size of $75.1 billion, with subsequent growth to exceed $149 billion by 2019.[1]

Presently, dendrimers are viewed as one of the most preeminent and actively researched platforms in this rapidly emerging field of *nanomedicine.* More specifically, these precise nanostructures are presently receiving intense attention in the rapidly growing area of "dendrimer-based drug delivery." This explosive activity is largely attributed to a growing list of unique architecturally driven properties manifested by dendrimers, which includes the following:

[1] B. Martineau, *Genetic Engineering & Biotechnology News*, October 15, 2010, 14–15.

- Precise synthetic control over: size, shape, and surface chemistry to produce nanostructures that scale closely to proteins, yet do not exhibit immunogenic responses.
- Well defined, versatile surface/interior chemistry that may be engineered to deliver therapeutic levels of conjugated pro-drugs, nanocontainer, drug encapsulation features, targeting group/selected biodistribution properties in concert with designed surface moieties that exhibit acceptable toxicity properties and safety margins.
- Precise size calibrated nanostructures that may be suitably decorated with appropriate imaging or stimuli responsive moieties for *in vivo* "theranostic" applications.
- Well-defined nanostructure sizes and features (i.e., self-immolative/biodegradable) suitable for engineering desirable excretion modes.

Professor Yiyun Cheng from East China Normal University has assembled an international team of esteemed dendrimer pioneers and researchers for the purpose of sharing their valued perspectives on all facets of *Dendrimer-Based Drug Delivery—From Theory to Practice*. In this comprehensive survey, a number of critical issues are analyzed that bridge the critical path from fundamental concepts, design, synthesis, analytical methodologies, biological assessment to the practical use of dendrimers for drug delivery applications. More specifically, major points of emphasis may be categorized and summarized as follows:

- Introduction to dendrimer-based drug delivery systems, synthesis of dendrimers, physicochemical/biological properties of dendrimers and dendrimer complexes, synthesis and biological evaluations of dendrimer-based prodrugs, and the effect of dendrimers on the therapeutic properties of drugs: *Chapters 1–5*;
- The importance of biocompatibility to dendrimer-based drug delivery systems, and strategies used to improve the biocompatibility of dendrimers including stimuli-responsive, degradable, and self-immolative dendrimers: *Chapters 6–8*;
- Applications of dendrimers in the delivery of DNA and siRNA, including complex structures, *in vitro* and *in vivo* transfection efficiency, and potential administration routes, and the synthesis and pharmaceutical applications of glycodendrimers: *Chapters 9–11*;
- Nuclear magnetic resonance techniques in the analysis of dendrimer-based drug delivery systems, and the applications of dendrimers in magnetic resonance imaging and computed tomography: *Chapters 12–14*.

In summary, based on the experience/quality of authorship and the range of critical issues reviewed, this book represents a unique collection of know-how for understanding and practicing unprecedented new drug delivery strategies in the context of nanomedicine. This book should serve as a valuable resource for both academic and commercial investigators who are seeking promising new strategies for the safe and effective delivery of *in vivo* therapies, imaging and diagnostics.

DONALD A. TOMALIA

PREFACE

Dendrimers are hot research points and have been widely used in supramolecular chemistry, host–guest chemistry, electrochemistry, photochemistry, as templates for nanoparticle synthesis, as scaffolds for catalysts, and in drug and gene delivery. Among these applications, biomedical applications of dendrimers have attracted increasing interest during the past decade. Because of the unique opportunities, issues, and challenges involved with exploiting dendrimers for drug delivery, there is a need for a book to help pharmacists and related scientists understand and work with this new class of promising biomaterials. This timely book covers topics including dendrimer history, synthesis, physicochemical properties, principles in drug delivery, and applications in miscellaneous biomedical fields, and provides practical suggestions for the design and optimization of dendrimer-based drug delivery systems.

This book includes 14 chapters. Chapter 1 presents a historical view on dendrimer chemistry and gives supramolecular perspectives on dendrimers. Chapter 2 focuses on the physicochemical properties of dendrimers and dendrimer complexes. Chapter 3 discusses the use of dendrimers to tailor the physicochemical and therapeutic properties of loaded drugs. In Chapter 4, Caminade and Majoral summarize the biological properties of phosphorus dendrimers that were developed in their laboratory. Chapter 5 reports the synthesis and biological applications of dendrimer-based prodrugs. Chapter 6 aims at the safety of dendrimers and proposes several strategies to improve the biocompatibility of dendrimers. Chapter 7 emphasizes the importance of dendrimer degradability for drug delivery. Chapter 8 focuses on the design of stimuli-responsive dendrimers for biomedical purpose. Chapter 9 presents dendrimer-based gene delivery systems. The administration routes and *in vivo* evaluations of dendrimer/DNAs complexes are also discussed. Chapter 10 also introduces dendrimer applications in gene delivery but emphasizes triazine dendrimers that were developed

in Simanek's research group. In Chapter 11, Roy and coworkers introduce the use of carbohydrate-functionalized dendrimers as drug delivery Trojan horses. Chapter 12 relates the applications of NMR techniques in the analysis of dendrimer-based drug formulations. In Chapters 13 and 14, Shi et al. introduce the applications of dendrimers in magnetic resonance imaging and computed tomography imaging.

This book is directed primarily at the pharmaceutical sciences, and aims to be the definitive reference book for scientists in the field of biomaterials, nanomedicine, drug delivery systems, pharmacy, and dendrimer chemistry. It is my hope that it can stimulate the interest of researchers from these fields.

YIYUN CHENG

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Many people have helped with the book *Dendrimer-Based Drug Delivery Systems: From Theory to Practice*, and here is my chance to express my acknowledgments.

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Finally, I would like to dedicate this book to my wife, Jiepin Yang, for her assistance and encouragement during the preparation of this book.

YIYUN CHENG

CONTRIBUTORS

Marique E. Aucamp, Unit for Drug Research and Development, Faculty of Health Sciences, North-West University, South Africa

Hongdong Cai, College of Materials Science and Engineering, Donghua University, P.R. China

Anne-Marie Caminade, Laboratoire de Chimie de Coordination du CNRS, France

Yoann M. Chabre, Pharmaqam–Groupe de Recherche en Chimie Thérapeutique, Université du Québec à Montréal, Canada

Yiyun Cheng, School of Life Sciences, East China Normal University, P.R. China

Antony D'Emanuele, School of Pharmacy and Biomedical Sciences, University of Central Lancashire, UK

Melgardt M. De Villiers, School of Pharmacy, University of Wisconsin—Madison, WI, USA

Xueyan Feng, Department of Chemistry, University of Science and Technology of China, P.R. China

Marc Gingras, CNRS, UMR 7325, 163 Avenue de Luminy, 13288 Marseille, France; Aix-Marseille University, CINaM, 13288 Marseille, France

Jingjing Hu, Department of Chemistry, University of Science and Technology of China, P.R. China

Toyoko Imae, Graduate Institute of Engineering and Department of Chemical Engineering, National Taiwan University of Science and Technology, Taiwan, R.O.C

Thomas Kissel, Department of Pharmaceutics and Biopharmacy, Philipps-Universität, Germany

Chie Kojima, Nanoscience and Nanotechnology Research Center (N2RC), Research Organization for the 21st Century, Osaka Prefecture University, Japan

Wilna Liebenberg, Unit for Drug Research and Development, Faculty of Health Sciences, North-West University, South Africa

Yiwen Li, Department of Polymer Science, College of Polymer Science and Polymer Engineering, The University of Akron, Akron, OH, USA

Jean-Pierre Majoral, Laboratoire de Chimie de Coordination du CNRS, France

Olivia M. Merkel, Department of Pharmaceutics and Biopharmacy, Philipps-Universität, Germany

Meredith A. Mintzer, Deparments of Biomedical Engineering and Chemistry, Boston University, Boston, MA, USA

Charles N. Moorefield, Departments of Polymer Science and Chemistry, Maurice Morton Institute of Polymer Science, The University of Akron, Akron, OH, USA

Mohammad Najlah, Faculty of Pharmacy, Albaath University, Syria

George R. Newkome, Departments of Polymer Science and Chemistry, Maurice Morton Institute of Polymer Science, The University of Akron, Akron, OH, USA

Chen Peng, College of Materials Science and Engineering, Donghua University, P.R. China

Sujith Perera, Departments of Polymer Science and Chemistry, Maurice Morton Institute of Polymer Science, The University of Akron, Akron, OH, USA

Myriam Roy, CNRS, UMR 7325, 163 Avenue de Luminy, 13288 Marseille, France; Aix-Marseille University, CINaM, 13288 Marseille, France

René Roy, Pharmaqam–Groupe de Recherche en Chimie Thérapeutique, Université du Québec à Montréal, Canada

M.J. Santander-Ortega, Department of Pharmacy and Pharmaceutical Technology, University of Santiago de Compostela, Spain

A.G. Schätzlein, Department of Pharmacy and Biological Chemistry, The School of Pharmacy, London, UK

Mingwu Shen, College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, P.R. China

Xiangyang Shi, College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, P.R. China

Eric E. Simanek, Department of Chemistry, Texas Christian University, TX, USA

Nicole Stieger, Unit for Drug Research and Development, Faculty of Health Sciences, North-West University, South Africa

Donald A. Tomalia, NanoSynthons, LLC, National Dendrimer and Nanotechnology Center, MI, USA

I.F. Uchegbu, Department of Pharmacy and Biological Chemistry, The School of Pharmacy, London, UK

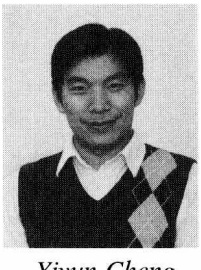
Tongwen Xu, Department of Chemistry, University of Science and Technology of China, P.R. China

Kun Yang, Department of Chemistry, University of Science and Technology of China, P.R. China

Libo Zhao, Department of Chemistry, University of Science and Technology of China, P.R. China

Zhengyuan Zhou, School of Pharmacy and Biomedical Sciences, University of Central Lancashire, UK

ABOUT THE EDITOR



Yiyun Cheng

Yiyun Cheng is a Full Professor of Biomedical Engineering at School of Life Sciences, East China Normal University. He received his PhD from University of Science and Technology of China under the mentorship of Professor Yunyu Shi and was a postdoctoral fellow at Washington University in St. Louis with Professor Younan Xia. Yiyun won the CAS President's Excellent Award, the Excellent PhD Thesis Award of the Chinese Academy of Science, and the Shanghai "Dawn Scholar". He was the Regional Editor of Current Drug Discovery Technologies and an editorial board member of five international journals. He was invited as a reviewer for more than 40 international journals and has published more than 40 peer-reviewed manuscripts including publications such as Nature Materials, Chemical Society Reviews, and Journal of the American Chemical Society, with a total citation of more than 800 by other research groups. His research interests are focused on the biomedical applications of dendrimers and other dendritic polymers.

CONTENTS

1

DENDRIMER CHEMISTRY: SUPRAMOLECULAR PERSPECTIVES AND APPLICATIONS

CHARLES N. MOOREFIELD, SUJITH PERERA, AND GEORGE R. NEWKOME

"There are many beautiful molecular architectures, it is just that some are easier to access than others."

Roald Hoffman, Nobel Prize in Chemistry, 1981

1.1. INTRODUCTION

1.1.1. Historical Background

Dendritic chemistry, from its initial development to its application in the construction of utilitarian devices and materials, has provided a great amount of proverbial cement for interdisciplinary integration. Similar to polymer (or macromolecular) chemistry, conceptualized and postulated by luminaries such as Flory [1–3] (Nobel—1974) and Staudinger (Nobel—1953) who provided a new foundation for material sciences, dendrimer chemistry has generated another new level of scaffolding upon which a myriad of potential uses are being explored and exploited.

First introduced as "cascade" molecules due to their repeating motif by Vögtle and coworkers [4] in 1978, materials analogously termed arborols (derived from the Latin word arbor for tree) and dendrimers (derived from the Greek word dendro for tree) were reported by Newkome et al. [5] and Tomalia et al. [6] both in 1985, respectively. While these reports specifically addressed the potential to craft branching molecular architectures with multiple terminal functionality and repetitive branch junctures

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