Poly(amidoamine) (PAMAM) dendrimers: from biomimicry to drug delivery and biomedical applications

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Poly(amidoamine) (PAMAM) dendrimers are the first complete dendrimer family to be synthesized, characterized and commercialized. Based on this extensive activity, they are recognized as a unique new class of synthetic nanostructures. Dendrimers allow the precise control of size, shape and placement of functional groups that is desirable for many life science applications. From this perspective, this review focuses on crucial properties of biomimetic dendrimers that will broaden the potential for their use as macromolecular vectors in novel drug delivery and biomedical applications.

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▼ Dendritic architecture is undoubtedly one of the most pervasive topologies observed universally throughout biological systems. These patterns are found at virtually all dimensional length scales (a term that refers to the best use of space). They appear in many diverse prototypes including those that can be measured in m (e.g. tree branching and roots), in circulatory topologies in the human anatomy (e.g. lungs, kidney, liver, spleen) that are found in mm and cm, or in cerebral neurons in µm. The reasons for such extensive mimicry at all dimensional length scales is not entirely clear. However, it could be speculated that these architectures have evolved to provide maximum interfaces for optimum energy extraction and distribution, nutrient extraction and distribution or information storage and retrieval. To our knowledge, there are only two examples of molecular level (nm) dendritic structures in biological systems; in each case, they are derived from polysaccharides. These include glycogen, amylopectin and proteoglycans. The former is involved in energy storage in plants and animals, and the latter are important constituents that determine the viscoelastic properties of connective tissue.

On analysis of these ubiquitous dendritic patterns it is evident that these highly branched architectures offer unique interfacial and functional performance advantages at all levels in the biologic hierarchy. The object of this review will be to study the biomimicry of various natural biological entities found in dendrimers and to track the influence that these properties have had on the development of dendrimers and on their commercial use in several life science applications. Particular emphasis will be placed on the first and most extensively studied family of dendrimers; namely, the poly(amidoamine) (PAMAM) dendrimers.

Synthesis of dendritic architecture

Staudinger initiated a synthetic macromolecular revolution 65 years ago, with the introduction of his 'macromolecular hypothesis'[1]. This seminal event has led to the evolution of three major macromolecular architectures, namely: linear (class I), cross-linked (bridged; class II) and branched types (class III). These three architectural classes are recognized as traditional synthetic polymers. In all these classes, structures or architectures are produced by largely statistical polymerization processes, rather than exact distribution processes (Fig. 1). These processes produce polydispersed (i.e. M_w/M_n >2–10) products of many different molecular weights. In general, these are not structure-controlled macromolecular architectures such as those observed in biological systems. However, considerable progress has occurred recently in the areas of living anionic[2], cationic[3] and radical polymerizations[4].

As early as 1979 the first synthetic strategies to produce monodispersed, structure-controlled,

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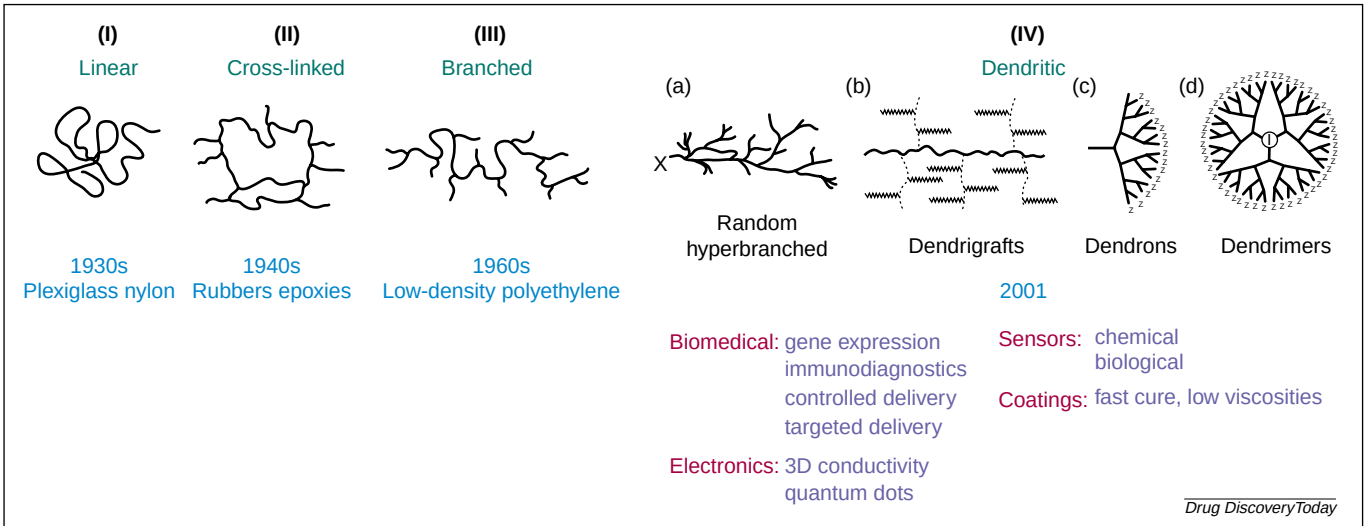

Figure 1. Four major classes of macromolecular architecture. Traditional synthetic polymers: (I) linear, (II) cross-linked (bridged) and (III) branched. Structure controlled polymers (IV) dendritic.

dendritic macromolecules in ordinary laboratory glassware were initiated[5]. Although dendrimer structures exhibit structural control reminiscent of biological systems, the synthetic approaches did not require biological components. They did, however, involve significant innovation and digression from classical organic synthesis methods. Commercial quantities (kg) of controlled macromolecular structures with polydispersities of 1.0005–1.10 are now routinely synthesized using traditional organic reagents and monomers, such as ethylenediamine and alkyl acrylates. These new structures are referred to as dendrons or dendrimers.

Since 1979[6], two major strategies have evolved for dendrimer synthesis. The first was the divergent method in which growth of a dendron (molecular tree) originates from a core site (root) (Fig. 2). During the 1980s, virtually all dendritic polymers were produced by construction from the root of the molecular tree. This approach involved assembling monomeric modules in a radial, branch-upon-branch motif according to certain dendritic rules and principles[7]. This divergent approach is currently the preferred commercial route used by worldwide producers including Dendrimax (Ann Arbor, MI, USA), DSM Fine Chemicals (Geleen, The Netherlands) and The Perstorp Group (Perstorp, Sweden).

A second method that was pioneered by Fréchet and colleagues[8] is the convergent growth process. It proceeds from what will become the dendron molecular surface (i.e. from the leaves of the molecular tree) inward to a reactive focal point at the root (Fig. 2). This leads to the formation of a single reactive dendron. To obtain a dendrimer structure, several dendrons are reacted with a multi-functional core to yield such a product. Using these two synthetic

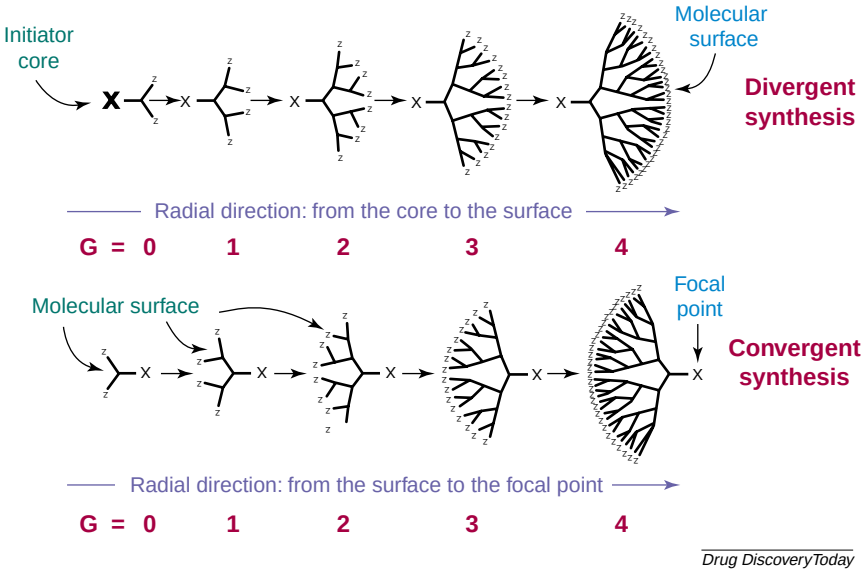

Figure 2. Two principle synthetic methods for constructing dendritic macromolecules (dendrons): **(a)** the divergent method, in which the synthesis begins from a polyfunctional core and continues radially outwards by successive stepwise activation and condensation, **(b)** the convergent method in which the synthesis begins at what will be the periphery of the final macromolecule and proceeds inwards.

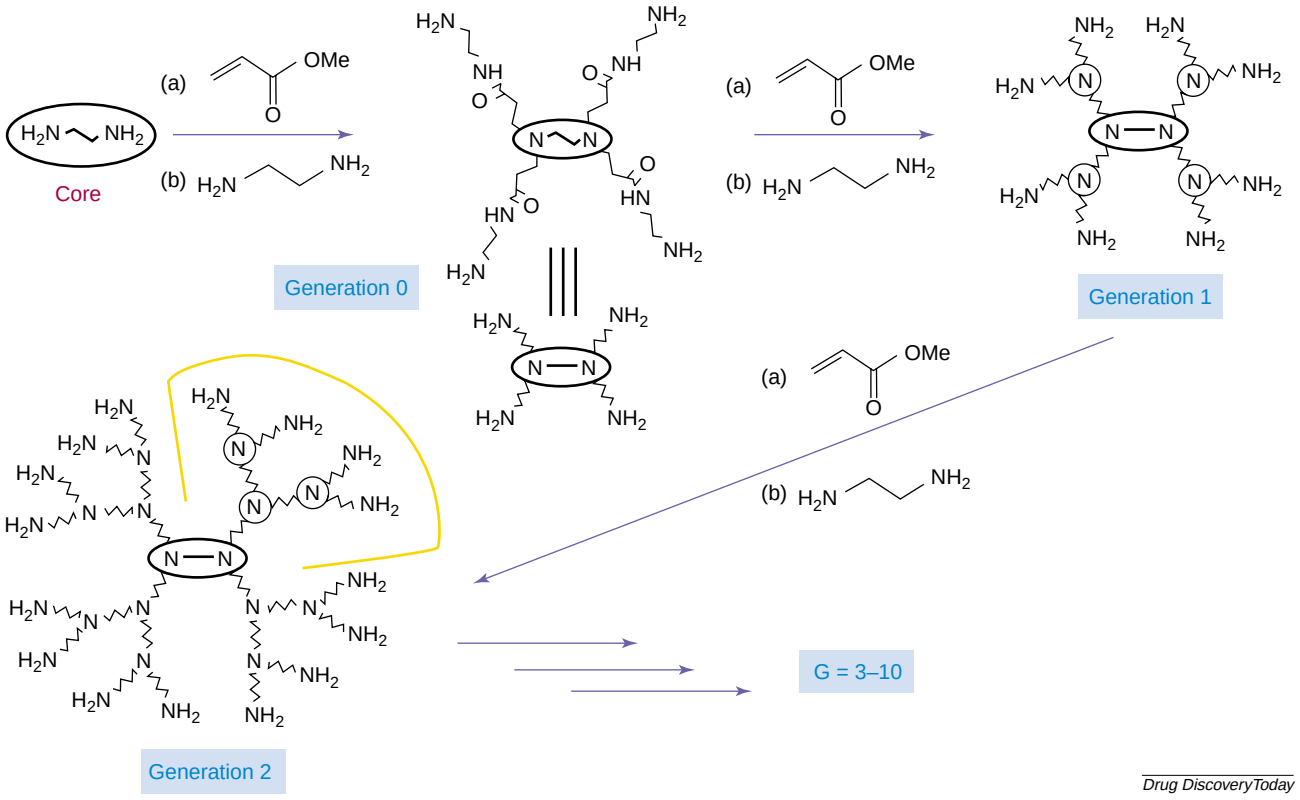

Figure 3. Synthesis of tetra-functional poly(amidoamine) (PAMAM) dendrimers: exhaustive Michael addition of amino groups with methyl acrylate, followed by amidation of the resulting esters with ethylenediamine.

strategies, >100 compositionally different dendrimer families have been synthesized and these are reviewed in other literature[9–13].

Box 1. Propagation mathematics

Where: N_c = core, N_b = branch cell multiplicities and G = generation. Mathematically defined values for surface groups (Z), molecular formulae and molecular weights (MW) as a function of generation for the (ethylenediamine core) poly(amidoamine) (PAMAM) dendrimer family.

Number of surface groups $(Z) = N_c N_b^G$

Number of branch cells $(BC) = N_c\left[\frac{N_b^G - 1}{N_b - 1}\right] =$ Number of covalent bonds formed/generation

Molecular weights $(MW) = M_c + N_c\left[M_{RU}\left(\frac{N_b^G - 1}{N_b - 1}\right) + M_t N_b^G\right]$

PAMAM dendrimers were the first complete dendrimer family to be synthesized, characterized and commercialized[6,14]. They are synthesized by the 'divergent' method. This method involves a two-step iterative reaction sequence that produces concentric shells (generations) of dendritic β-alanine units around a central initiator core (Fig. 3). This PAMAM core-shell architecture grows linearly in diameter as a function of added shells (generations). Meanwhile, the surface groups amplify exponentially at each generation according to dendritic-branching mathematics described in Box 1. As a consequence, 'tethered congestion' occurs at a certain generation to produce 'geometrically closed' nanostructures that exhibit guest–host container properties, which will be discussed later.

For the PAMAM dendrimer family (Fig. 3), initiated from an ethylenediamine core ($N_c = 4$) with a branch cell multiplicity ($N_b = 2$), the expected mass values of 517, 1430, 3256, 6909, 14,215 and so on, double, approximately, from generation to generation. These values are verified routinely by electrospray or matrix-assisted laser desorption mass spectroscopy (MALDI) methods. Polydispersity values (M_w/M_n) are routinely obtained that range from 1.000002–1.005 for this series. The diameters of these

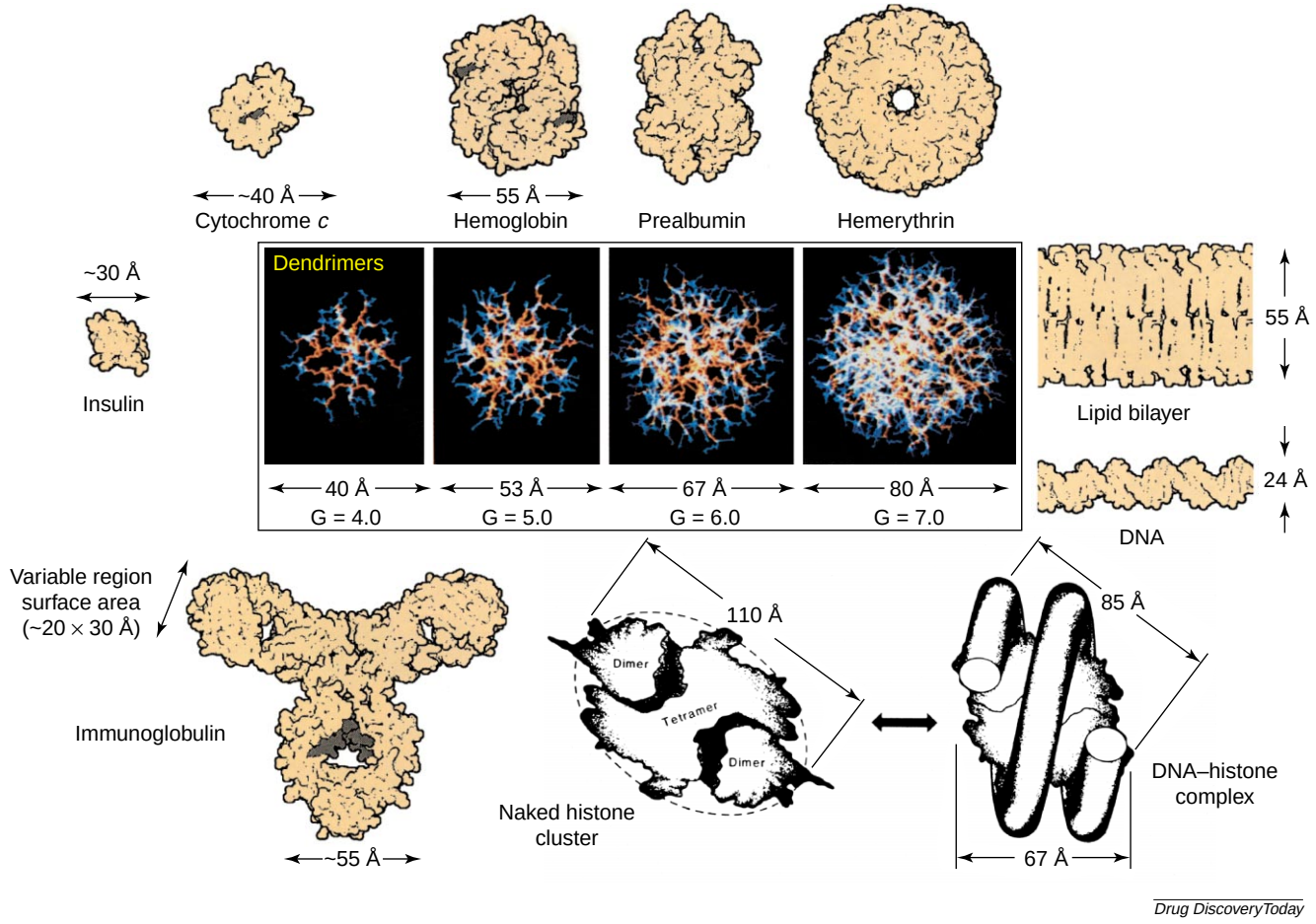

Figure 4. A dimensionally scaled comparison of a series of poly(amidoamine) (PAMAM) dendrimers (NH_3 core; G = 4–7) with a variety of proteins, a typical lipid-bilayer membrane and DNA, indicating the closely matched size and contours of important proteins and bioassemblies.

spheroids increase systematically at a rate of approximately 1 nm per generation. At least 50 other dendrimer families, possessing compositionally different interiors (i.e. carbon, nitrogen, silicon, sulfur, phosphorus or metals) and multiplicity values of N_c = 1–100 and N_b = 2–5 have been synthesized and characterized[15]. There is, of course, the possibility of errors or defects in these divergent dendrimer constructions; however, their monodispersity is remarkable based on electrophoretic[16] and mass spectroscopy measurements[11].

Comparison of PAMAM dendrimers to proteins

In addition to the extraordinary structural control at nanoscale size observed with dendrimers, another outstanding feature is their actual mimicry of globular proteins. Based on their systematic, dimensional length scaling (Fig. 4), electrophoretic[16] (Fig. 5) and other biomimetic properties[17–20], they are often referred to as 'artificial proteins'. Within the PAMAM dendrimer family, they

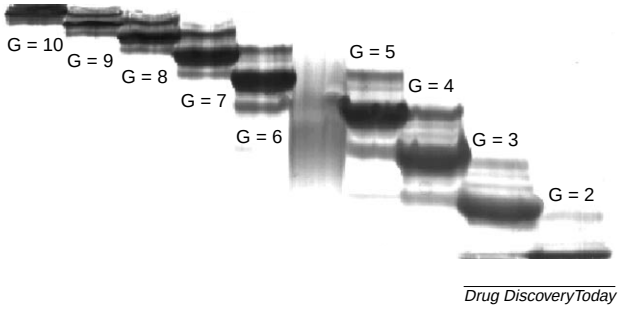

Figure 5. Electrophoretogram of a series of poly(amidoamine) (PAMAM) dendrimers (ethylenediamine core; G = 2–10) analyzed on a 5–40% T-polyacrylamide gel. A 0.1 M citric acid buffer, pH 3.0, was used as the run buffer in both the upper and lower tanks. The unlabelled smear in the middle of the gel is a proprietary sample. The middle band in each lane corresponds to the monodendrimers as a function of generation (G). The slowest bands in each dendrimer lane are dimers of that generation that can be compared with G = 1 bands that migrate at the greatest speed in each lane.

closely match the sizes and contours of many important proteins and bioassemblies. For example, insulin (≈30 Å), cytochrome C (≈40 Å) and hemoglobin (≈55 Å) are approximately the same size and shape as generations 3, 4 and 5, respectively, of ammonia-core PAMAM dendrimers (Fig. 4).

By contrast, generations 5 and 6 PAMAM dendrimers have diameters that are approximately equivalent to the ubiquitous lipid bilayer membranes of biological cells. DNA duplexes (≈24 Å width) form stable complexes with histone clusters (≈110 Å × 80 Å) to condense and store DNA within the nucleosome of cells. Undoubtedly, this size and shape scaling relationship accounts for the extraordinary stability of DNA–PAMAM dendrimer complexes (generations 7–10), as well as the enhanced gene expression observed for these 'histone mimics' compared with lower generation (generations 1–5) PAMAM dendrimers[21,22].

These fundamental properties have led to the commercial use of PAMAM dendrimers as globular protein replacements for immunodiagnostics[23–25] and *in vitro* gene expression applications [Qiagen (Chatsworth, CA, USA; www.qiagen.com) *Transfection Resource Book 1999*]. Although there are many similarities between dendrimers and globular proteins, it is also important to note significant differences. Whereas globular proteins are tertiary structures resulting from the intricate folding of sequenced linear structure, they are extremely fragile and susceptible to denaturing conditions, such as temperature, light and pH. Furthermore, folded proteins generally produce densely packed interiors and surfaces possessing highly unpredictable heterogeneous domains of functionality, and hydrophobic and hydrophilic regions. By contrast, dendrimers are known to be robust, covalently fixed, three-dimensional structures possessing both solvent-filled interior hollowness (nanoscale container) properties, as well as homogenous mathematically defined surface functionality (nano-scaffolding)[12]. More importantly, PAMAM dendrimers have been determined to be non-immunogenic and exhibit low mammalian toxicity, especially when their surface contains anionic or neutral groups, such as carboxylic or hydroxylic functionalities[26].

The dualistic role of dendrimers as either endo- or exo-receptors

The field of dendritic supramolecular chemistry is young. As recently as three years ago, fewer than six papers could be found on the subject (J.C.M. Hest, PhD thesis, University of Eindhoven, 1996); this field has since expanded dramatically[12]. In 1990[27], it was noted that dendrimers could function as unimolecular endo-receptors (nano-containers) manifesting non-covalent chemistry reminiscent of traditional regular and inverse micelles or liposomes. Furthermore, it was observed that dendrimers function as nano-scaffolding, exhibiting a high propensity to cluster or complex in an exo-receptor fashion with a wide variety of biological polymers (e.g. DNA, proteins) or metals. In the following sections, recent work in this area is discussed; however, more comprehensive reviews are available in the literature[9,12].

Mimicry of classical regular micelles

Based on qualitative evidence, Newkome and coworkers hypothesized the analogy between dendrimers and regular micelles[28]. Simultaneously, Tomalia and coworkers reported the direct observation of sodium carboxylated PAMAM dendrimers by electron microscopy[6], which proved experimentally that dendrimers clearly possess topologies reminiscent of regular classical micelles. It was also noted from electron micrographs that a large population of individual dendrimers possessed hollowness, which might be because of the peripheral stacking association of terminal head groups (i.e. non-covalent functional group interactions similar to pi stacking). This was experimentally confirmed[29] by studying the importance of branch-cell symmetry as a requisite for interior solvent-filled void-space. Such interior hollowness is observed in essentially all symmetrically branched dendrimers, but does not appear to exist in asymmetrically branched dendrimers, such as those described by Denkewalter[30–33]. Furthermore, experimentally determined hydrodynamic dimensions[29], molecular shapes and a comparison of dendrimer surface groups with similar parameters in traditional micelles added further support to this hypothesis[29,34,35].

One of the best experimental demonstrations of dendrimeric 'unimolecular micelle' properties was reported by Turro and colleagues[36]. In this work, a hydrophobic 12-carbon alkylene chain was designed into the core of a homologous series of PAMAM dendrimers (i.e. generation = 2, 3 and 4) to mimic the hydrophobic and hydrophilic core-shell topology of a regular micelle. The hosting properties of this series towards a hydrophobic guest molecule (e.g. Nile red – a hydrophobic, fluorescing molecule) were then compared with a PAMAM dendrimer series possessing non-hydrophobic cores (e.g. NH_3 and ethylenediamine). Dramatically enhanced emission of the hydrophobic dye was noted in aqueous solution in the presence of the hydrophobic versus the hydrophilic cored dendrimers.

Mimicry of liposomes

The unique dualistic property, consisting of micelle-like topology combined with interior void space (usually associated with liposomes) was first noted for dendrimers in 1989[37]. Subsequent NMR studies and computer-assisted

simulations by Goddard and colleagues[38]; molecular inclusion work by Newkome[39]; and extensive photochemical probe experiments by Turro and coworkers[36,40–42] have demonstrated that symmetrically branched dendrimers can be viewed as unimolecular micelles (nanoscale container-molecules). Depending on the nature of their surface groups and interiors, these dendrimers can manifest behavior reminiscent of either regular[36] or inverse micelles[43], but with unique differences and advantages. The incarceration of guest molecules (either organic or metals) within dendrimers was first described between 1989–1990 and was referred to as unimolecular encapsulation[27].

In a more recent study, Meijer and coworkers[44,45] enhanced this earlier concept by modifying dendrimer surfaces to induce 'unimolecular encapsulation' behavior[27]. They referred to this new construction as the 'dendrimer box'. Surface-modifying of generation-5 poly(propylene imine) (PPI) dendrimers[44] with 1-phenylalanine or other amino acids[46] induced dendrimer encapsulation properties by the formation of dense, hydrogen-bonded surface shells with solid-state character. Small guest-molecules were captured in such dendrimer interiors and were unable to escape even after extensive dialysis[45]. The maximum amount of entrapped guest molecules was directly proportional to the shape and the size of the guest molecules, as well as to the amount, shape and size of the available internal dendrimer cavities. For example, four large guest-molecules (e.g. Rose Bengal, Rhodamide B or New Coccine) and 8–10 small guest-molecules (e.g. *para*-nitrobenzoic acid and nitrophenol) could be simultaneously encapsulated within these PPI dendrimers that contain four large and 12 smaller cavities. Remarkably, this dendrimer box could also be opened to release either all or some of the entrapped guest molecules[45]. For example, partial hydrolysis of the hydrogen-bonded shell liberated only the small guest-molecules, whereas total hydrolysis (with 12N HCl for 2 h at reflux) released all sizes of entrapped molecules.

Shape-dependent cargo space

Although the 'dendritic-box' concept demonstrates the unique shape-dependent 'cargo space' that can be found in certain dendrimers, it does not offer a practical means for delivering and releasing therapeutic drugs under physiological conditions. A major objective of our recent group effort has been the resolution of these problems.

Just as biological cells possess cytoskeleton components (e.g. α- and β-tubulins and microtubules) that define both the shape of the cell and facilitate certain trafficking within the cytoplasm, such mimicry exists within the (cytoskeleton-like) interior of a dendrimer. It is widely recognized that dendrimer interiors can be readily designed and reconfigured to define a vast combinatorial array of spatial cavities, such as hydrophobic and hydrophilic domains, ligand or acid–base complexation sites.

The robust covalent structural features of dendrimers offer a variety of defined sizes and shapes (i.e. cargo spaces) and permit extensive dendrimer surface modifications to effectively control guest-molecule entry and exit parameters. From a thermodynamic perspective, free and complexed guest-molecules (i.e. drugs) can be distinguished by finite energy barriers related to the ease of entry and departure to dendrimer cavities. If the drug molecule is significantly large or incompatible with either the dimension, or hydrophilic or lipophilic character, of the dendrimer cavity, a complex might not form, or the guest might only be partially incarcerated within the dendrimer host. A hydrophobic drug would be expected to associate with a dendrimer interior to achieve maximum contact between its hydrophobic components and comparable domains within the dendrimer. The hydrophobic component of a guest molecule would be expected to isolate itself from the outer interface of the dendrimer complex to afford minimum contact with polar and aqueous domains (i.e. physiological media). Notably, the hydrophobic and hydrophilic properties, as well as other supramolecular (i.e. non-covalent binding, acid–base reaction) properties, of these spatial binding-sites are expected to strongly influence these guest–host relationships. Analysis of a typical symmetrically

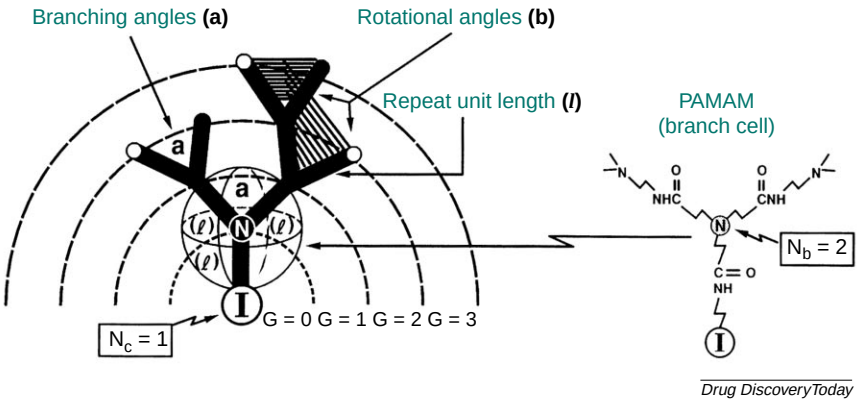

Figure 6. Branch cell parameters: branching angles **(a)**, rotational angles **(b)**, repeat unit length ***(l)*** and branch cell multiplicity (N_b) are the crucial parameters that determine cargo-space properties within the interior lattice of a dendrimer.

branched dendritic lattice makes it apparent that there are other subtle, and yet important, parameters that could control the interior space of a dendrimer and influence guest–host interactions. These include crucial branch-cell components, such as: branching angles (Fig. 6; a), rotation angles (Fig. 6; b) and repeat-unit segment length (Fig. 6; *l*)[38]. Of equal importance are the spatial, physicochemical and multiplicity properties of the core. Some of these principles have been well demonstrated in the 'unimolecular micelle' work by Turro and colleagues[36] where the influence of size, shape and acid–base complexation parameters for other dendrimeric systems are described.

Within a homologous PAMAM dendrimer series, the effect of changing the dendrimer-core dimensional-length scale on dendrimer guest–host properties was studied. Specifically, a series of poly(hydroxyl)-surfaced PAMAM dendrimers that differed by one carbon atom in the central core unit (i.e. 2C = ethylenediamine; 3C = 1,3-diaminopropane; 4C = 1,4-diaminobutane; 5C = 1,5-diaminopentane; 6C = 1,6-diaminohexane) and interior and surface groups as depicted in Fig. 7 were synthesized. A series of three aromatic carboxylic acids, differing systematically by one aromatic ring, were examined as guest-molecule probes. They were combined with core-modified dendrimers possessing 24 and 48 hydroxylic groups, respectively. This combination produced solid 'inclusion complexes' that are described in detail in the literature[47,48].

The relative amounts of guest-molecule incarcerated within these various dendrimer inclusion complexes produced the profiles shown in Fig. 8; the following trends could be noted:

- In general, all dendrimeric hosts accommodated larger amounts of the smaller guest-molecule (e.g. a higher molar uptake was noted for benzoic versus 1-naphthoic or 9-anthracene carboxylic acid). This was particularly significant for the more congested dendrimer surface (i.e. 48-OH; Fig. 8b).
- Uptake maxima values that were specific to both the core size and the specific guest-probe were noted. This might be related to the combination of shape and lipophilicity manifested by the guest probe.
- In all guest probe examples, there was a decrease in the molar uptake as the core was enhanced beyond an ideal dimension (e.g. up to 5–6 carbons).

It is, therefore, obvious that both core size and surface congestion dramatically affect the 'cargo-space' of the dendrimer host. Furthermore, it is apparent that the size and shape of the guest probe can significantly affect maximum loading as a function of core size.

Finally, it should also be noted that for the dendrimers G = 2 (24-OH) and G = 3 (48-OH), the guest probes had desirable exiting properties from the host, as a function of time, when redissolved in water. Performing these same experiments on a more surface-congested dendrimer in this homologous series [i.e. G = 4 (96-OH)] appeared to produce 'dendritic-box' behavior. Although guest molecules could be incarcerated within the interior, it was difficult for them to exit, as determined by analysis after extensive dialysis.

The promise of macromolecular drug delivery

Since their introduction some 30 years ago, supramolecular (self-assembling) vectors, such as liposomes, have had isolated successes in drug delivery applications; for example, DaumpXome® (Nexstar Pharmaceuticals, Boulder, CO, USA) and Doxil® (Sequus Pharmaceuticals, Menlo Park, CA, USA).

Recently, there appears to be a significant renaissance in the macromolecular drug delivery field[49,50]; this revolutionary concept was first introduced by Ringsdorf in the

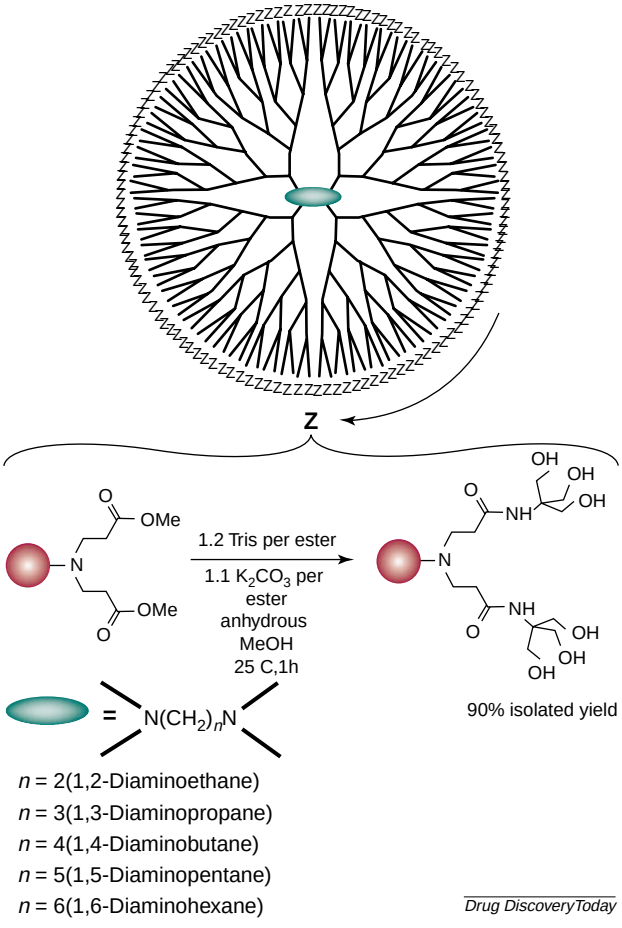

Figure 7. The surface modification of poly(amidoamine) (PAMAM) dendrimers with hydrophilic groups prepared by nucleophilic attack of tri-hydroxymethyl aminomethane (Tris) on the ester terminated dendrimer.

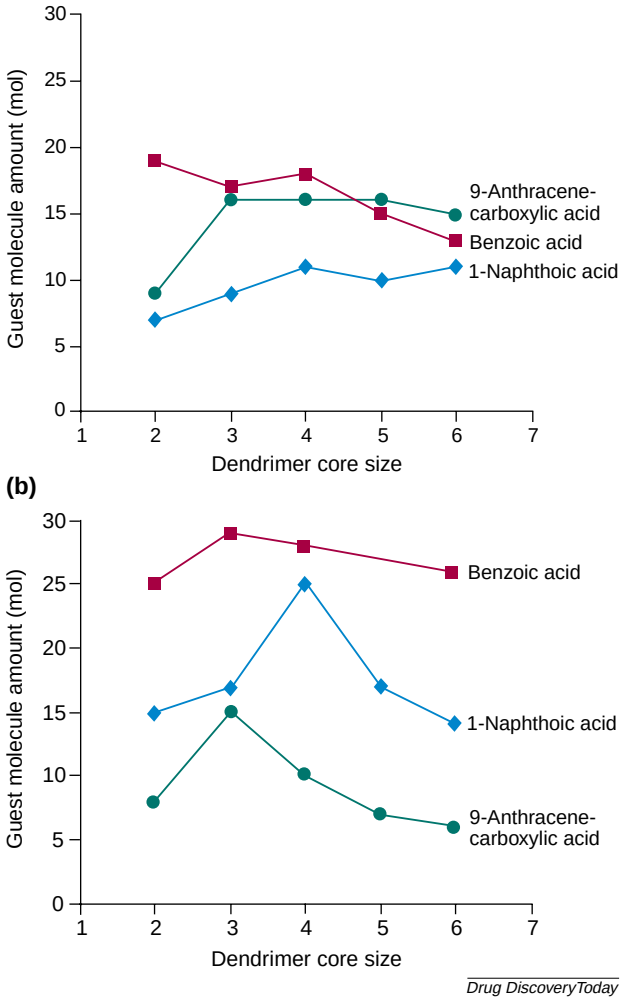

Figure 8. Host–guest interactions between dendrimers and hydrophobic guests, which are sparingly soluble in water. As a result of different internal cavity diameters, each class of dendrimeric host offers a different degree of inclusion complex formation. **(a)** Comparison of molar uptake between benzoic, 1-naphthoic and 9-anthracenecarboxylic acid by G = 2* (24-OH). **(b)** Comparison of molar uptake of between benzoic, 1-naphthoic and 9-anthracenecarboxylic acid by G=3* (48-OH).

mid-1970s[51]. Since then, a wide spectrum of therapeutic agents has been utilized almost exclusively with the traditional polymer classes described previously, namely: linear, cross-linked and branched [Fig. 1; (I), (II) and (III), respectively]. Pioneering work by Duncan[49,52–56], Maeda[55–58], Langer[59], Kopecek[60–64] and others[65] has extensively shown that polymeric drug vectors offer many outstanding advantages as a versatile strategy for more effective delivery of therapeutic drugs to disease sites. Commercial translations of these advantages have emerged; at least four polymer-anticancer conjugates and two polymeric gamma-camera imaging agents[49] have been developed based on *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer vectors. Several of these prototypes have progressed into Phase I and Phase II clinical trials and early results have generated considerable interest[49].

Recently, there has been keen interest in polymeric vectors that could be targeted for site-specific pharmacotherapy[50]. The development of new synthetic options and strategies both in the polymer field and in bioconjugation techniques has great potential for macromolecular drug delivery, bio-imaging and other biomedical applications.

Macromolecular vectors in biomedical and drug delivery applications

A consensus of significant properties deemed desirable in an ideal macromolecular drug delivery vector, bio-imaging or biomedical prototype could include many of the features noted in Box 2. In spite of recent clinical progress and success, this list contains many challenges that cannot be met or optimized with traditional polymer properties and architectures.

In summary, many of these challenges could have solutions offered by the dendritic polymer properties described in this account. An extensive review by Bieniarz[66] highlights many of these unique properties in crucial biomedical applications such as: immunodiagnostics, magnetic-resonance contrast agents, glycodendrimers for pathogen pacification[67], gene transfection[22] and drug delivery[68].

More recent work by Fréchet and colleagues[68] and Duncan and coworkers[69] has highlighted the unique drug-loading capabilities and targeting features offered by dendrimers. In this context, it is appropriate to note that such properties are found in commercially available PAMAM dendrimers: recent work[70] has confirmed earlier reports[71] that PAMAM dendrimers develop predictable nanoscale container and nanoscale surface-scaffolding properties. Unique periodic properties develop as a function of generation enhancement and are a consequence of mathematically defined surface-group amplification. Core-tethered amplifications transform dendrimers from open, flexible scaffolding (generation = 0–3) to semi-rigid container-type structures (generation = 4–6). These container-type host structures exhibit guest-molecule permeability. By contrast, the rigid surface-scaffolding structures (generation = 7–10) manifest limited surface-permeability. A vast array of surface functionalities can be designed to control gating properties for departure and entry from these container molecules. These unique architectural features offer many new options for presentation and/or incarceration of pharmaceuticals, targeting groups or imaging moieties. These biomedical functions could be conjugated or incarcerated independently or in combination.

Box 2. Properties of an ideal macromolecular drug delivery or biomedical vector

- Structural control over size and shape of drug or imaging-agent cargo-space.
- Biocompatible, non-toxic polymer/pendant functionality.
- Precise, nanoscale-container and/or scaffolding properties with high drug or imaging-agent capacity features.
- Well-defined scaffolding and/or surface modifiable functionality for cell-specific targeting moieties.
- Lack of immunogenicity.
- Appropriate cellular adhesion, endocytosis and intracellular trafficking to allow therapeutic delivery or imaging in the cytoplasm or nucleus.
- Acceptable bioelimination or biodegradation.
- Controlled or triggerable drug release.
- Molecular level isolation and protection of the drug against inactivation during transit to target cells.
- Minimal nonspecific cellular and blood-protein binding properties.
- Ease of consistent, reproducible, clinical grade synthesis.

Biomedically important functions, such as targeting, fluorescence, photon absorption, chelation or paramagnetic imaging could be amplified on the surface of the dendrimers by external surface conjugation. Conversely, these functions could be selectively internalized using well demonstrated protocols described in this review and elsewhere in the literature[47,48,70,72,73].

Conclusions

Clearly, certain pervasive biological patterns and biomimicry have played a role in the discovery and development of many biomedical applications for dendrimers. Within the past five years, at least 3000 papers and patents have been published in the dendritic polymer field. Many of these investigations were specifically focused on new biomedical applications.

It is well known that natural polymers such as silk, wool and cotton were replaced with nylon and other linear (class I) synthetic polymers and natural rubber was replaced with synthetic (class II) cross-linked synthetic polymers ~50–60 years ago[1]. From this perspective, it might be realistic to consider the possibilities of replacing or enhancing many crucial biological polymers (e.g. proteins) that are known to influence health or disease. The remarkable similarity of dendrimer size-scales, precise structure control and general physicochemical properties compared with globular proteins, antibodies and enzymes already suggest potential roles for dendrimers in the emerging field of proteomics. Based on the repertoire of unprecedented properties offered by dendritic polymers, it is expected that dendritic polymers will play a significant role in the development of new biomedical devices and strategies for the treatment of human disease.

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