Dendrimers and dendritic polymers in drug delivery

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The unique properties of dendrimers, such as their high degree of branching, multivalency, globular architecture and well-defined molecular weight, make them promising new scaffolds for drug delivery. In the past decade, research has increased on the design and synthesis of biocompatible dendrimers and their application to many areas of bioscience including drug delivery, immunology and the development of vaccines, antimicrobials and antivirals. Recent progress has been made in the application of biocompatible dendrimers to cancer treatment, including their use as delivery systems for potent anticancer drugs such as cisplatin and doxorubicin, as well as agents for both boron neutron capture therapy and photodynamic therapy.

Dendrimers are highly branched, globular macromolecules with many arms emanating from a central core [1,2]. The stepwise synthesis of dendrimers affords molecules with a highly regular branching pattern, a unique molecular weight or a low polydispersity index, and a well-defined number of peripheral groups. Therefore, dendrimers with perfect branching resulting from stepwise synthetic processes are distinct from the more readily accessed but less well-defined hyperbranched polymers with irregular branching obtained by polymerization processes. The first reports of dendrimers were published about two decades ago [3,4], but those early studies focused on their syntheses and their chemical and physical properties, and it is only in the past decade that researchers have begun to explore the potential of dendrimers in biological applications. In recent years, dendrimers have shown promise in fields ranging from gene delivery to magnetic resonance imaging to the development of vaccines, antivirals, antibacterials and anticancer therapeutics [5–8].

The derivatization of low molecular weight and protein-based therapeutics with polymers has been shown to improve their pharmacokinetic and pharmacodynamic properties. For example, the conjugation of polyethylene oxide (PEO) to the proteins interferon α-2b [9] and filgrastim [10] has led to clinical treatments for chronic hepatitis C and chemotherapy-induced neutropenia, respectively. However, the utility of PEO for conjugating low molecular weight drugs is limited by its lack of polyvalency.

A comparison of the features of dendrimers with those of linear polymers shows that the dendritic architecture can provide several advantages for drug delivery applications. For example, the controlled multivalency of dendrimers can be used to attach several drug molecules, targeting groups and solubilizing groups to the periphery of the dendrimers in a well-defined manner. In addition, the low polydispersity of dendrimers should provide reproducible pharmacokinetic behavior in contrast to that of some linear polymers containing fractions with vastly different molecular weight within a given sample. Furthermore, the more globular shape of dendrimers, as opposed to the random coil structure of most linear polymers, could affect their biological properties, leading to the discovery of interesting effects related to macromolecular architecture. Because polymers have shown great promise

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in the development of anticancer drug delivery systems [11], the application of dendrimers in this area is particularly interesting.

The focus of this review is the development of biocompatible dendrimers and their application to a range of methods for treating cancer, including conventional chemotherapeutics, boron neutron capture therapy and photodynamic therapy. In this context, the unique advantages and limitations of dendritic drug delivery systems are highlighted.

Development of biocompatible dendrimers

The rapid emergence of dendrimers in biological applications has been accompanied by a growth in the number of dendrimer backbones designed to be water soluble and biocompatible. Commercially available polyamidoamine (PAMAM) dendrimers (Figure 1a), prepared by the divergent growth approach of Tomalia *et al.* [3], are one of the most widely used dendrimer scaffolds in biology [12]. Despite their broad applicability, it is generally necessary to modify the surface amine groups of these dendrimers with neutral or anionic moieties to avoid the toxicity and liver accumulation associated with their polycationic surfaces [13,14]. Polypropyleneimine dendrimers have been commercialized and investigated for their biological application, but the presence of multiple cationic amine groups leads to significant toxicity [13]. Polyaryl ether dendrimers (Figure 1b), developed by Fréchet and Hawker [15], have been tested for drug delivery applications, but their poor water solubility necessitates the extensive use of solubilizing groups at their periphery [16,17].

In recent years, much effort has been devoted to the preparation of dendrimers that are designed to be highly biocompatible and water soluble. In addition, some dendrimers have been designed to be biodegradable, and monomer units that are chemical intermediates or products in metabolic pathways have been incorporated. For example, several peptide-based dendrimers, such as those based on polylysine (Figure 1c) [18], have been reported, and have been developed as promising vaccine, antiviral and antibacterial candidates after suitable peripheral modifications [19]. In addition, dendrimers incorporating carbohydrate moieties at their core, branch points or periphery have been widely explored and are emerging as promising immunological tools because of their multivalent binding capacity [20,21].

A dendritic analog of the highly biocompatible PEO has been recently prepared by Fréchet and co-workers [22] as a promising backbone for biological applications. Fréchet and colleagues [23,24] have also recently explored polyester dendrimers based on the monomer 2,2-bis(hydroxymethyl)propionic acid (Figure 1d) and their hybrids with PEO as candidates for the development of anticancer drug delivery systems. Various polyester dendrimers incorporating monomers such as glycerol, succinic acid, phenylalanine and lactic acid (Figure 1e) have been prepared by Grinstaff *et al.* [25], and their potential use in tissue engineering has been demonstrated. Dendritic polymers incorporating glycerol monomers have been developed by the groups of Lindhorst [26], Frey [27] and Haag [28] (Figure 1f). Several other dendrimer families, such as the amides synthesized by Schluter *et al.* [29] and the triazines produced by Simanek *et al.* [30], might also prove to be useful for biological applications.

Delivery of anticancer drugs by dendrimers and dendritic polymers

In addition to improving drug properties such as solubility and plasma circulation time [31], polymeric carriers can also facilitate the passive targeting of drugs to solid tumors [32]. This targeting is possible because of the increased permeability of tumor vasculature to macromolecules and because of limited lymphatic drainage. Combined, these factors lead to the selective accumulation of macromolecules in tumor tissue – a phenomenon termed the 'enhanced permeation and retention' (EPR) effect. The unique properties of dendrimers, when compared with linear polymers, make them interesting candidates for the development of delivery systems for anticancer drugs.

Noncovalent encapsulation of drugs

Initial studies of dendrimers as potential delivery systems focused on their use as unimolecular micelles and 'dendritic boxes' for the noncovalent encapsulation of drug molecules. For example, in early studies, DNA was complexed with PAMAM dendrimers for gene delivery applications [33], and hydrophobic drugs and dye molecules were incorporated into various dendrimer cores [34–37]. An advantage of using dendritic unimolecular micelles rather than conventional polymeric micelles is that the micellar structure is maintained at all concentrations because the hydrophobic segments are covalently connected. However, this approach suffers from a general drawback in that it is difficult to control the release of molecules from the dendrimer core. In some cases, harsh conditions are required [35], whereas in others the encapsulated drug is not well retained and the molecules are released relatively rapidly [16,38].

Although the introduction of stabilizing PEO chains on the dendrimer periphery has expanded the scope of dendritic unimolecular micelles to incorporate anticancer drugs such as 5-fluorouracil [39], methotrexate [38] and doxorubicin [38] and can slow the drug release rates in these systems to some extent, this method has yet to be demonstrated as a general strategy. A promising new approach to controlling the release of drugs from the encapsulating micellar compartment involves the use of hybrids of PEO and dendrimers with pH-sensitive hydrophobic acetal groups on the dendrimer periphery [40]. Loss of the hydrophobic groups on acetal hydrolysis at mildly acidic pH triggers disruption of the micelle and release of the payload.

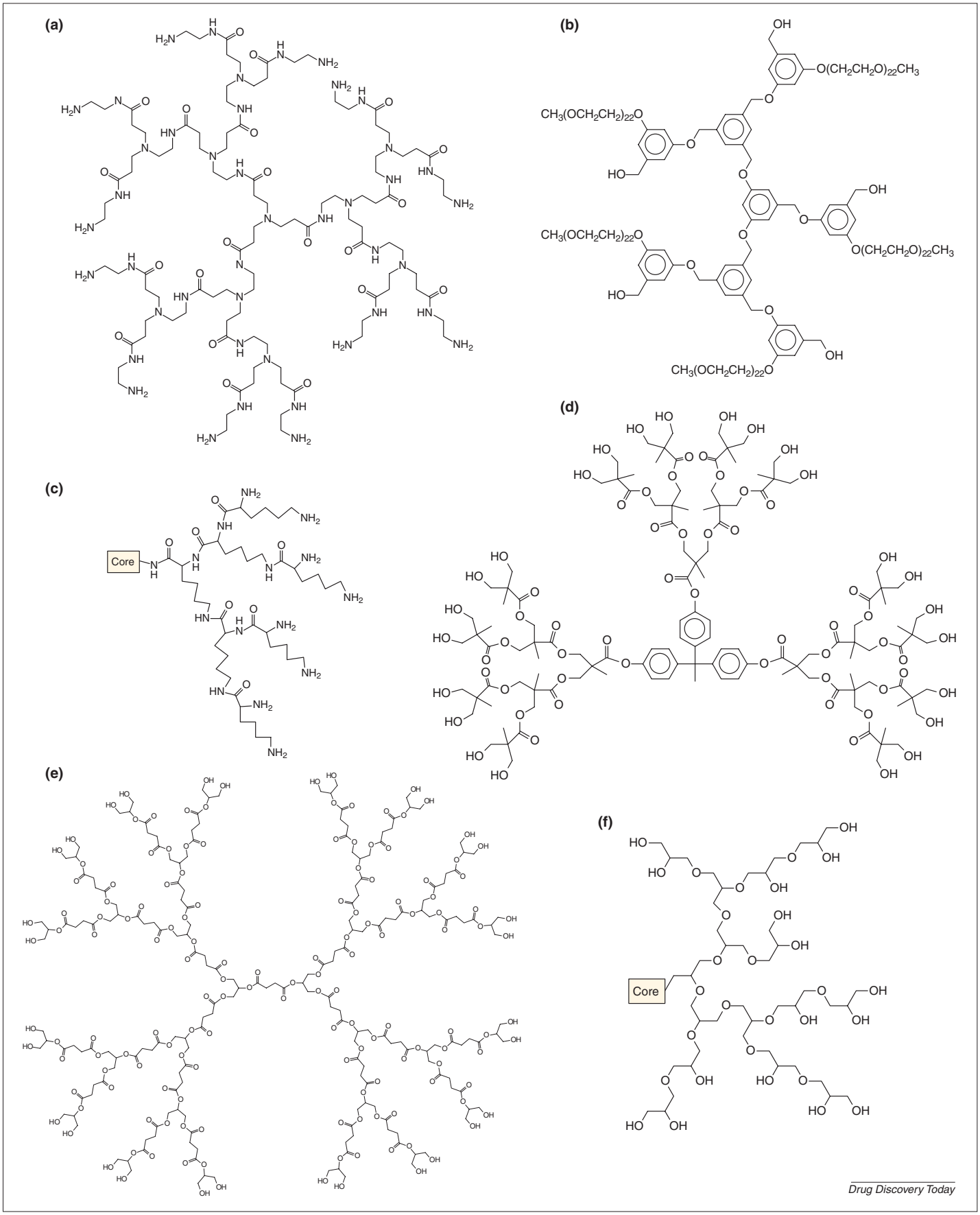

FIGURE 1

Structures of biocompatible dendrimers that have been tested for drug delivery applications. (a) PAMAM dendrimer. **(b)** Polyaryl ether dendrimer. **(c)** Polylysine dendron. **(d)** Polyester dendrimer based on 2,2-bis(hydroxymethyl)propionic acid. **(e)** Polyester dendrimer based on glycerol and succinic acid. **(f)** Dendritic polyglycerol.

Covalent dendrimer–drug conjugates

An alternative approach to the development of dendrimers as anticancer drug carriers is to exploit their well-defined multivalency for the covalent attachment of drug molecules to the dendrimer periphery. The drug loading can be tuned by varying the generation number of the dendrimer, and release of the drug can be controlled by incorporating degradable linkages between the drug and dendrimer. For example, Duncan and co-workers [41,42] have prepared conjugates of PAMAM dendrimers with cisplatin, a potent anticancer drug with nonspecific toxicity and poor water solubility. The conjugates show increased solubility, decreased systemic toxicity and selective accumulation in solid tumors. Furthermore, the dendrimer–platinum complex has been found to show increased efficacy relative to cisplatin in the treatment of subcutaneous B16F10 melanoma. In addition, Zhou *et al.* [43] have described the preparation of PAMAM dendrimers from a cyclic tetraamine core and the subsequent attachment of 5-fluorouracil to the dendrimer periphery. These conjugates release free 5-fluorouracil on incubation in phosphate-buffered saline.

Conjugates of the antitumor agent Ara-C and PEO–dendrimer hybrids have been prepared by two different approaches. In one study, the dendron was based on aspartic acid units and Ara-C was conjugated via its amine group by various linkers including amides and carbamates [44]. In a separate study, the bicarboxylic amino acid L-2-aminoadipic acid provided the branching unit of the dendron, and the amine of Ara-C was conjugated directly to the peripheral carboxylic acid groups of the dendron [45]. This prodrug strategy was found to improve the blood residence time of the drug and to increase its stability towards degradation. Starlike carriers of the anticancer drug doxorubicin have been prepared by the conjugation of poly[*N*-(2-hydroxypropyl)methacrylamide] macromonomers to PAMAM dendrimers, followed by attachment of the drug to the polymer arms by a biodegradable peptide spacer. The compact structure of the star polymer results in slower rates of enzyme-mediated drug release, thereby decreasing the cytotoxicity of the conjugate [46].

In early studies directed at developing drug carriers with tumor cell specificity, Fréchet and co-workers [47] prepared multivalent conjugates of folic acid or the antitumor drug methotrexate and polyaryl ether dendrimers. Although the presence of several copies of folic acid or the hydrophilic drug molecule on the periphery of the dendrimer renders these conjugates water soluble, the water solubility of the polyaryl ether dendrimers can be increased further by attaching PEO chains to the periphery [16]. By using a careful synthetic strategy with two different chain end functionalities, it is also possible to attach both hydrophobic model drugs and PEO moieties to the dendrimer periphery in a controlled manner [17]. These model studies provided an early demonstration of the advantage of the stepwise synthesis and the controlled multivalency of dendrimers for drug delivery.

The preparation of multivalent folic acid conjugates of dendrimers [47] has important implications for targeting to tumor cells, and the multivalent character of dendrimers facilitates the attachment of various payloads, including targeting, diagnostic and therapeutic molecules, as well as combinations of these agents. Because expression of the folate receptor is amplified in several human cancers and restricted in most normal tissues [48], folic acid is an interesting candidate for the active targeting of dendrimer–drug conjugates to tumors. Inspired by the concepts of Esfand and Tomalia [12], and the multivalent dendrimer–folate and dendrimer–methotrexate conjugates of Fréchet and co-workers [47], Quintana *et al.* [49] prepared analogous PAMAM dendrimers with methotrexate conjugated to their periphery via either a stable amide or an ester linkage that could be hydrolyzed under biological conditions. As expected, the introduction of folic acid into these conjugates was found to enhance their cellular uptake, resulting in an increase in cytotoxicity of the methotrexate ester conjugate relative to that of the free drug *in vitro*.

Aliphatic polyester dendrimers based on 2,2-bis(hydroxymethyl)propionic acid are promising dendrimer backbones for the development of anticancer drug conjugates. In initial studies, a water-soluble polyester dendrimer was found to be biocompatible *in vitro* and *in vivo* [24]. Biodistribution studies in mice showed that the fourth-generation dendrimer with a molecular weight of 3800 had a circulation half-life of less than 10 min and was rapidly excreted in the urine. Although the observed lack of accumulation of the dendrimer in vital organs is a desirable feature for many biological applications, a longer half-life is required to obtain passive tumor targeting via the EPR effect.

Because the rate of renal filtration is based on hydrodynamic volume, such that larger molecules are eliminated more slowly [50], one approach to increasing the half-life is to make the dendrimer larger. However, the synthetic preparation of well-defined high-generation dendrimers is time consuming and, as a result of the globular architectures of the dendrimers, the increase in hydrodynamic volume is modest. In an alternative approach, hybrids of polyester dendrimers and PEO star polymers have been prepared (Figure 2a) with an increase in molecular weight to 22,000 [23]. PEO was chosen because it is highly biocompatible [51] and available in low polydispersity (polydispersity index of 1.02), thereby providing hybrids with similar polydispersity. Hybrid polymers conjugated to doxorubicin via a hydrazone linkage have been prepared. The hydrazone linkage is stable at the physiological pH of 7.4, but is designed to undergo hydrolysis on uptake of the polymers by endocytosis and subsequent trafficking of the conjugate to mildly acidic subcellular organelles

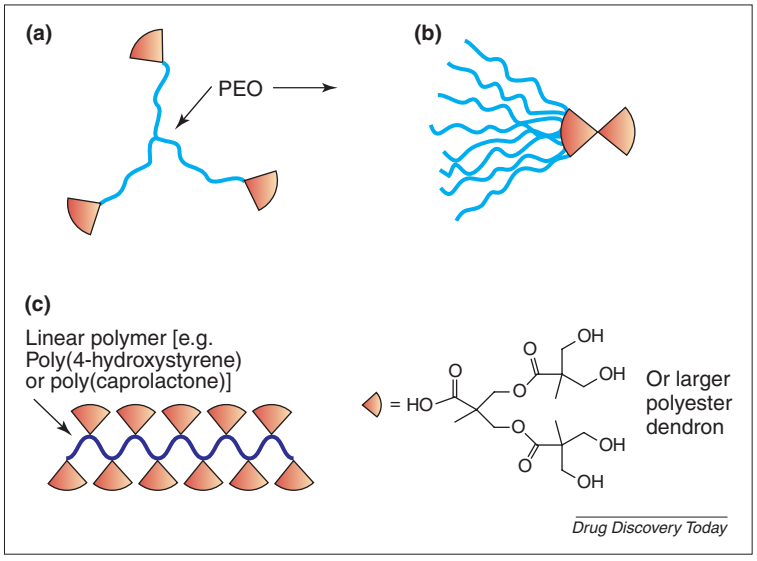

FIGURE 2

Polyester dendrimer-linear polymer hybrids. (a) Hybrid of polyester dendrons and a PEO star in which the multivalent dendron can carry several copies of drug and the linear PEO provides solubility. **(b)** 'Bow-tie' hybrid of polyester dendrimers and PEO. **(c)** Polyester dendronized linear polymer.

such as endosomes and lysosomes [52]. These drug conjugates show an increased circulation time of more than 1 h and are toxic to a range of tumor cell lines [24]. Evaluation of these hybrids of polyester dendrimers and PEO star polymers as anticancer drug delivery systems is ongoing.

In addition to supplying a multivalent backbone for drug attachment, dendrimers also provide access to various new polymer architectures that are potentially relevant to drug delivery applications. For example, we [53] have recently prepared 'bow-tie' hybrids of polyester dendrimers and PEO (Figure 2b) with various molecular weights and architectures by tuning the number of PEO arms and their molecular weights. A library of polymers with molecular weights ranging from 20,000 to 160,000 was prepared. These new carriers are nontoxic and biodegradable *in vitro*, and biodistribution studies *in vivo* show that carriers with a molecular weight of more than 40,000 are generally long circulating with half-lives greater than 24 h. The more branched carriers are excreted at a slower rate into the urine by glomerular filtration, probably as a consequence of their decreased flexibility and ability to reptate (axially diffuse) through pores relative to linear polymers. Considerable levels of the high molecular weight, long-circulating bow-tie polymers accumulate in subcutaneous B16F10 solid tumors via the EPR effect, making these carriers promising for chemotherapy applications.

Recent developments in polymer and dendrimer chemistry have also provided access to a new class of macromolecules termed 'dendronized polymers' – that is, linear polymers that bear dendrons at each repeat unit. As a result of steric interactions, at high-generation numbers, dendronized polymers are thought to attain extended, rigidified conformations. Grayson and Fréchet [54] and Lee *et al.* [55] have prepared polyester dendronized polymers bearing polyester dendrons based on backbones ranging from nondegradable poly(4-hydroxy)styrene [54] to biodegradable polymers such as substituted polycaprolactone (Figure 2c) [55]. In recent biodistribution studies, these molecules have shown interesting pharmacokinetic behavior, differing from that displayed by linear polymers with equivalent molecular weight and hydrodynamic volume. Furthermore, as a result of their long circulation half-lives and numerous peripheral groups for the attachment of drugs, targeting moieties and solubilizing groups, these polymers also show promise for drug delivery applications.

Application of dendrimers to boron neutron capture therapy

Boron neutron capture therapy is a cancer treatment based on a nuclear capture reaction [56,57]. When ^{10}B is irradiated with low energy or thermal neutrons, highly energetic α-particles and ^{7}Li ions are produced that are toxic to tumor cells. To achieve the desired effects, it is necessary to deliver ^{10}B to tumor cells at a concentration of at least 10^9 atoms per cell. High levels of boron in tumor tissue can be achieved by using boronated antibodies that are targeted towards tumor antigens [58]; however, the direct attachment of large numbers of boron-containing molecules to antibodies can impair the solubilities and targeting efficiencies of the antibodies [59].

The use of dendrimers as boron carriers for antibody conjugation was inspired by their well-defined structure and multivalency. A representation of a targeted dendritic carrier for boron neutron capture therapy is shown in Figure 3. In initial studies, Barth *et al.* [60] conjugated isocyanato polyhedral borane $[Na(CH_3)_3NB_{10}H_8NCO]$ to the periphery of second- and fourth-generation PAMAM dendrimers [60]. The boronated dendrimers were then conjugated to the monoclonal antibody IB16-6, which is directed at the murine B16 melanoma. However, in biodistribution studies, the conjugates accumulated in the liver and the spleen.

In subsequent studies, boronated PAMAM dendrimers were designed to target the epidermal growth factor (EGF) receptor, a cell surface receptor that is frequently overexpressed in brain tumors [61]. The dendrimers were covalently linked to EGF and the resulting conjugates were found to be effectively endocytosed *in vitro*, resulting in an accumulation of boron in cell lysosomes [62]. However, on intravenous injection into rats bearing intracerebral implants of a C6 glioma transfected with the gene encoding the EGF receptor, these boron carriers were taken up by the liver and showed low levels of accumulation in the tumor [63].

Another approach to targeting the EGF receptor has involved the conjugation of a [G-5] PAMAM dendrimer carrying 1100 boron atoms to cetuximab, a monoclonal

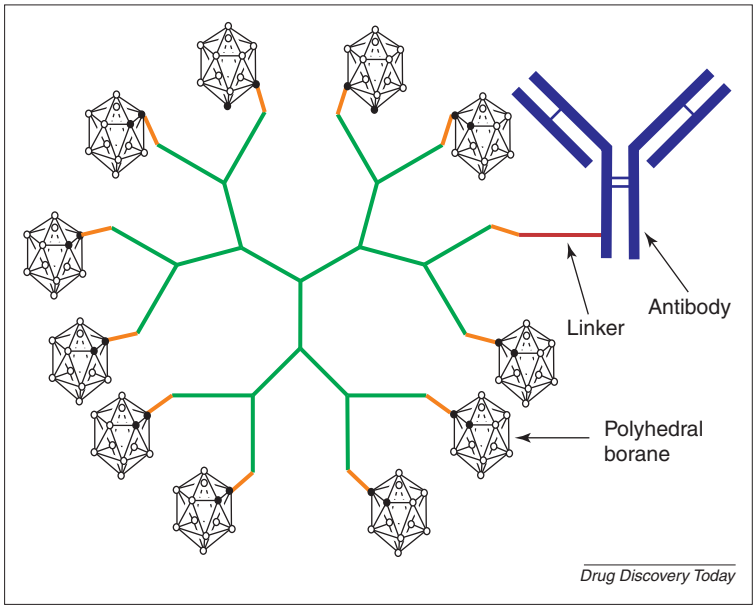

FIGURE 3

An antibody-targeted dendritic boron carrier for boron neutron capture therapy.

antibody specific for the EGF receptor [64]. *In vivo* studies showed that, after intratumoral injection, the conjugates were present at an almost tenfold greater concentration in brain tumors than in normal brain tissue. This conjugation strategy has the added benefit that cetuximab itself can lead to cell cycle arrest by blocking the binding of EGF and transforming growth factor-α, both of which are involved in cell signaling pathways, thereby providing a synergistic effect [65].

To reduce the liver uptake observed for boronated PAMAM dendrimer conjugates, researchers have recently introduced PEO chains, in addition to borane clusters, to the dendrimer periphery to provide steric shielding [66]. As compared with a dendrimer with no PEO chains, the amount of liver uptake was found to be less for some PEO-conjugated dendrimers (e.g. those with an average of 1.0–1.5 chains of PEO with a molecular weight of 2000), but higher for other dendrimers with more PEO chains (e.g. those with 11 chains of PEO with a molecular weight of 550). Folic acid moieties were also conjugated to the ends of the PEO chain to enhance the uptake of the dendrimers by tumors overexpressing folate receptors [66]. Although this strategy was successful in enhancing localization of the molecules to tumors in mice bearing 24JK-FBP tumors expressing the folate receptor, it also led to an increase in uptake of the dendrimers by the liver and kidneys. Because the uptake of these dendrimers by the reticuloendothelial system appears to depend on various factors, further investigation is necessary to optimize their performance.

Polylysine dendrimers with several carborane moieties on the periphery and a peptide spacer at the focal point have also been prepared [67]. The peptide spacer contains a cysteine residue with a reactive thiol for selective coupling to targeting molecules such as antibodies. A fluorescent dansyl group and PEO chain can be also conjugated to the linker for spectroscopic monitoring and water solubility, respectively. A single carborane cluster has been coupled to a dendritic polyalcohol for water solubility by Yamamoto and co-workers [68]; by contrast, Newkome *et al.* [69] have covalently incorporated carboranyl groups near the core of dendritic unimolecular micelles. However, to the best of our knowledge, a full biological evaluation of these systems has not been reported.

Dendrimers in photodynamic therapy

One of the newest developments in the dendrimer field is their application to photodynamic therapy (PDT). This cancer treatment involves the administration of a light-activated photosensitizing drug that selectively concentrates in diseased tissue [70]. Subsequent activation of the photosensitizer leads to the generation of reactive oxygen species, primarily singlet oxygen, that damage intracellular species such as lipids and amino acid residues through oxidation, ultimately leading to cell death. Some disadvantages of the currently used photosensitizer systems include skin phototoxicity, poor selectivity for tumor tissue, poor water solubility and difficulties in the treatment of solid tumors because of the impermeability of skin and tissues to the visible light required to excite the chromophores.

The possibility of improving the properties of dendrimers through appropriate functionalization of their periphery makes dendrimers promising carriers for photosensitizers. The use of 5-aminolevulinic acid (ALA) is one approach to PDT based on dendrimers. ALA is a natural precursor of the photosensitizer protoporphyrin IX (PIX), and its administration is known to increase cellular concentrations of PIX [71]. In this approach, tumor selectivity is based on increased levels of heme biosynthesis and decreased levels of heme degradation in tumor cells. Edwards and co-workers [72] have prepared well-defined dendritic molecules with up to 18 ALA moieties conjugated to the periphery by ester linkages that can be hydrolyzed in cellular conditions. This delivery vehicle has been shown to result in increased production of PIX relative to free ALA and in higher toxicity after irradiation. To develop these molecules further for *in vivo* applications, it will probably be necessary to improve their tumor targeting properties by increasing their molecular weight or by conjugating them to a targeting signal.

Polyaryl ether dendrimer porphyrins with either 32 quaternary ammonium groups (cationic) or 32 carboxylic acid (anionic) groups on their periphery have been prepared [73] and compared with PIX. The dendrimeric porphyrins and PIX were found to have similar photophysical properties but different properties in cell culture. In contrast to PIX, which can diffuse across plasma

membranes, experimental results suggested that the dendrimers entered cells by endocytosis and that the cationic dendrimer entered cells more rapidly. Furthermore, although PIX was present throughout the cell (except the nucleus), as assessed by its diffuse fluorescence in confocal microscopic images, the dendrimers remained localized in intracellular compartments such as lysosomes. Although both dendrimers showed a lower toxicity in the dark than PIX, the cationic dendrimer was significantly more toxic than PIX after photoirradiation. The increased toxicity of the cationic dendrimer porphyrin is thought to result from its electrostatic association with cell membranes.

To improve the potential of this promising PDT system for *in vivo* applications, cationic dendrimer porphyrins have been electrostatically assembled with linear PEO–polyaspartic acid block copolymers to form spherical micelles [74]. The PEO surface of these micelles is designed to prolong the circulation of the carriers in the blood and to enhance tumor accumulation mediated by the EPR effect. In comparison to the dendrimer porphyrin alone, the cellular uptake of the micelles was found to be three times slower but, when normalized to the amount of porphyrin taken up, the micelles showed about 40 times greater photodynamic efficacy. This has been attributed to the decreased tendency of the micellar dendrimer porphyrin to aggregate under physiological conditions, resulting in a higher yield of singlet oxygen. A potential disadvantage of this system is that only one drug molecule can be loaded in each micelle. The dendrimer porphyrins used in the study have an absorption maximum at 559 nm, and the development of photodynamic systems with increased absorbance at longer wavelengths is desirable because of the increased permeability of tissue to near-infrared and infrared light. Towards this goal, water-soluble polymer conjugates of metallo-phthalocyanines with an absorption maximum at 675nm have been prepared [75].

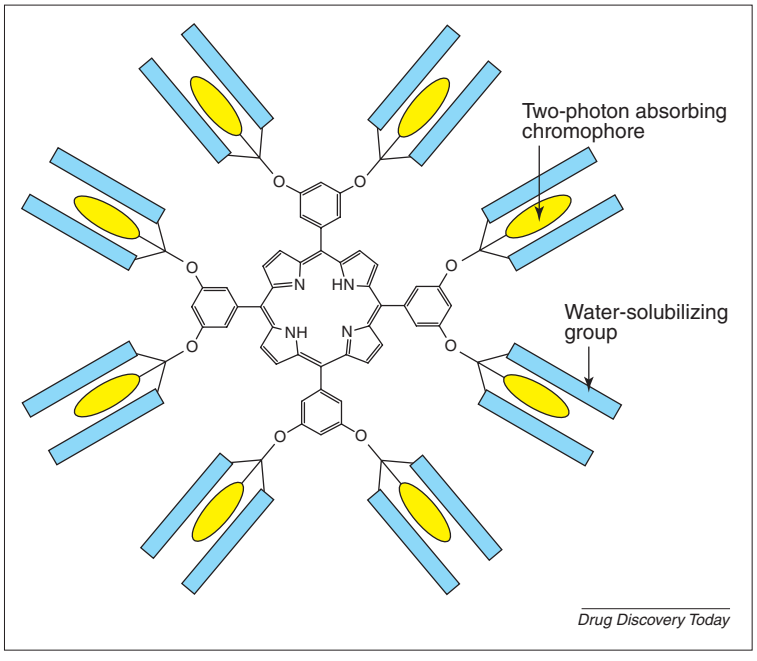

FIGURE 4

A water-soluble dendrimer porphyrin incorporating two-photon absorbing chromophores for photodynamic therapy.

Another approach with great promise for deeper tissue penetration is based on two-photon excitation with near-infrared lasers [76]. Because the possibility of two-photon absorption depends quadratically on the intensity of incident light, this process also provides the opportunity for increased spatial resolution in treating tumors through irradiation with one or more focused laser beams. Although the cross-section of two-photon absorption is typically small, when compared with that of one-photon absorption, Fréchet and co-workers [77] have recently used the multivalent aspect of the dendrimer scaffold to conjugate several two-photon absorbing chromophores to a porphyrin core. This system has been shown to generate singlet oxygen efficiently on irradiation at 780 nm. Current studies are aimed at preparing a water-soluble system through the attachment of several solubilizing groups to the dendrimer periphery (Figure 4).

Conclusions and future prospects

The application of dendrimers to biological systems has experienced rapid growth in the past decade. Recent research has shown that dendrimers are useful tools for studying fundamental problems and, with their desirable globular structure and polyvalent character, they can also present practical solutions to drug delivery issues such as solubility, biodistribution and targeting. Similarly, dendritic structures are likely to find uses in applications involving multifunction nanoparticulate systems combining targeting, imaging, diagnostics and therapy.

One of the areas that remain to be addressed in more detail is the biodistribution behavior of dendrimers. For example, it is still a challenge to prepare dendritic polymers that circulate in the blood long enough to accumulate at target sites, but that can be also eliminated from the body at a reasonable rate to avoid long-term buildup. In addition, the tissue localization of dendritic polymers is still difficult to predict in advance and more studies are required to determine the effect of peripheral dendritic groups on these properties. An additional area that has just begun to be investigated is the release of drugs from dendritic polymers. The steric hindrance associated with the dense globular dendritic architecture makes the engineering of enzymatically cleavable linkages difficult; however, dendrimers are useful scaffolds for the exploitation of various alternative release mechanisms including cascade release. Some work in this area has been recently reported [78–80].

Although the additional effort required for the stepwise synthesis of large dendrimers means that these molecules must possess distinct advantages over their linear polymer analogs to be useful in practical terms, recent research has shown that dendrimers do indeed have many unique features

that warrant their further exploration in drug discovery.

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