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REVIEW

Recent Advances on Crosslinked Dendritic Networks

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ABSTRACT: The branched architectures of dendritic polymers display a large number of end groups, and dendrimers have been extensively evaluated as scaffolds in a large array of research fields, including biomedicine and nanotechnology. From the number of potential applications that require advanced crosslinked films, dendritic macromolecules are attractive as scaffolds that deliver on promising crosslinked three-dimensional (3D) networks. This review briefly covers a description of the family of functional dendritic polymers, ranging from dendrimers and dendrons to hyperbranched polymers and dendritic linear hybrids. The review also contains a detailed report on proposed chemistries for the exploitation of dendritic materials as scaffolds in the field of advanced networks. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 39876.

KEYWORDS: dendrimers; hyperbranched polymers; crosslinking; gels; supramolecular structures

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INTRODUCTION

Since the mid-1980s, dendritic materials have attracted much attention in the field of polymer science[1–3] due to their highly branched structure and large number of peripheral end groups that result in distinctively different properties compared to traditional linear polymers. In this critical review, a short introduction to the field of dendritic macromolecules is followed by a discussion of relevant network formation strategies. Research breakthroughs are highlighted with respect to the current subgroups in the dendritic polymer family. Finally, a brief outlook on possible future developments is presented.

Dendritic Structures: An Overview

Dendritic polymers are highly branched structures that present a large number of peripheral functional groups that are exposed to their surrounding environment. As a result, they have a compact and nonentangled structure, which gives them distinctive rheological properties, such as lower viscosity compared to traditional linear polymers. The low viscosity of dendrimer solutions has enabled their use in the formation of gels through in situ injection.[4]

The dendritic family is continuously expanding and includes a large number of different substructures,[5] of which some of the most common can be seen in Figure 1. These advanced architectures, as well as the large variety of functionalities available at the periphery, makes the dendritic family of materials highly desirable for many applications in materials science.[6,7]

Of the available dendritic materials, monodisperse dendrimers are by far the most complex to construct. Their synthesis typically involves stepwise growth and activation reactions of branching AB_x-monomers, where A and B react selectively with each other. Traditional synthesis of dendrimers can follow either a convergent or a divergent growth approach, starting from the periphery or the core, respectively. In both cases, robust chemical reactions are used with tedious purification steps after each completed reaction. Even though dendrimers are complicated polymers to obtain, their layered (generation) and monodisperse architectures enable researchers to use them as high precision polymers with a straightforward structure-to-property correlation. The syntheses of dendrimers are schematically depicted in Figure 2, along with the faster and more facile synthesis of hyperbranched polymers.

With the introduction of robust organic concepts, namely click reactions, rapid and facile synthesis of dendrimers has been realized by so-called accelerated growth approaches.[2,8,9] By utilizing orthogonal coupling reactions, the activation steps become obsolete, making the synthesis route more effective and reducing the number of reaction steps by 50%.[10]

Apart from perfect dendritic structures such as dendrimers and dendrons, the dendritic family also comprises hyperbranched polymers, dendronized polymers, and dendritic–linear hybrids. Hyperbranched polymers are structurally imperfect dendritic structures with a set of properties that is similar to that of the corresponding dendrimers.[11,12] The concept of

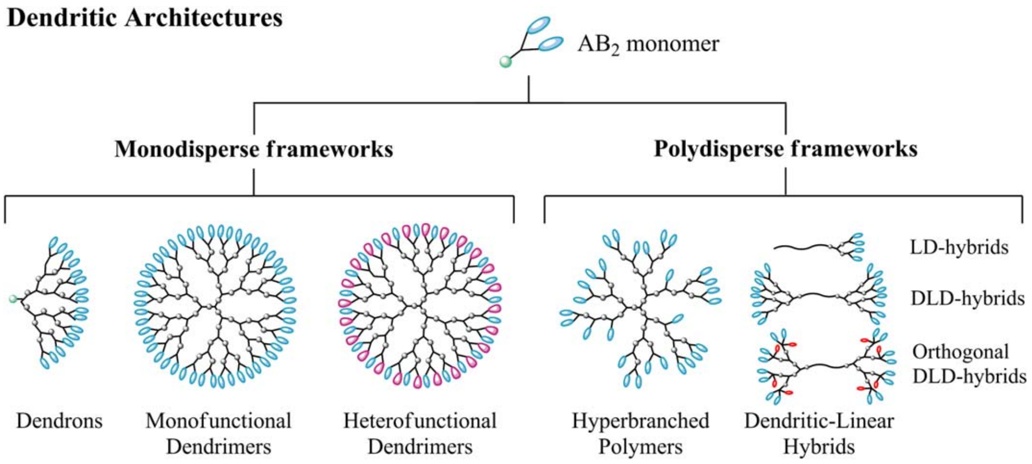


Figure 1. A selection of proposed dendritic polymers of monodisperse and polydisperse nature. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

pseudogeneration is used to characterize hyperbranched structures, where a hyperbranched polymer of pseudogeneration two has the same number of end groups and theoretical molecular weight as a dendrimer of generation two. In comparison to dendrimers and dendrons, hyperbranched polymers can be synthesized in large scale through one-pot procedures, which enables commercial availability and promotes the use of hyperbranched polymers in application-driven research.[12–14]

The hybridization between dendritic and linear polymer blocks into dendritic–linear hybrids has received much attention in recent years. By amalgamating a linear polymer with a dendritic element, the benefits of both individual structures are combined into a single macromolecule. The linear block can provide features such as increased molecular weight, solubility, crystallinity, and chain entanglements, while the dendritic block delivers a larger number of functional groups, concentrated specifically within the hybridized structure. The coupling of dendritic and linear blocks differs depending on the final targeted structure, where, for example, the coupling of two dendritic segments to a dual-functional linear polymer results in dendritic–linear–dendritic (DLD) hybrids, as shown in Figure 1.[2,15]

Dendritic structures with a large variety of functional groups have been developed over the years, including more sophisticated scaffolds that express more than one type of functionality, so called "heterofunctional dendrimers".[16,17] The increased use of dendrimers today is reflected by the number of commercial sources that provide dendritic materials. These are shown in Figure 3 along with other commonly used dendritic structures that will be mentioned in this review.

General Network Formation Strategies

Depending on the components used, network formation can be a result of covalent bond formation, ionic interactions, or physical entanglements, for example, via van der Waals interactions or hydrogen bonds. The strategy used for network formation may influence the properties of the resulting network. Network structures that can absorb fluids are commonly called "gels". A distinction can be made between hydrogels, which swell in water, and organogels, which swell in organic solvents.

Covalently crosslinked networks are the most common systems, and they are considered to yield materials with high mechanical, thermal, and chemical stability.[18] With a few exceptions, covalently crosslinked systems are irreversible. This is a result of the large enthalpy difference between the starting materials and the product causing a barrier in energy, which prevents reverse reactions. From the myriad of different routes that can be used to achieve covalent crosslinking, the most common strategy exploits radical processes initiated using UV irradiation or exposure to elevated temperatures. In both cases, an initiator is used to generate radicals, which react with reactive functional groups on the monomers or polymers that are used as starting materials. Traditional free-radical processes are inhibited by the presence of oxygen and known to generate networks with poor structural control. Commonly, gelation occurs already at low monomer conversions for free-radical systems, which further restricts the level of structural control of the network. UV-initiated thiol-ene coupling (TEC) reactions, on the other hand, proceed via a free-radical step-growth process that has a delayed gelation point, typically taking place at 50% conversion of thiol and ene groups.[19] TEC reactions involve an addition of a thiol across a carbon–carbon unsaturated bond, can proceed efficiently in the presence of oxygen, and are tolerant toward various solvents and functional groups.[8,9,20] An example of a more specific covalent network formation approach is coupling by means of click chemistry.[21] By using macromers that are end-functionalized with "clickable" groups as starting materials, a high level of control over network formation and crosslinking density can be achieved.

Network formation can also be a result of ionic interactions, which rely on electrostatic attraction between oppositely charged groups. These interactions are generally weaker than covalent bonds, and, as the interactions are of an electrochemical nature, they become responsive to external stimuli such as changes in pH, solvent, and salt concentration.[22] In some cases, ionic networks can be disrupted and later regenerated in a phenomenon

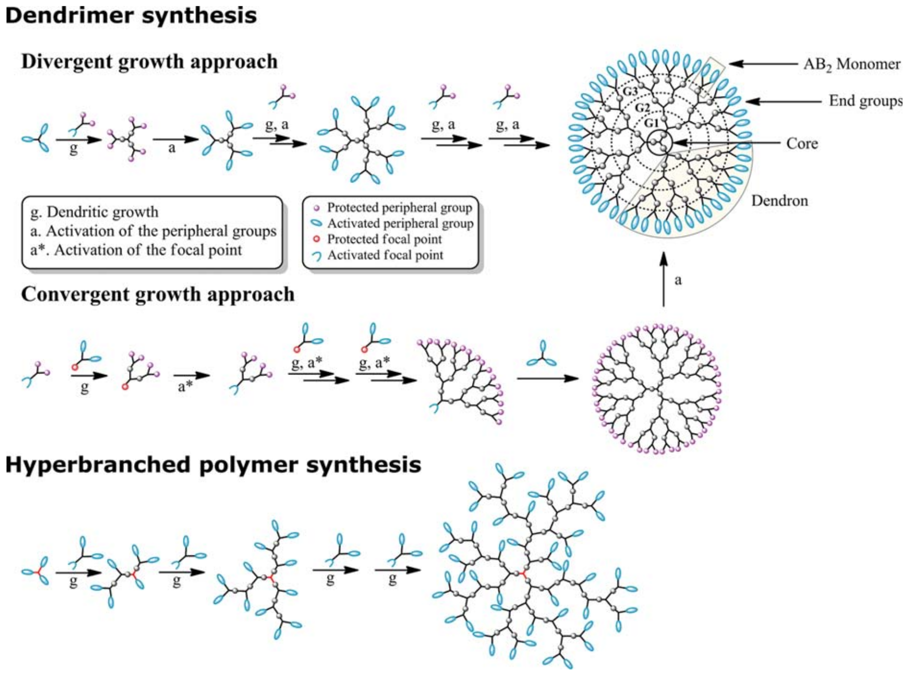


Figure 2. Schematic representation of the divergent and convergent growth approaches to monodisperse dendrimers as well as the synthesis of polydisperse hyperbranched polymers. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

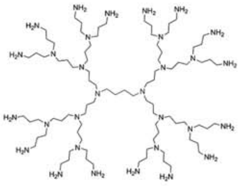
denoted as "self-healing".[23] Table I summarizes all dendritic network concepts discussed in this review.

Network Concepts Based on Dendrimers and Dendrons

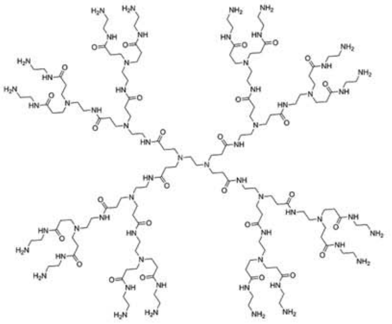
Published reports on network formation with dendritic structures include studies with several different types of dendrimers and are aimed toward many different applications. There has been some interest in a combination of dendritic structures and nanoparticles in networks, because of the interesting properties of dendritic materials as binders. In 2001, Amis et al. produced a polymer–nanoparticle composite, where dendrimers of commercial poly(amido amine) (PAMAM) functioned as a template for the formation of nanoparticles inside a poly(2-hydroxyethyl methacrylate) (p(HEMA)) matrix.[24] A semi-interpenetrating network (semi-IPN) was prepared by dissolving PAMAM in HEMA, which was then polymerized and crosslinked with poly(ethylene glycol) diacrylate (PEGDA) using azobisisobutyronitrile (AIBN) as the initiator. By forming a semi-IPN with uniformly dispersed PAMAM dendrimers trapped in a p(HEMA) network, the authors achieved a template for nanoparticle formation. While swollen in water, metal ions of gold, platinum, and copper accumulated inside the dendrimer structures within the network because of electrostatic attraction or coordination to amine groups on the dendrimer. Reduction of metal ions resulted in nanocomposites with very well-dispersed and uniform nanoclusters. The size of the nanoclusters could further be controlled by altering the generation of the dendrimer. This approach could therefore enable a new level of control for the synthesis of templated nanocomposites.

A similar concept was used in 2002 by Dvornic et al.[25] In this study, amine-terminated PAMAM dendrimers (G0–G5) were first functionalized with organosilicone end groups, which could be used for further functionalization to give dendrimers that could be crosslinked. Depending on the structure of the organosilicone end group, two types of crosslinking methods were used: silanol condensation reactions and free radical reactions. The resulting covalently crosslinked networks contained both hydrophilic and hydrophobic domains, regardless of the crosslinking method. The hydrophilic PAMAM domains were found to have an affinity to both inorganic and organic compounds, enabling the use of these networks as templates for the organization of metal-based nanoparticles, and as carriers for drugs and catalysts. These crosslinked systems were demonstrated to have good film-forming characteristics, making the materials interesting for the production of protective and functional coatings. PAMAMs functionalized with organosilicone groups are now referred to as poly(amido organosilicone) (PAMAMOS) and are supplied by Dendritech, Incorporated. Dvornic et al. have also investigated the use of PAMAMOS networks for the templating of copper nanoclusters.[26] This study showed that, for a limiting amount of copper(II) of about 5%, the metal cations were only deposited in the hydrophilic PAMAM domains of the dendrimer network. A larger amount of Cu(II), however, resulted in networks with Cu(II) located in the organosilicone domains as well. The metal ions remained well-dispersed throughout the entire network. After reduction of the metal ions, the materials possessed interesting electrical properties, with conductivities comparable to common semiconducting materials such as polypyrrol and polyaniline, suggesting that the materials could be utilized as electrically semiconducting nanocomposites.

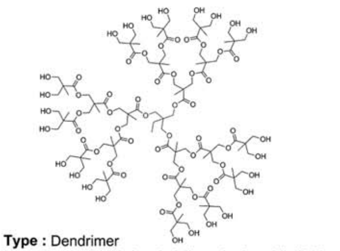
A more application-driven study on dendrimer networks as support for metal nanoparticles was recently reported by Karakhanov et al.[27] Here a poly(propylene imine) (PPI) dendrimer-based network was shown to stabilize a palladium catalyst for hydrogenation of unsaturated compounds. The amine functional PPI



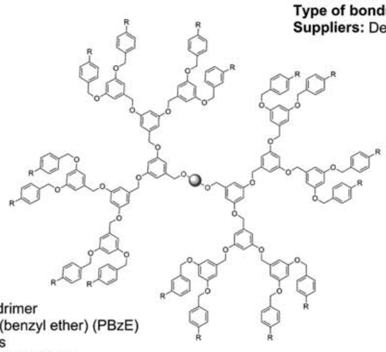
Type : Dendrimer
Name: Poly(propylene imine) (PPI)
Core: Varies
Type of bonds: Amines
Supplier: DSM IP Assets B.V.



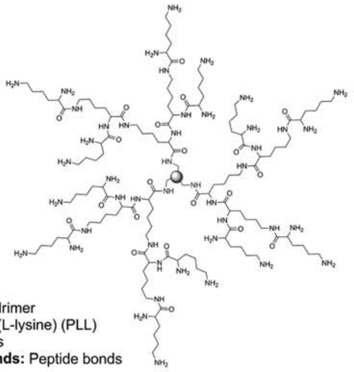
Type : Dendrimer
Name: Poly(amido amine) (PAMAM)
Core: Varies
Type of bonds: Amides, amines
Suppliers: Dendritech Inc., Sigma Aldrich



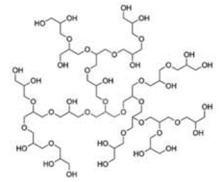
Type : Dendrimer
Name: Poly(2,2-bis(methylol)propionic acid) (P(bis-MPA))
Core: TMP
Type of bonds: Esters
Suppliers: Polymer Factory Sweden AB, Sigma Aldrich



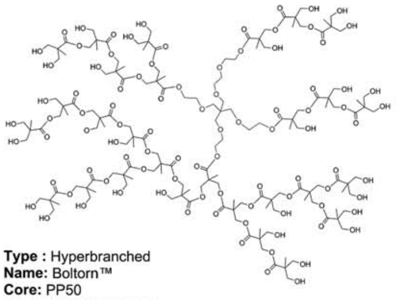
Type : Dendrimer
Name: Poly(benzyl ether) (PBzE)
Core: Varies
Type of bonds: Ethers
Suppliers: -



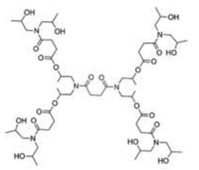
Type : Dendrimer
Name: Poly(L-lysine) (PLL)
Core: Varies
Type of bonds: Peptide bonds
Suppliers: -



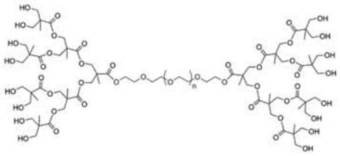
Type : Hyperbranched
Name: Poly(glycerol)
Core: Glycerol
Type of bonds: Ethers
Suppliers: Hyperpolymers GmbH



Type : Hyperbranched
Name: Boltorn™
Core: PP50
Type of bonds: Esters
Suppliers: Perstorp, Sigma Aldrich, Polymer Factory Sweden AB



Type: Hyperbranched
Name: Hybrane®
Core: Varies
Type of bonds: Esters, amides
Suppliers: DSM IP Assets B.V., Polymer Factory Sweden AB



Type: DLD-Hybrid
Name: -
Core: PEG
Type of bonds: Ethers (L), esters (D)
Suppliers: Polymer Factory Sweden AB

Figure 3. Common dendritic structures discussed in this review and some common commercially available dendritic structures.

dendrimers (G1 and G3) were synthesized via a previously reported procedure[28] and crosslinked using 1,4-butylene diisocyanate (BDI) or 1,6-hexamethylene diisocyanate (HMDI). The dendrimer networks were then used to encapsulate and stabilize palladium nanoparticles. The activity of the dendrimer-supported Pd catalyst was evaluated through the hydrogenation of a large number of styrene-derived substrates and found to be more effective than the conventional Pd/C catalysts.[27]

The use of dendritic networks is also of interest in biomedical applications. In 2004, the use of hydrogels formed from biocompatible lysine-based peptide dendrons was investigated in corneal incision repair.[4] The lysine-based dendrons were synthesized by a divergent strategy and functionalized with cystein. The peripheral cysteine units were then crosslinked using PEG-dialdehyde (PEG-DA) as the crosslinking unit. The formed hydrogels (referred to as D-Lys$_3$Cys$_4$-PEG-DA in Figure 4)

Table I. Summary of the Dendritic Network Concepts Discussed in This Review

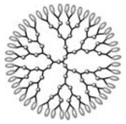
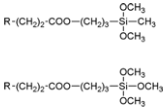
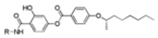
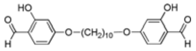
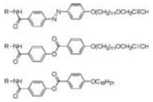
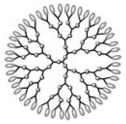
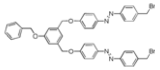
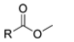
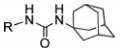
Dendritic category	Type	Core	End groups	Crosslinker	Network	Application
 Dendrimers	PAMAM	Ethane-1,2-diamine (EDA)	R-NH_2	-	Semi IPN	Template for inorganic nanoparticle formation[24]
	PAMAM-OS	Ethane-1,2-diamine (EDA)	 $R\text{-}(CH_2)_2\text{-}COO\text{-}(CH_2)_3\text{-}\overset{OCH_3}{\underset{OCH_3}{Si}}\text{-}CH_3$ $R\text{-}(CH_2)_2\text{-}COO\text{-}(CH_2)_3\text{-}\overset{OCH_3}{\underset{OCH_3}{Si}}\text{-}OCH_3$	(3-acryloxypropyl)dimethoxymethyl silane (DMOMS)(3-acryloxypropyl)trimethoxysilane (TMOS)Tetraethoxylsilane (TEOS)α,ω-telechelic poly(dimethylsiloxane) disilanol (PDMS)or without crosslinking agent	Covalent	Template for nanoparticle formation, carrier for drugs and catalysts[25,26]
	PPI	Diamine buthane (DAB)	R-NH_2	1,6-hexamethylene diisocyanate (HMDI)1,4-butylene diisocyanate (BDI)	Covalent	Support for Pd nanoparticles as catalyst for hydrogenation[27]
	PPI	Diamine buthane (DAB)	R-NH_2 		Covalent condensation reaction	Liquid crystalline dendrimer network[32]
	PPI	Diamine buthane (DAB)		pentaerythritol tetra(3-mercaptopropionate) (PETMP)	Covalent, UV-initiated	Photoresponsive liquid crystalline network[33]
 Dendrimers	PBzE			-	Physical interactions	Multi-stimuli responsive hydrogels[34]
	PPI	Diamine buthane (DAB)		 telechelic oligo(THF)	Ionic interactions, hydrogen bonding	Ionic transient network structures[35]
	PPI	Diamine buthane (DAB)	R-NH_3^+	Polyanionic network ofpoly(acrylic acid-*co*-N,N-methylene-bis-acrylamide) orpoly(sodium 2-acrylamido-2-ethylpropanesulfonate-*co*-	IPN: Covalent and ionic interactions	Hydrogels[36]

TABLE I. *Continued*

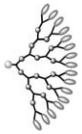
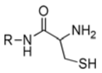
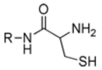
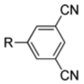
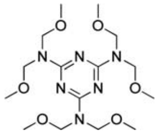
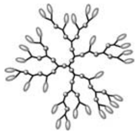
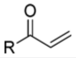
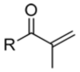
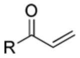
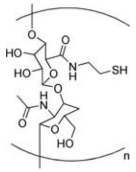
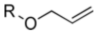
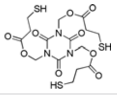
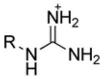
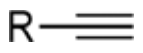
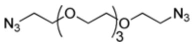
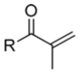
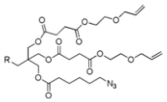
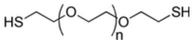
Dendritic category	Type	Core	End groups	Crosslinker	Network	Application
				N,Nmethylene-bis-acrylamide)		
 Dendrons	PPI	Diamine buthane (DAB)	R–NH_2	Poly(ethylene glycol dicarboxylic acid) (PEG-diCOOH)(756 or 4756 g/mol)	Ionic interactions	Hydrogels with self-healing characteristics[37]
	Poly(L-lysine)	Methyl 2,6-diamino hexanoate		Poly(ethylene glycol dialdehyde) (PEG-DA, 3400 g/mol))	Covalent	Hydrogel sealant for corneal incision repair[4]
	Poly(L-lysine)	Methyl 2,6-diamino hexanoate		PEG-propionaldehyde (P-Ald PEG), PEG-butyraldehyde (B-Ald PEG),PEG-2-oxoethyl succinate (E-Ald PEG)	Covalent	Hydrogel sealant for corneal incision repair[31]
	PBzE	Benzyl alcohol		–	Physical interactions, π-π-stacking	Organogels[38]
	Bis-MPA	PP50	R–OH		Covalent heat	Composites[43,44]
 Hyperbranched	Bis-MPA	TMP		–	Covalent UV-initiated	Drugrelease hydrogel[46]
	Glycerol	Glycerol		–	Covalent UV-initiated, pH	Drug delivery and tissue engineering[48]
	–	ethyl 2-bromo isobutyrate			Covalent Michael addition	In situ tissue engineering, scaffolds in biomedicine[56]

TABLE I. *Continued*

Dendritic category	Type	Core	End groups	Crosslinker	Network	Application
 DLD-Hybrids	Bis-MPA	Poly ethylene glycol (PEG)			Covalent UV-initiated	Hydrogels for tissue engineering[51]
	Bis-MPA	Poly ethylene glycol (PEG)		Clay nano sheets	Ionic, spontaneous	Responsive hydrogels[49]
	Bis-MPA	Poly ethylene glycol di azide			Covalent, CuAAC click	Hydrogels for tissue engineering[50]
	Glycerol Succinic	Poly ethylene glycol (PEG)		–	Covalent UV-initiated	Cornea laceration repair[52]
	Bis-MPA	Poly ethylene glycol (PEG)			Covalent UV-initiated	Artificial extra cellular matrices[55]

The network concepts are presented with respect to dendrimer category, type of polymer (Figure 3), core, end groups (where R is used to indicate the dendritic main structure), crosslinker used in network formation, network strategy, and suggested applications.

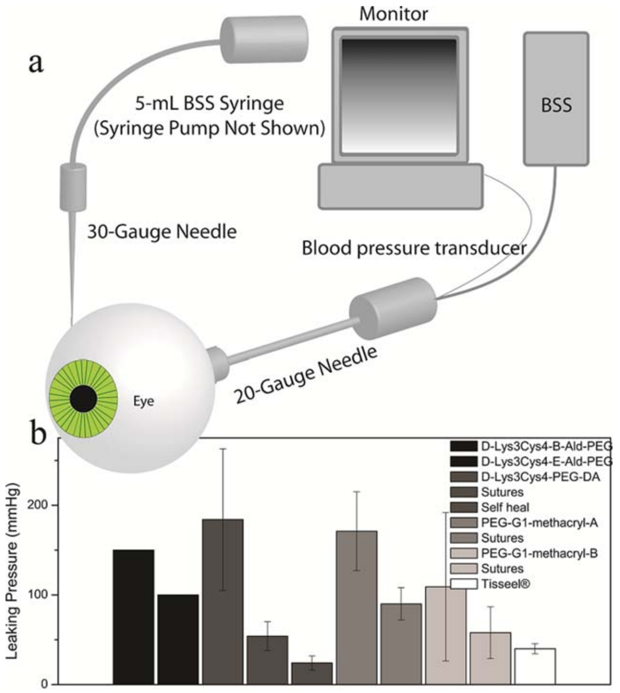


Figure 4. (a) Test setup for leaking pressure test on cornea laceration repair. (b) Compilation of leaking pressures for sealants reported in this review. Values taken from the same study are depicted with the same color to facilitate comparison. Compiled from Refs. 2,28,50−52. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

showed promising characteristics for corneal incision repair. Five min after sealing the incision with the hydrogel, saline solution was injected via a syringe pump until leakage was observed, and the leaking pressure was recorded. Incisions repaired with the hydrogel sealant had a leaking pressure of 184 ± 79 mmHg. As a comparison, self-sealed incisions showed a leaking pressure of 24 ± 8 mmHg, and suture-treated incisions showed a leaking pressure of 54 ± 16 mmHg. This simple and fast method of corneal incision repair showed great promise.

Later research on dendritic hydrogels for corneal incision repair was summarized in two reviews by Grinstaff in 2007 and 2008.[29,30] More recently, in 2011, Grinstaff et al. continued to investigate dendrons of lysine with cystein at the periphery (D-Lys_3Cys_4).[31] Hydrogels were formed from three aldehyde functional PEGs: PEG-propionaldehyde (P-Ald PEG), PEG-butyraldehyde (B-Ald PEG), and PEG-2-oxoethyl succinate (E-Ald PEG), where E-Ald PEG also had an ester next to the aldehyde end group. Crosslinking of the dendron with the aldehyde functional PEGs yielded thiazolidine linkages susceptible to hydrolysis. For E-Ald PEG, rearrangement of the formed thiazolidine linkage resulted in a pseudoproline linkage, which is more stable than the thiazolidine linkage and therefore has a longer degradation time. Degradation of the hydrogels was evaluated during storage in Dulbecco's phosphate-buffered saline. Hydrogels with thiazolidine linkages from P-Ald PEG and B-Ald PEG had degradation times of 3 h and 1.5 weeks, respectively, while hydrogels of E-Ald PEG with pseudoproline linkages had a degradation time of 6 months. This showed that the degradation time of the hydrogels could be controlled by varying the PEG compound of the hydrogels. The mechanical properties could also be tuned by varying the PEG component, and formed hydrogels had compressive moduli between 20 and 1000 kPa. Cytotoxicity was evaluated via a cell viability test on rabbit corneal fibroblast and conducted for all hydrogel components as well as for the prepared hydrogels. Results showed excellent cell viability for all samples, with only a small reduction in viability for cells treated with 50 wt% of the hydrogel with E-Ald PEG. Adhesion to corneal tissue was tested by joining two strips of corneal tissue from rabbit eyes with a small amount of hydrogel mixture. The hydrogels were allowed to cure for 5 min before the strips were pulled apart using a crosshead speed of 0.5 mm/s. The adhesive strength was shown to increase with polymer content, up to around 700 kPa for a polymer content of 50 wt% for the hydrogel from B-Ald PEG. Finally, the leaking pressure of corneal incisions sealed with the hydrogels was measured. Hydrogels from B-Ald PEG with thiazolidine linkages could withstand the highest pressure, with a leaking pressure of above 150 mmHg. All tested hydrogels, as well as sutures, showed a leaking pressure well above 12 mmHg, which is the average intraocular pressure in the human eye. By varying the composition of the hydrogels, both the mechanical properties and the degradation behavior could be tuned for a desired application. The hydrogels prepared in this study are referred to as D-Lys_3Cys_4-B-Ald-PEG, and D-Lys_3Cys_4-E-Ald-PEG in Figure 4, which compares the leaking pressures for all hydrogels intended for corneal incision repair that are mentioned in this review.

Marcos et al. first reported on the use of dendrimers for liquid crystalline (LC) dendritic networks in 2005 with the synthesis of LC networks based on a G4 PPI dendrimer.[32] In this work, monoaldehyde functional mesogenic units and dialdehyde units were coupled to dendrimers to enable the formation of a network with liquid crystalline behavior. More recently, stimuli-responsive dendritic LC networks were synthesized by Omenat et al.[33] Here, PPI dendrimers were functionalized with mesogenic units, with and without a terminal alkyne available for crosslinking, to introduce LC properties. The dendrimer structures were designed with azobenzene photo-responsive units in the core. Terminal alkyne groups of the functionalized dendrimers were crosslinked with a tetrafunctional thiol on glass substrates. Orientation of the dendrimer films was achieved via shearing, and the LC behavior was investigated using polarized optical microscopy (POM). Extinction was observed when the rubbing direction was perpendicular to the transmission, but after a 45° rotation, transmission was observed, confirming the orientation of the material. Apart from the liquid crystalline characteristics of the networks, the azobenzene units also made the networks photo-responsive. The photo-responsive behavior of the dendritic networks was demonstrated by irradiation with UV light. Freestanding films of the LC network were cut into rectangular pieces, with the length of the pieces either parallel or perpendicular to the orientation direction. Upon irradiation with UV light, parallel films bent toward the light, while perpendicular pieces bent away from the light source.[33]

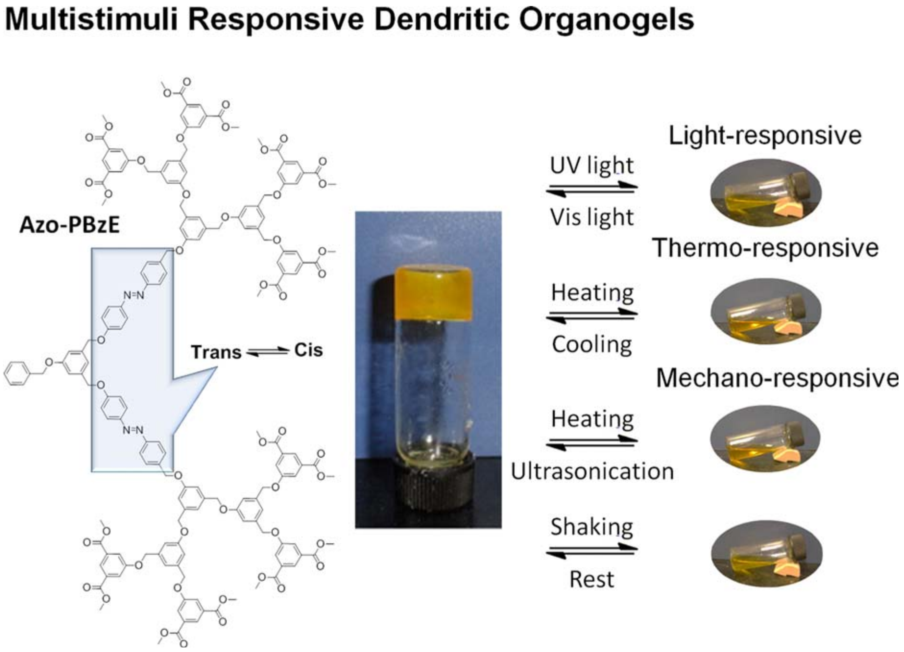


Figure 5. Multistimuli responsive dendritic organogels from azo-functional pBzE. Adapted with permission from Ref. 34. Copyright 2012 American Chemical Society. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Another example of a dendrimer-based stimuli responsive network was shown by Fan et al. in 2012.[34] A third generation poly(benzyl ether) (PBzE) dendron was synthesized with photoresponsive azobenzene groups near the focal point (Azo-G3 PBzE), showing that physically stabile crosslinked gels of Azo-G3 PBzE could be formed in most organic solvents through heating–cooling cycles and by sonication. These organogels showed response to several external stimuli, including temperature, mechanical stimuli, light, and ultrasound, as shown in Figure 5. For example, heating the formed gels caused them to lose their gel properties. The gels began to flow upon subjection to UV light, but were regenerated by irradiation with visible light, demonstrating the light–responsive behavior of the gels.

A noncovalent crosslinking strategy was introduced in a study by Meijer et al. in 2005, which detailed the construction of ionic networks based on a G5 PPI dendrimer end-functionalized with adamantylurea groups.[35] These dendrimers were able to complex with guest molecules of monodisperse oligo(tetrahydrofurane) (oligo(THF)) functionalized with urea and carboxylic acid groups. Complexation was achieved through a combination of ionic interactions between the protonated tertiary amine of the dendrimer and the terminal carboxylic acids of the guest molecules, as well as hydrogen bonding between urea groups on both the dendrimer and the guest, as shown in Figure 6. Usage of difunctional oligo(THF)s as guest molecules resulted in network formation in chloroform. The complexation between dendrimer and guest molecules was found to be both specific and directional, enabling the formation of well-defined ionic networks. Another ionic approach was shown by Kabanov et al., who exploited covalently crosslinked polyanionic hydrogels with low crosslink density, which were further swelled with cationic protonated amine functional PPI dendrimers.[36] The ionic interactions gave interpenetrating networks, with dendrimers ionically coupled to available sites on the anionic polymer. A combination of covalent and ionic crosslink strategies resulted in an elegant methodology toward interpenetrating networks for the development of advanced materials.

Another example of ionic dendrimer networks was recently published by Hvilsted et al., who reported on a facile method for the synthesis of supramolecular ionic networks based on PPI dendrimers.[37] The dendrimers were ionically crosslinked into hydrogels using dicarboxylic acid functionalized PEGs. The authors suggested that the produced polymer networks could have self-healing properties; however, this was not demonstrated.

Another interesting concept in the area of network formation is networks formed via self-assembly utilizing nonionic interactions. This concept was touched upon by Fan et al. with an investigation on the driving force for the gelation of dendritic poly(benzyl ether) (PBzE).[38] Fan et al. showed that dendrons of PBzE with peripheral isophthalonitrile rings were highly efficient as organogelators. The driving force for gelation was found to be strong multiple π–π stacking of the isophthalonitrile rings, and nonspecific hydrogen bonding. Single-crystal X-ray diffraction revealed that the isophthalonitrile rings were coplanar with internal benzyl rings, and thus the key to the self-assembly of the gel. The isophthalonitrile moiety provided a new strategy for the formation of self-assembled organogels.

Network Concepts Based on Hyperbranched Polymer Structures

The simple and large scale synthesis of hyperbranched polymers, compared to dendrimers and dendrons, enables the employment of hyperbranched polymers as promising scaffolds for

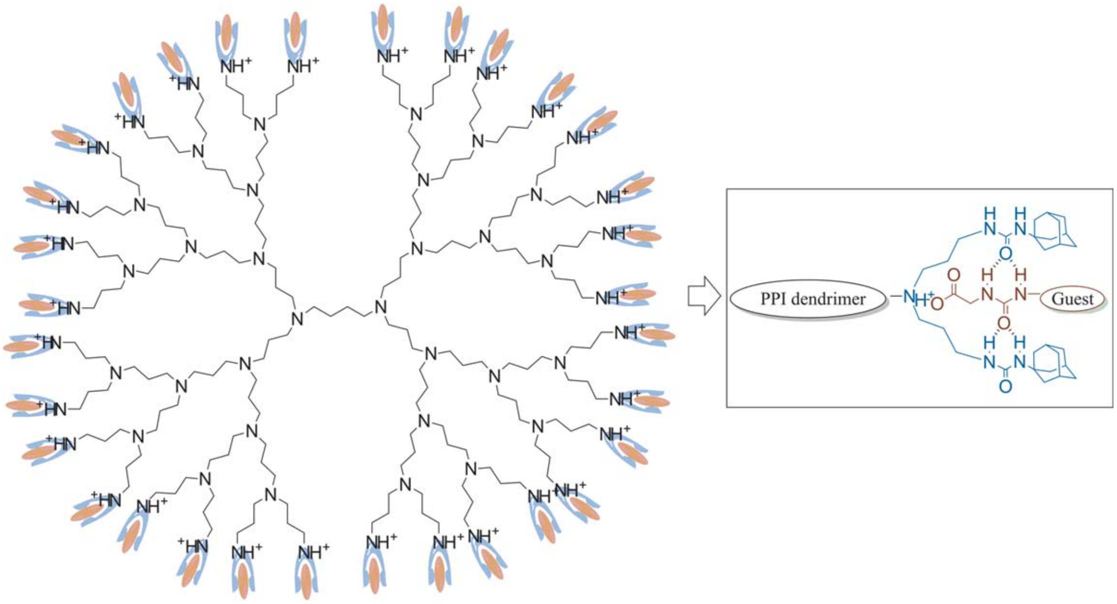


Figure 6. Schematic structure of the PPI-based ionic dendrimer used to encapsulate guest molecules in the study by Meijer et al. (left). Enlargement of the structure of the complex between peripheral groups on the dendrimer and guest molecules (right). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

application-driven research. The use of hyperbranched polymers in the field of tissue engineering is appealing, because a lack of chain entanglements and a high concentration of functional groups at the periphery lead to highly reactive polymers suitable for crosslinking and further reactions.[13,39–41] Because of their biocompatibility, simple synthetic strategy, and wide availability, both dendrimers and hyperbranched polymers based on 2,2-bis(methylol)propionic acid (bis-MPA) have been extensively studied for a myriad of applications.[42] Boltorn is a commercially available hyperbranched polymer based on bis-MPA that can be synthesized through straightforward Fischer esterification reactions.[42]

In 2010, Hult et al. reported on thermally cured nanocomposites based on montmorillonite clay nano sheets (CNS), Boltorn H30, polyol TONE 0301 for added flexibility, and hexakis(methoxymethyl)melamine (HMMM) as crosslinker, as shown in Figure 7(a).[43] Three formulations containing 0, 1, and 3 wt% CMS were prepared and then casted in 50 μm thin transparent films, as shown in Figure 7(b). Evaluation using micrographs and X-ray diffraction (XRD) revealed exfoliated CNS in the polymer composites, as shown in Figure 7(c). The CMS content was shown to have little or no impact on the adhesion and flexibility of the films; however, increasing clay content resulted in an increase in both scratch resistance and surface hardness, as well as increased T_g and storage modulus. In a later study by Hult et al., porous nanofiber papers were soaked in a methanol solution of Boltorn H30 and HMMM and consecutively crosslinked by hot pressing at 10 MPa, 140°C, and for 20 min.[44] Again, the addition of clay nanoparticles resulted in an increased T_g, from 48°C for the matrix to 71°C for composites containing 55 v% nanofibers of 20 nm in diameter. The increased T_g was believed to be a result of interactions between the matrix and the hydroxyl functional fibers causing a decreased mobility. With this study, a new nanocomposite methodology was suggested, in which the fiber reinforcement was covalently attached to the polymer matrix.

Commercial hyperbranched polymers have also received attention in other areas. In 2004 Dodiuk-Kenig et al.[45] replaced part of the 2,2-bis-[p-(2-hydroxy-3-methacryloyloxypropoxy)-phenyl]propane (Bis-GMA), commonly found in dental adhesives, with different commercially available hyperbranched polymers:

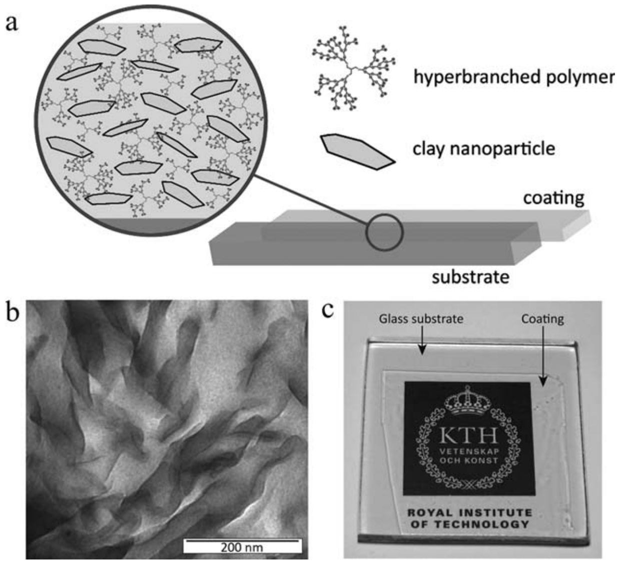


Figure 7. (a) Schematic picture of films with exfoliated CNS. (b) Coating on a glass substrate where the transparency of the film can be seen. (c) TEM micrograph of film containing 3 wt % CNS displaying the exfoliated structure. Adapted with permission from Ref. 43. Copyright 2010 American Chemical Society.

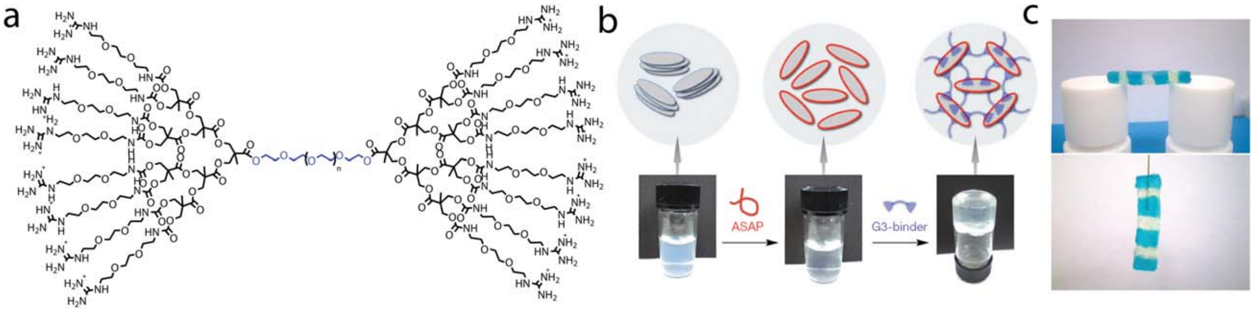


Figure 8. (a) Structure of DLD PEG-p(bis-MPA) G3 binder decorated with guanidinium at the periphery. (b) The chain of events leading to a stable gel between clay nano sheets and polymeric cationic binder. (c) Display of self-healing properties of gels resulting from G3 binder and clay nano sheets. Adapted with permission from Ref. 49. Copyright 2010 Macmillan Publishers Ltd. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Hybrane, Epox with either a rigid core or a semi-flexible core, and Boltorn. A significant increase in the mechanical properties of the formulation was associated with the addition of hyperbranched polyester amide (Hybrane), a trend not shown for other evaluated hyperbranched resins. An addition of less than 0.5 wt% of all tested hyperbranched polymers led to an increased crosslinking density, increased compressive strength, and decreased shrinkage upon curing. An addition above 0.5 wt% of the hyperbranched compound led to plasticization and hence a decreased compressive strength and increased shrinkage. The addition of Hybrane also led to increased shear strength and increased adhesion to bovine dentine, while addition of Epox had the opposite effect.

Another investigation in the field of biomedicine by Yang et al. describes the fabrication of drug-loaded hydrogels based on hyperbranched polyester (HPE).[46] A fourth pseudogeneration HPE based on bis-MPA with a 2-ethyl-2-(hydroxymethyl)propane-1,3-diol (TMP) core was synthesized according to the literature[47] and then functionalized using acryloyl chloride at three molar ratios with respect to functional groups: 40, 50, and 60%. A molar ratio of 50% of acryloyl chloride was found to result in a degree of substitution (DS) of 31.5%. The hydrophobic cavities within the globular structure of the HPE with DS 31.5% were used to encapsulate hydrophobic drugs, after which crosslinking of the acrylate moieties using UV resulted in hydrogel formation. By controlling the solid content, the compression modulus could be tuned from 3.5 kPa (40% solid content) up to 30 kPa (60% solid content). The drug release characteristics and cell adhesion of the resulting hydrogels were evaluated, and results suggested that the systems could be used in tissue engineering.

Hyperbranched polyglycerol decorated with peripheral methacrylate groups has been evaluated as biomedical hydrogels by Hennink et al.[48] By controlling the degree of substitution of methacrylate groups and the solid content, hydrogels with tunable swelling and mechanical properties were obtained. With increasing DS, an increase in storage modulus was observed, with moduli ranging from 50 kPa ($DS = 11$) up to 250 kPa ($DS = 28$); and a decrease in swelling was observed from a ratio of 1.5 ($DS=11$) to 1.2 ($DS = 28$). An increase in solid content was found to result in gels with increased storage modulus.

Network Concepts Based on Dendritic–Linear Hybrids

By amalgamating linear polymers with dendritic counterparts, a wide range of novel hybrid block copolymers can be obtained, with properties that can be traced to each individual block.[15] This combination of properties from linear and dendritic polymers creates an array of possibilities in the development of crosslinked materials. An interesting example of networks based on DLD hybrids was described by Aida et al.[49] They divergently grew up to third generation bis-MPA dendrons from the end groups of PEG diol ($M_n = 10650$ g/mol) and subsequently decorated the periphery with guanidinium, a strong cationic group, as shown in Figure 8(a). The DLD hybrids were thereafter used as organic binders, and, upon mixing with CNS, spontaneous gelation occurred as a consequence of strong ionic interactions between the dendrons and the CNSs. By using 5% CNSs, 0.38% third generation DLD binder, and 0.15% sodium polyacrylate (ASAP), mechanically stable clay reinforced hydrogels with a storage modulus of 0.5 MPa were achieved. Figure 8(b) shows the chain of events of network formation. The hydrogels displayed thermal stability up to 80°C, where boiling of water began to occur; self-healing properties with a fast recovery rate when cut and pressed together; and stability in water and tetrahydrofuran (THF). Figure 8(c) shows the self-healing properties of these gels. Two separate gels, one with blue dye and one without dye, were prepared, cut with a razor, and immediately pressed together; resulting in a self-healed gel with strength to bear its own weight in both suspension and when hanging vertically.

Another network concept with DLD hybrids was used in 2010, when Sanyal et al. reported on the use of Copper(I)-catalyzed Azide–Alkyne Cycloaddition (CuAAC) for the formation of DLD hybrids of PEG-diazide coupled with bis-MPA-based dendrons of the second and third generation, having an alkyne functional focal point.[50] The hybrids were further functionalized with alkyne anhydride to give DLD macromolecular crosslinkers with 8 or 16 peripheral alkyne groups in total, for G2 and G3, respectively. The material was subsequently crosslinked with diazide triethylene glycol through CuAAC click reaction to give dendritic hydrogels. Unreacted alkyne groups were shown to be available for additional functionalization with azide functional compounds, including fluorescent dyes and bioactive biotin, providing a versatile hydrogel platform with potential use in biomedical applications.

A similar hybridization concept by Malkoch et al. described the synthesis of DLD hybrids comprising linear PEG and hyperbranched bis-MPA blocks.[51] PEGs of different molecular weights ($M_n = 2\ 000$, 6 000, 20 000 g/mol) were used as templates for the dendronization of bis-MPA using acid catalyzed polycondensation reactions. A library of DLD-hybrids, ranging from second to seventh generation with functional group densities reaching up to 256 groups, was produced. Water-soluble DLDs with 20k PEG of generation three to four were postfunctionalized with allyl moieties and crosslinked with tris[2-(3-mercaptopropionyloxy)ethyl] isocyanurate (triazine thiol) or TMP-trismercapto propionate (TMP-thiol) via UV-initiated thiol-ene chemistry. The third generation hybrid crosslinked with triazine thiol displayed the largest swelling of around 750% and had a tensile modulus of 47 kPa**.** The highest tensile modulus was observed for the fourth generation hybrid crosslinked with TMP-thiol, with a value of 557 kPa and a swelling of 250%.

Other PEG-based hybrids were reported by Grinstaff et al., who produced DLD-hybrids based on glycerol and succinic acid from first to third generation with a PEG core ($M_n = 3400$ g/mol) (DLD-1).[52] All three generations were functionalized using methacrylic anhydride to yield photo crosslinkable resins that were evaluated as tissue sealants in cornea laceration repair. The repair was carried out by depositing 4 μL of dendritic sealant on a 4.1 mm long linear laceration, followed by photo polymerization using an argon laser. The sealant pressure was measured by injecting saline solution in the anterior chamber via a syringe through the scleral wall until the repair leaked. The total pressure was measured and used to quantify the strength of the repair. A leaking pressure of 90 ± 18 mmHg was measured for conventional sutures. The first generation DLD-hybrid (PEG-G1-methacryl-1) synthesized in this study was found to outperform sutures with regards to sealant pressure, with a pressure of 171 ± 44 mmHg, and the total procedure time for the repair was approximately one fifth of that using sutures. In a consecutive study, Grinstaff and Kim and coworkers evaluated PEG, glycerol, and succinic acid methacrylated first generation DLD-hybrid (PEG-G1-methacryl-2) and sutures for a cornea repair. Both a linear wound (4.1 mm) and a stellate wound (4 x 3 mm^2) were evaluated, and the performance of the sealants was compared with that of conventional sutures.[53] The linear wound displayed a leaking pressure of 78.8 ± 27.8 mmHg for sutures and 109.6 ± 82.7 mmHg for the PEG-G1-methacryl-2 adhesive. The stellate wound had a mean pressure of 57.8 ± 28.9 mmHg for sutures and 78.7 ± 59.6 mmHg for the G1 adhesive. A larger standard deviation could be noted for the tissue sealant, but the conclusion was that both sutures and sealant could withstand the requirements for cornea laceration repair. In comparison, the commonly used fibrin sealant Tisseel has a leaking pressure of around 40 ± 5.6 mmHg for a 3-mm linear laceration.[54] The highest expected pressure inside the eye is ∼60 mmHg, recorded for sneezing or coughing.[31]

Most recently, Malkoch et al. described the synthesis of dual-functional DLD hybrids based on PEG and bis-MPA.[55] By using PEG as a hydrophilic block, first and second generation orthogonally functionalized DLDs were constructed using an AB$_2$C monomer displaying two allyl groups and one azide. The addition of the azide functionality provided an opportunity for controlled functionalization via CuAAC click chemistry. Biotin, L-dopamine (DOPA) and D-mannose (Man), all biomedically relevant groups, were coupled to the hybrids, which were subsequently crosslinked with a thiol functional 2 kDa PEG as a crosslinker utilizing thiol-ene chemistry. By varying the molecular weight of the PEG core and the generation of the dendritic segment, the modulus could be tuned to mimic that of tissues in the body, from soft brain tissue (0.1–1 kPa) to stiff osteoid collagen (25–40 k Pa). The dendritic hydrogels displayed high cell viability toward human dermal fibroblasts. The low toxicity, coupled with tunable moduli, apparent degradation possibilities, and azides available for further functionalization rendered scaffolds suitable for artificial extra cellular matrices.

CONCLUSIONS

This review details the potential applications for networks based on dendritic structures, ranging through materials for catalytic processes, composite materials, and biomedical applications, to mention a few. As the field of dendritic structures is a fast growing area, the development of new advanced dendritic structures will increase the number of possible applications. The large number of possible functionalities that can be incorporated into a dendritic structure and networks enable the use of a wide range of crosslinking strategies, which in turn provide an extensive platform for the development of dendritic networks. Much research regarding the synthesis of networks based on dendritic structures is being conducted on readily available, already commercial dendritic alternatives. As the market for dendritic polymers continues to develop, we envision that the area for dendritic network structures will gain more interest.

ACKNOWLEDGMENTS

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