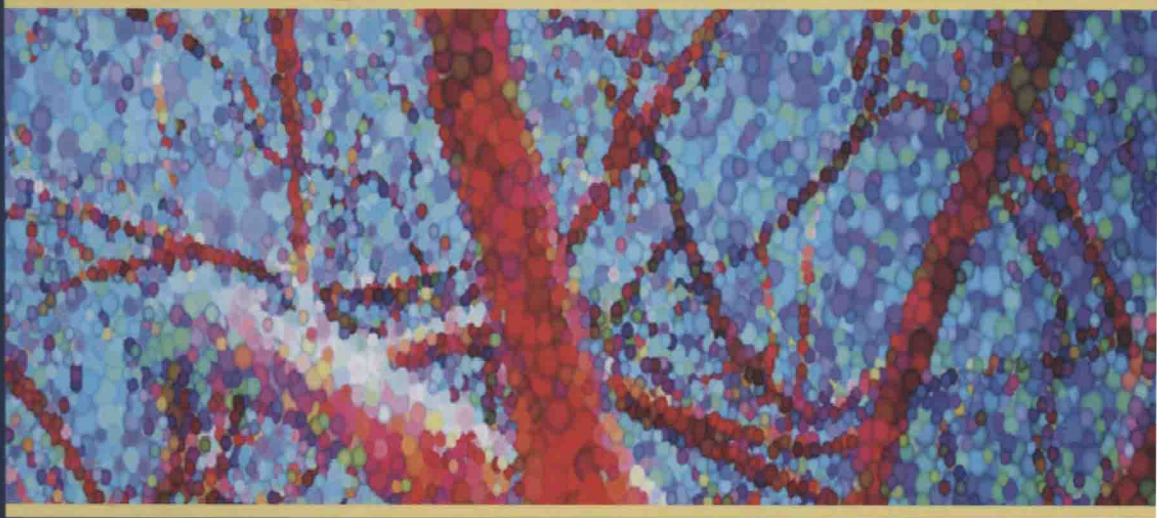
Dendrimers in Nanomedicine



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Preface

Dendrimers are synthetically produced monodisperse polymeric nanostructures with a tree-like, highly branched architecture. They are routinely synthesized as tunable "nanostructures" that may be designed and regulated as a function of their size, shape, surface chemistry, and interior void space. The word "dendron" is also encountered and accounts for "one branch" of the tree or one elementary building block which shows a functionality at its focal point. A variety of dendrimers are available, and each has biological properties such as polyvalency, self-assembling, electrostatic interactions, chemical stability, low cytotoxicity, and solubility. Since the beginning of their history, hundreds of dendritic structures have been elaborated and some of them are now commercially available (Chapter 1). Indeed, dendrimers offer a plethora of applications deriving from the intrinsic properties of polymers but also and especially from their characteristics: on-surface easily accessible functions, porosity, flexibility of the internal branches, presence of functionalized cavities, accessibility to the core, and of course multivalency and cooperativity. These are extremely adaptable materials, with respect to their structure, flexibility, porosity or morphology, which can all be tuned at will.

Nanomaterials, and dendrimers as such, are increasingly becoming part of our daily lives as they are used as imaging agents, coatings, and wound dressings, in cosmetics, and for drug or gene delivery and photodynamic therapy. Their versatile properties lead to their desirability and exploitation in new products and, of course, in competitive production processes.

This book will appeal to anyone involved in nanobiotechnology, macromolecular science, cancer therapy, tissues repair, and siRNA delivery research as it covers research on dendrimer-based or dendrimer–nanoparticles hybrid nanodevices for use in nanomedicine, including aspects from materials sciences, biology, various diagnostic methodologies, and computer simulation.

Chapter 1 is a general introduction on dendrimers summarizing their classical (divergent, convergent, or orthogonal convergent growths) versus accelerated (hypercore approach, hypermonomer method, double-exponential method, the "two-steps approach") syntheses and main characterizations.

The second chapter covers recent advances in dendrimer–nanoparticle conjugates as efficient tools in nanomedicine. It highlights that dendrimer-based organic/inorganic hybrids made of gold, metal oxides (iron, manganese), up-conversion nanoparticles, or quantum dots represent highly advanced pharmaceutical tools, able to target a specific type of cell or organ, to be tracked while doing it, and to deliver a specific drug in situ. For example, due to their high colloidal stability, administration of dendronized hybrids of small size can be done through intravenous injection, which is less intrusive and more efficient and goes toward a "better life" medicine method.

Chapter 3 deals with dendritic polymers for the repair of tissues. As the clinical demands increase for better approaches to repair damaged or diseased tissues, so do the design requirements for the materials to be used. For tissue repair the dendrimers or dendritic macromolecules are crosslinked to form hydrogels. This chapter describes the state of the art with these different dendritic hydrogel formulations, including their design requirements, the synthetic routes, the measurement and determination of their properties, and the evaluation of their in vitro and in vivo performances for tissue repair. Chapter 4 concerns a specific class of dendritic materials called polyglycerols. It not only outlines the chemistry and structural diversification of dendritic polyglycerols (dPGs) but also highlights how forms guide functions through features of dPGs architecture, and ends up to application areas in nanomedicine. Chapter 5 reviews the theranostic potential of dendronized iron oxide nanoparticles and how to master their shapes and compositions to tailor magnetic hyperthermia properties, or how to tune their organic coating to reach efficient magnetic resonance imaging (MRI) contrast enhancement.

The search for new anti-inflammatory drugs is an area of strong interest, related to several health issues, but dendrimer-based anti-inflammatory strategies are rather scarce. Chapter 6 presents different strategies that have been proposed in the past years and among them (i) the cargo-loading approach (non-covalent

association of anti-inflammatory drugs with dendrimers), (ii) the pro-drug approach (anti-inflammatory drugs linked to dendrimers, with a possible control over the drug release), and (iii) dendrimers having intrinsic anti-inflammatory properties.

Chapter 7 is devoted to structurally flexible and amphiphilic poly(amidoamine) dendrimers as non-viral vectors for siRNA delivery. Although viral vectors are very effective for siRNA delivery, increasing concerns over their safety and immunogenicity substantiate the need to develop alternative nonviral vectors. Chapter 7 shows how structurally flexible and amphiphilic PAMAM dendrimers can outperform the commercially available siRNA delivery agents and promote functional siRNA delivery in various cells including human primary and stem cells as well as in animal models.

Chapter 8 reviews dendrimers as nanomedicine in cancer therapy (targeted drug delivery, gene therapy, brain delivery) or as efficient theranostic platforms and gives helpful future prospects.

Then, a detailed chapter on pharmacokinetics and biodistribution issues of dendrimers (Chapter 9) will help the reader choosing the right structures for successful transfer from bench to bedside. This chapter therefore gives an overview of the current understanding of the pharmacokinetic and biodistribution behavior of dendrimers, and how this can be dictated by physicochemical properties. The last chapter (10) is devoted to molecular modeling of dendrimers. Indeed, simulations can provide unique insight into shape, size, and overall features of dendrimers in different conditions, which constitutes the first milestone to understand the dendrimers' properties. In general, computer-aided simulations constitute an important platform to characterize the dendrimers' behavior on a multiscale level: from understanding the features of the dendrimer, to molecular recognition and self-assembly.

Good reading!

Delphine Felder-Flesch

Contents

Chapter 1

General Introduction on Dendrimers, Classical versus Accelerated Syntheses and Characterizations

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1.1 General Introduction

The word "dendrimer" comes from the Greek words, *δένδρον* or *dendros*, which translates to "tree-like" for their shape and *meros* meaning "part of" for the reminiscence of their chemical structure made by additional monomers.[1] In 1978, Egon Buhleier, Winfried Wehner, and Fritz Vögtle were the first to publish a paper on a new type of polymer, the polypropylene-imine (PPI), that was "capable of binding ionic guests or molecules in a Host-Guest interaction, and obtained through a synthetic pathways allowing a frequent repetition of similar steps. These new "cascade molecules," made by a repetitive monomer addition and an activation of the obtained branched molecules, gave birth to a new class of step-by-step synthesized molecules: the dendrimers.[2]

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The first dendrimers published by Fritz Vögtle in 1978[2] were prepared via a *divergent growth* like those elaborated by R. G. Denkewalter at Allied Corporation in 1981,[5] Donald Tomalia at Dow Chemical Co. in 1983 and 1985[1,6] and George Newkome in 1985.[7] The *convergent growth* was later introduced, in 1990, by Jean M. J. Fréchet.[8]

Dendrimers are typically 2 to 20 nm in diameter and are composed of combinations of core types such as ethylene diamine (EDA), diaminobutyl (DAB), polyamidoamine (PAMAM), polypropylimine (PPI). They also have different surface residues such as amine, carboxyl, and alcoholic groups to name but a few.

Dendrimers can be divided in three distinct regions: the core, the interior (or branches), and the periphery (surface groups).

A variety of dendrimers are available, and each has properties such as polyvalency, self-assembling, electrostatic interactions, chemical stability, low cytotoxicity, and solubility. The well-defined molecular compositions, sizes, and shapes of PAMAM dendrimers have also made them particularly attractive as (1) scaffolds for paramagnetic metal ions in magnetic resonance imaging and (2) templates for the synthesis of metal-bearing nanoparticles with tunable electronic, optical, catalytic, and biologic activity.

Since the beginning of their history, hundreds of dendritic structures have been elaborated and among them Vögtle's PPI, Tomalia's polyamidoamine (PAMAM), Denkewalter's poly(L-lysine) (PLL), Newkome's polyamide, Grinstaff's polyester (PGLSA-OH) and Hult's poly(2,2-bis(hydroxymethyl)propionic acid (bis-MPA)) structures.[9] These dendrimers are commercially available from providers like Dendritech Inc. (PAMAM), Frontier Scientific Inc. (Newkome's polyamides), Colcom (poly(L-lysine)), Polymer Factory (bis-MPA), and DSM (PPI).[10]

Dendrimers are often compared to their forebears, the polymers, but they are never obtained by polymerization. Dendritic