**Recent Advances in Targeted Drug Delivery Approaches Using Dendritic Polymers**

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<th>Biomaterials Science</th>
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<td>BM-MRV-10-2014-000351.R1</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Minireview</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>10-Nov-2014</td>
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Recent Advances in Targeted Drug Delivery Approaches Using Dendritic Polymers

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Abstract

Since first synthesized over 30 years ago, dendrimers have seen rapid translation into various biomedical applications. A number of reports have not only demonstrated their clinical utility, but revealed novel design approaches and strategies based on the elucidation of underlying mechanisms governing their biological interactions. This review focuses on presenting the latest advances in dendrimer design, discussing the current mechanistic understandings, and highlighting recent developments and targeted approaches using dendrimers in drug/gene delivery.
1. Introduction

Since their inception in the late 1970s, dendrimers have received a great deal of scientific attention for their unique material properties, developing biomedical applications ranging from therapeutic delivery, to use as diagnostic tools.\textsuperscript{1-4} Recent advances have not only brought about the beginnings of their clinical translation, but have also revealed new insights into their biological interactions, leading to novel design strategies.\textsuperscript{5} As nanoscale (2-20 nm), hyperbranched polymers with a well-defined chemical structure and close-to-monodispersity, dendrimers are particularly well suited for precise size control and surface functionalization, allowing for their modification with drugs, imaging agents, surface charges, and targeting moieties.\textsuperscript{6,7} These unique properties have made them be considered one of the most promising nanocarrier platforms for biomedical applications, including several recent \textit{in vivo} applications and two clinical trials (Table 1). This mini-review will focus on highlighting the key design aspects of these dendrimers and other dendritic nanomaterials, with a focus on their most recent biomedical advances in targeted drug/gene delivery.

2. Characteristics of Dendrimers

2.1 Synthetic Approaches

Dendrimer synthesis can be largely broken down into one of the two methods: convergent and divergent synthesis (Figure 1). Divergent synthesis, a widely adopted method, was first developed by Tomalia and coworkers in the late 1970s, characterized by its radial growth of the dendrimer from the central core components through sequential activation and condensation reactions.\textsuperscript{8,9} However, despite its relatively easy and straightforward synthetic route, this methodology is limited by incomplete reaction coupling, often causing branching defects in the final products.\textsuperscript{2} In order to overcome these complications, many utilize the convergent method developed by Hawker and Frechét, in which individual branched segments, or dendrons, are coupled to a multifunctional core molecule.\textsuperscript{10} While a good method for generating low generation dendrimers, the increased number of reaction steps and steric hindrance of large dendrons make obtaining high yields of greater generation dendrimers problematic using the convergent approaches. A variety of other methods have been developed more recently in an attempt to overcome issues associated with either the divergent or convergent protocols.\textsuperscript{11,12}
These include double-stage convergent growth,\textsuperscript{13} orthogonal synthesis,\textsuperscript{14} double exponential growth,\textsuperscript{15} and orthogonal coupling.\textsuperscript{16} These approaches can be used to produce a wide range of dendritic polymers with potential biomedical applications, most commonly including poly(amidoamine) (PAMAM), poly(L-lysine) (PLL), poly(propylenimine) (PPI), carbosilane (C-Si), triazole-based, polyester, and poly(ethylene oxide) dendrimers.

2.2 Dendritic Polymers as Nanocarriers

Dendrimers have been most heavily explored for their potential as nanocarriers.\textsuperscript{17, 18} Bioactive functional molecules such as therapeutic agents and imaging probes can be either directly conjugated to the surface or encapsulated within the void volume of the polymer itself, of which advantages and disadvantages have been comprehensively outlined elsewhere (Figure 2).\textsuperscript{19} Typically, given that a drug can be chemically modified, conjugation can confer unique advantages over encapsulation, including increased stability and tailored release kinetics via stimuli-responsive cleavable linkers (Figure 2). These traits have been utilized for a variety of targeted cancer applications.\textsuperscript{20} For instance, Satsangi and coworkers recently developed PAMAM dendrimers conjugated to the anticancer drug paclitaxel (PTX) through a cathepsin B cleavable tetrapeptide.\textsuperscript{21} The drug conjugate displayed enhanced efficacy specific to cell lines with greater cathepsin B activity, and demonstrated a greater reduction in tumor size compared to free PTX in an MDA-MB-231 mouse model.

Although chemical conjugation confers unique advantages for targeted delivery, it is limited by the need for drugs with chemically modifiable groups. One approach to overcome this has been to complex with drugs either via encapsulation or electrostatic complexation.\textsuperscript{22-24} It is typically more difficult to obtain high loadings and controlled release profiles from complexed drugs; however, several groups have recently been investigating the ability for surface modification to govern encapsulation and release.\textsuperscript{25, 26} For example, it has been demonstrated that neutral, acetylated PAMAM dendrimers are able to more stably encapsulate the anionic dyes Congo red and indocyanine green compared to cationic, amine-terminated dendrimers.\textsuperscript{27} Similarly, Zhang et al. have demonstrated that the dendrimer surface can be used to tailor the release of the anticancer drug doxorubicin (DOX).\textsuperscript{28} In contrast to carboxyl-modified PAMAM dendrimers that exhibited rapid drug release, their neutral hydroxyl and acetyl-modified counterparts displayed extended release patterns. These findings suggest that surface modification is a viable
method for increasing the stability of dendrimer-drug complexes, allowing for their potential use in vivo.

2.3 Dendrimers as Gene Delivery Vectors

Dendrimers have been used not only for the delivery of small molecules, but have also demonstrated potential for the delivery of oligonucleotides. Cationic, amine-terminated dendrimers are able to complex with the anionic phosphate backbone of DNA and RNA to form stable dendriplexes. These nanoscale complexes are capable of protecting the genetic materials from serum degradation, increasing circulation times, and providing added functionalities such as concurrent drug loading and addition of targeting ligands. Unlike linear cationic polymers, the flexible architecture and surface functionality of dendrimers can be tailored to achieve high delivery efficiencies.

For instance, Zhou and coworkers developed triethanolamine (TEA) core, PAMAM dendrimers which exhibited enhanced flexibility compared to traditional amine core PAMAM dendrimers. Using both computational and experimental techniques, they demonstrated that the increased flexibility allowed for the formation of more stable oligonucleotide-dendrimer complexes, enhancing the delivery and transfection of both plasmid DNA and short interfering RNA.

Another approach for enhancing transfection abilities of dendriplexes is to modify the dendrimer surface. Interestingly, recent reports have demonstrated the ability for fluorination to aid in the transfection of oligonucleotides, specifically due to the ability to achieve high efficiencies at low amine-to-phosphate ratios (N/P). The lower N/P ratios of these dendrimers can decrease their toxicities compared to unmodified amine-terminated dendrimers, supporting their potential for in vivo gene delivery, and may provide a simple method for enhancing dendrimer-mediated transfection without requiring novel synthetic strategies. Wang et al. have demonstrated that partially fluorinated G5 PAMAM dendrimers can display higher cellular uptake than unmodified dendrimers, facilitate endosomal escape, and confer greater transfection in serum containing media than the commercially available Lipofectamine at N/P ratios as low as 0.5-1.5, while maintaining minimal cytotoxicity. Elsewhere, fluorination of benzoic acid-modified dendrimers and PPI dendrimers has demonstrated similar effect of transfection enhancements, including in three-dimensional cell culture models. These findings suggest that fluorination
of dendrimers could be potentially used to overcome the toxicities associated with amine-terminated dendrimers without sacrificing transfection efficiency.

3. Nano-Bio Interactions of Dendritic Polymers

3.1 Pharmacokinetics of Dendrimers

Much of the focus of dendrimers for biomedical applications derives from the ability to tailor their biological interactions through size and surface modifications, allowing them to navigate a wide range of biological barriers.\textsuperscript{5, 42, 43} For instance, dendrimer size and systemic circulation abilities are closely intertwined.\textsuperscript{44} Whereas smaller generation (G2-G4) PAMAM dendrimers are rapidly eliminated through the kidneys, larger dendrimers are typically associated with uptake by the organs of the reticuloendothelial system (RES), as demonstrated by significant liver and spleen accumulation.\textsuperscript{42, 45} Kobayashi and coauthors have suggested that G7 PAMAM dendrimers are able to exhibit the greatest circulation time due to their ability to evade rapid renal clearance, while avoiding the increased RES uptake that plagues G8 and G9 PAMAM dendrimers.\textsuperscript{46, 47} The rapid elimination kinetics has considered one of the drawbacks of dendrimers, hindering the fast translation of dendrimers for systemic approaches. Several strategies for overcoming the decreased circulation time and recognition by the RES system have involved the conjugation of the water soluble, nonfouling polymer poly(ethylene glycol), or PEG, to the dendrimer surface to increase size and water solubility, all with limited immune recognition.\textsuperscript{45, 48-54} Taking it another step further, Wu and coworkers have produced novel G4 oligo(ethylene glycol) (OEG)-based dendrimers for the systemic delivery of gemcitabine (GEM) in solid tumor treatment.\textsuperscript{55} The dendrimer containing the greatest molecular weight of OEG (900 Da) on the surface displayed the most significant enhancement in circulation time, contributing to higher tumor accumulation and permeation than the dendrimers with lower molecular weight OEGs.

Surface charge of dendrimers has also been demonstrated to significantly impact biodistribution, and can be tailored to produce desired effects, regardless of the route of administration.\textsuperscript{43, 45, 50, 56, 57} It has been shown that anionic dendrimers are associated with 10-20 fold enhanced circulation times compared to their cationic counterparts, likely due to decreased non-specific and vasculature binding, in addition to better metabolic stability.\textsuperscript{45, 50} Surface charge can also be
used to modulate the intra-tissue distributions of dendrimers. Our group previously
demonstrated that the transdermal permeation of dendrimers through the outermost layer of skin,
the stratum corneum (SC), is dependent on both size and surface charge of dendrimers, with
neutral or negatively charged G2 PAMAM dendrimers exhibiting greater permeation, while their
larger or cationic counterparts are retained in the skin, most likely due to strong interactions with
the anionic components of the SC.\textsuperscript{57, 58}

3.2 Cellular Interactions of Dendritic Polymers

Just as the pharmacokinetics of dendrimers is governed by size and surface characteristics, they
also play key roles in determining their cellular interactions and toxicities.\textsuperscript{50, 59} Cellular uptake
of dendrimers is a complex, intricate process dependent on a variety of factors, and can largely
govern dendrimer-mediated toxicities.\textsuperscript{7, 60-65} Cationic dendrimers, for example, form strong
electrostatic interactions with the negatively charged lipid bilayers, causing nano-scaled holes to
form thereby destabilizing the cellular membranes, which often leads to significant toxicity.\textsuperscript{61, 62, 66}
Generally, this effect is more prominent at higher generation dendrimers, likely due to the
greater density of positive surface charges and cellular contact area; however, these toxicities can
be overcome through surface modification. Neutral (acetylated) dendrimers have displayed IC\textsubscript{50}
values up to 20 mg/ml (or 400-fold increase), compared to those as low as 50 \(\mu\)g/ml with cationic
dendrimers, suggesting that surface modification is necessary for most biomedical
applications.\textsuperscript{50, 67-71} Additional surface modifications including conjugation with fatty acid and
carbohydrates are also known to decrease the toxicity of dendrimers.\textsuperscript{71, 72}

3.3 Ligand-Mediated Targeting Approaches

Dendrimers provide an ideal platform for forming strong, specific interactions utilizing ligand-
mediated targeting approaches due to their controlled size and surface density, ease of chemical
modification, and ability to deform, allowing for changes in the ligand orientation, promoting
tight specific binding.\textsuperscript{4, 73, 74} Furthermore, this flexibility, along with the hyperbranched structure
that increases the local ligand density, endows them with the ability to utilize the multivalent
binding effect, an observed exponential increase in binding avidity due to the simultaneous
coupling of multiple ligands and their receptors, and commonly displayed by binding
interactions found in nature.\textsuperscript{75-81} Dendrimer-mediated multivalent interactions have been
extensively studied for their targeting ability in several drug-delivery systems, especially for the
treatment of cancer. For example, the targeting of cancer cells overexpressing the folic
acid receptor (FR) through dendrimer conjugation of folate (FA) has been one of the most
heavily studied ligand-mediated targeting strategies. Hong and colleagues quantitatively
measured the binding avidities of G5 PAMAM dendrimers conjugated with folic acid (FA) and
found that binding avidities to folate-binding protein was enhanced up to 170,000-fold compared
to free FA. Interestingly, the exponential increase in binding avidity of the dendrimers were
diminished when more than approximately 7 FA molecules per dendrimer were conjugated,
indicating that an optimal ratio needs to be found depending on the degree of receptor expression
of the target cells and tumors.

Despite these findings, and due to inherent polydispersity in batch preparations of dendrimer
conjugates, the precise mechanistic reasoning for this observation remained elusive until
recently. In order to elucidate the avidity mechanism for the binding of FA-targeted dendrimers
to folate binding protein (FBP), and whether it was due to enhanced statistical rebinding events,
the previously suggested hypothesis, van Dongen and coauthors prepared dendrimers with
precise numbers of FA. Interestingly, on the time scale of the SPR experiments, a minimal
multivalent effect was seen, suggesting that van der Waals interactions between the polymer and
the protein facilitated by the initial FA-FBP binding event were potentially responsible for the
slow-onset, strong binding observed, an alternative mechanism proposed by Licata and
Tkachenko previously.

While dendrimers can be used to target cells with inherent specificity, it should also be noted that
the binding of ligands also has the potential to elicit pharmacological responses. For instance,
Modi et al. developed G5 PAMAM dendrimers conjugated with the follicle stimulating hormone
(FSH) to target tumorigenic ovarian cancer cells through the FSH receptor, but not the healthy
immature primordial follicles. Following intraperitoneal injections, targeted dendrimers
displayed not only significantly greater accumulation in the ovary and oviduct, but the binding to
the FSH receptor also resulted in down regulation of the anti-apoptotic protein survivin, an effect
likely facilitated by receptor-mediated action.

4. Overcoming Limitations Through Hybridization
4.1 Dendritic Block Copolymers

While dendrimers have demonstrated promise for targeted drug delivery applications, they are still plagued by limited drug loading abilities and rapid systemic clearance compared to larger PEGylated nanoparticles. In order to overcome these limitations, several groups have investigated the use of hybrid formulations combining characteristics of dendrimers with those of linear block copolymers, known for a higher drug loading capacity and enhanced circulation times (Figure 3A-B). For example, docetaxel (DTX) was encapsulated in a dendritic block copolymer (DBC)-based micelle delivery system made from semi-PAMAM-b-poly(D,L-lactic acid) (PLA) and demonstrated a prolonged drug clearance compared to a clinically used DTX injection. The paclitaxel-encapsulated DBC-based micelle formulation was reported to exhibit superior in vivo antitumor efficacy compared to Abraxane®, a paclitaxel/human serum albumin nanoaggregate. Recently, our group reported a self-assembled dendritic micelle that contains a hydrophobic core for drug loading and dense PEG exterior for enhanced stealth effect. Furthermore, due to their conical architecture, those PEGylated dendron-based copolymers (PDC) display critical micelle concentrations 1-2 orders of magnitude lower than linear diblock copolymer at comparable hydrophilic-lipophilic balance (HLB). Interestingly, they do not exhibit the surface charge-dependent cellular interactions, which were typically observed in the surface-modified dendrimers. Nevertheless, surface modification of the dendritic micelles has been shown to affect the drug loading capacity of the anticancer drug, as shown in our earlier report where carboxyl-terminated dendritic micelles allowed the most efficient drug encapsulation of endoxifen.

4.2 Hybrid Nanoparticle Formulations

Alternative recent approaches have involved the hybridization of dendrimers with alternative nanocarriers systems, including cyclodextrins, carbon nanotubes, and larger polymeric nanoparticles (NPs). For instance, despite their rapid clearance and limited circulation in vivo, the small size of dendrimers do allow them to exhibit enhanced tissue diffusivity compared to larger PEGylated NPs and utilize strong multivalent binding due to a localized high density of targeting ligands, which are advantageous characteristics in the treatment of solid tumors. In order to take advantage of these traits while protecting the dendrimers from rapid clearance, our group has focused on developing hybrid NPs consisting of FA-targeted G4...
PAMAM dendrimers encapsulated in larger 100-200 nm polymeric NPs composed of poly(ethylene glycol)-b-poly(D,L-lactide) (PEG-PLA) (Figure 3C). The hybrid NPs were able to demonstrate control over the targeting kinetics and release profiles of the encapsulated dendrimers to FR-overexpressing KB cells by modulating the molecular weight of the encapsulating PEG-PLA. Interestingly, following encapsulation the biodistribution and circulation profiles of the dendrimers became similar to those of larger PEGylated NPs, suggesting the protection by encapsulation as a means for enhancing their circulation times. Hybrid NPs also displayed enhanced tumor accumulation compared to targeted dendrimers alone, suggesting that the large size of the NP is able to utilize the enhanced permeability and retention (EPR) effect, known to promote the passive accumulation of NPs between 50-200 nm within the tumor due to impaired lymphatic drainage and leaky vasculature. After accumulating within the tumor, the much smaller dendrimers are expected to release and more efficiently permeate the tumor mass, as demonstrated using a multicellular tumor cell spheroid model.

5. Conclusion

Despite the recently performed intensive studies, novel biomedical applications and mechanistic insights into the use of dendritic polymers are still commonplace. Recently, novel conjugates have been developed, facilitating new targeting approaches and alternative designs to overcome biological challenges. Dendrimers and other dendritic NPs are clearly highly promising platforms, given their modularity tailoring their physicochemical and biological properties to achieve precise targeted outcomes. Despite these promising results, several barriers still limit the clinical translation of dendrimers, including short plasma circulation times, low drug loadings, and difficulties in controlling drug release and scale up of multifunctional dendrimers. Nonetheless, there are currently two dendrimer-based systems that have made it into clinical trials to date, including one for prevention of HIV infection, VivaGel™, and another for delivery of the anticancer drug docetaxel (Source: www.anzctr.org.au). To further expedite their use in the clinic, insights underpinning how dendritic NPs interact with biological systems will need to be obtained. In particular, sophisticated hybridization strategies may provide one such approach for addressing these issues, including the use of dendritic block copolymers or hybrid NPs, as they integrate the advantages of multiple delivery platforms while overcoming barriers associated with individual components.
5. Acknowledgement

This work was supported by NCI/NIH (grant# 1R01CA182528), NSF (grant# DMR-1409161), Alex’s Lemonade Stand Foundation for Childhood Cancer, and Leukemia & Lymphoma Society.
Table 1. Recent advances in the *in vivo* therapeutic applications of dendrimers

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5-Fluorouracil; 5-FU, Poly(amidoamine); PAMAM, Poly(l-lysine); PLL, Poly(ester-amide); PEA, Poly(ethylene oxide); PEO, Polyester; PE, Polyether-copolyester; PEPE, Poly(propylenimine); PPI, AMP; azamonophosphonate, N-acetyl cysteine; NAC
Figure 1. Most widely adopted approaches for dendrimer synthesis are divergent and convergent synthesis (A). Divergent synthesis focuses on the radial growth of dendritic polymers from a central point, whereas convergent approaches ligate individual dendrons to a multifunctional core. Commonly used dendrimers for biomedical applications, including PAMAM (B), PLL (C), PPI (D), C-Si (E), and polyester (F) dendrimers.
Figure 2. Release properties of drug encapsulated and conjugated dendrimers in water and phosphate-buffered saline (PBS). When small molecules are physically encapsulated in the dendrimer structure, the intra-molecular force between the small molecules and dendrimers might not be strong enough to withstand the neutralization of a buffer salt solution, which results in a burst release. In contrast, covalently conjugated small molecules are not released regardless of the ion strength of the solution. Reprinted with permission from *Advanced Drug Delivery Reviews*, 2005, *57*, 2203-2214. Copyright (2005) Elsevier.
Figure 3. Overcoming dendrimer limitations through hybridization. Preparation and self-assembly of PEGylated dendron block copolymers (A) form micelles capable of encapsulating drugs within their hydrophobic core. Dendron micelles (B) exhibit enhanced surface coverage by PEG (red) due to their conical architecture and enhanced stability compared to linear block copolymer micelles. Hybrid NPs (C) formed through dendrimer encapsulation within PEG-PLA NPs protect dendrimer from rapid systemic elimination while encapsulated dendrimers maintain enhanced tissue penetration abilities, as demonstrated in multicellular tumor spheroids. Reprinted in part with permission from Advanced Functional Materials, 2014, 24, 2442-2449 and Molecular Pharmaceutics, 2013, 10, 2157-2166. Copyright (2014) Wiley and (2013) American Chemical Society, respectively.
References


TOC Graphics

Synthesis of Dendrimers and their Modified Nanoparticles