PEG-dendritic block copolymers for biomedical applications

Ana Sousa-Herves, Ricardo Riguera and Eduardo Fernandez-Megia*

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The incorporation of poly(ethylene glycol) (PEG) chains at the focal point of dendrimers results in customizable platforms where the careful selection of the PEG length, the nature of the peripheral groups, and the structure and generation of the dendritic block entails materials for specific applications in the biomedical field. In this focus article, the synthesis, properties, and biomedical applications of PEG-dendritic block copolymers are discussed with examples in drug and gene delivery, tissue repair, and diagnosis.

Introduction

Dendrimers are synthetic tree-like macromolecules composed of repetitive layers of branching units that emerge from a central core (Fig. 1). They are prepared in a controlled iterative fashion, through generations with nil dispersity, precise molecular weight, and discrete properties.[1] Their globular architecture and size in the nanometer scale render dendrimers with applications in a plethora of fields from catalysis to materials science.[2] In addition, the inherent multivalency of dendrimers allows the controlled display of specific drugs, targeting and imaging agents of interest in drug delivery (DD) and other biomedical applications.[3]

Department of Organic Chemistry and Center for Research in Biological Chemistry and Molecular Materials (CIQUS), University of Santiago de Compostela (USC), Jenaro de la Fuente s/n, 15782 Santiago de Compostela, Spain. Tel: +34 8818 15727; E-mail: ef.megia@usc.es

Linear-dendritic block copolymers, originally described by the group of Fréchet in the early 1990's (Fig. 1),[4,5] constitute interesting dendritic structures with the ability to self-assemble in solution due to differences in the solubility properties of the blocks. Poly(ethylene glycol) (PEG) is a FDA-approved linear hydrophilic polymer widely used for engineering nanosystems for DD and diagnosis.[6] Its incorporation at the focal point of dendrimers grants the resulting block copolymers with stealth properties, increased solubility and circulation times in the blood stream, as well as with reduced toxicity and immunogenicity.

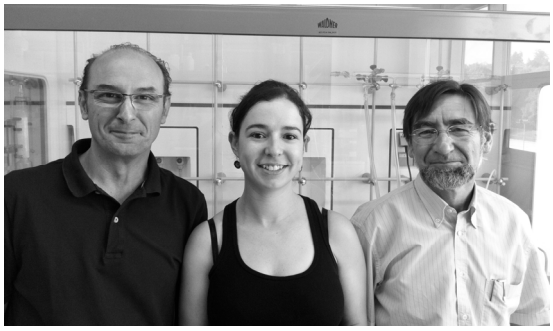
This focus article highlights the use of PEG-dendritic block copolymers as versatile multivalent structures for biomedical applications.

Synthesis of PEG-dendritic block copolymers

PEG-dendritic copolymers of the types AB diblock, ABA triblock, and star-shaped A_nB_n (A: dendritic block, B: PEG block) have been prepared following three main synthetic strategies (Fig. 1).[5]

a) Direct coupling between the end groups of linear polymers and the reactive focal point of dendritic wedges (dendrons). This was the strategy followed by Fréchet and coworkers in their pioneering preparation of PEG-dendritic block copolymers of the types AB and ABA with poly(benzyl ether) dendrons of generation 3 and 4 (G3, G4).[4]

b) Chain-first: In this approach the dendritic block is prepared in a divergent fashion from a PEG chain at the focal point by taking advantage of its properties as a soluble polymeric support. This strategy was first described by Chapman and coworkers in 1994 for the preparation of amphiphilic AB type copolymers incorporating ***N***-Boc protected poly-*L*-lysine (PLL) dendrons (up to G4).[7] The general scope



A.S.-H. (center) received BS (Hons) in Chemistry from USC in 2005. She is currently doing PhD studies at the group of R.R. and E.F.-M working on the preparation of dendritic nanostructures for biomedical applications.

R.R. (right) received a PhD in Chemistry from USC in 1973. In 1978 he was appointed Lecturer at USC and became Professor in 1990. His research covers bioactive natural products and methods for determination of absolute configuration. He is now interested on nanostructures and stimuli responsive polymers.

E.F.-M. (left) completed a PhD in Chemistry in 1995 at USC. After a postdoctoral stay at Cambridge University (Steven V. Ley) he returned to USC. He was appointed Profesor Titular in 2009. His research focuses on the interface between organic and polymer chemistry with emphasis on polymeric nanostructures for biomedical applications and the development of NMR tools for their characterization.

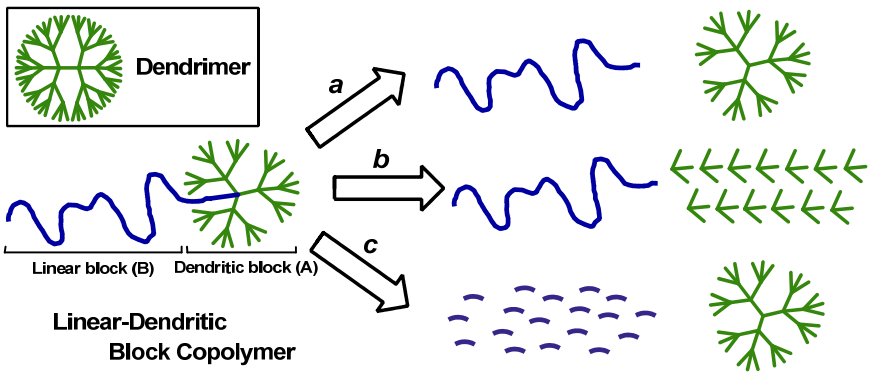


Figure 1. Synthetic strategies towards linear-dendritic block copolymers: a) Direct coupling, b) Chain-first, c) Dendron-first. Adapted from ref. 5.

of this route has later been demonstrated in the preparation of copolymers of PEG with various dendritic families, including bis-MPA [based on 2,2-bis(methylol)propionic acid],[8] poly(glycerol−succinic acid),[9] carbosilane,[10] poly(amido amine) (PAMAM),[11] gallic acid-triethylene glycol (GATG),[12] poly(benzyl ester),[13] triazine and carbosiloxane dendrimers.[14]

c) Dendron-first: In this approach, copolymers are obtained by polymerization of the linear block using a dendritic macroinitiator. This strategy, developed by the group of Fréchet in 1994 for the anionic ring-opening polymerization (ROP) of ε-caprolactone,[15] has been more recently applied by Gitsov and coworkers for the polymerization of ethylene oxide from a G3 poly(benzyl ether) dendron.[16]

Micelles for drug delivery

During the last decades, polymeric assemblies have attracted an enormous interest due to their potential applications as nanoreactors, nanotemplates, and in DD.[17] In this context, PEG–dendritic block copolymers are especially appealing due to their tunable ability (PEG length, dendrimer generation) to assemble into different nanostructures.[18] Micelles composed of a dendritic core surrounded by a palisade of flexible PEG chains have emerged as nanocarriers for the encapsulation or covalent incorporation of biologically relevant molecules. The PEG corona in these systems ensures colloidal stability, improved solubility, and long circulation times in the blood stream,[19] which in addition to their small size (usually below 150 nm) enables a passive accumulation into solid tumors thanks to the enhanced permeability and retention (EPR) effect.[20]

The tendency of amphiphilic PEG-dendritic block copolymers to self-aggregate in aqueous media was already revealed in the early reports by the groups of Fréchet[4] and Chapman.[7] A detailed study on the properties of ABA copolymers composed of PEG and poly (benzyl ether) dendrons showed formation of mono- or multimolecular micelles depending on dendrimer generation and solvent, and the possibility to encapsulate hydrophobic molecules with high efficiency for periods longer than 12 months.[21] Shortly after, again the group of Fréchet prepared related star-shaped (A_4B_4) copolymers and studied their aggregation behaviour as a function of solvent.[22] Similar studies on the aggregation of AB and ABA block copolymers with carbosilane,[10] triazine, and carbosiloxane dendrons[14] have also been performed.

Several reports have taken advantage of these aggregation properties for application in DD. In a series of relevant contributions, Fréchet and coworkers elegantly developed stimuli-responsive nanocarriers based on PEG-dendritic block copolymers. In their strategy towards micelles with pH-sensitivity at the characteristic low values of solid tumors and the endosome/lysosome cellular compartments (~5.0-6.0), hydrophobic groups were attached at the periphery of dendritic PLL or bis-MPA blocks using highly acid-sensitive acetal linkers (Fig. 2).[23] Polymeric micelles were formed (20-35 nm) in aqueous media at neutral pH that encapsulated the fluorescent probe Nile Red. At acidic pH, upon hydrolysis of the acetal groups, block copolymers became hydrophilic with concomitant destabilization of the micelles and release of the dye. Properties such as the rate of release, critical micelle concentration (CMC), and size could be tuned in this system by modifying the

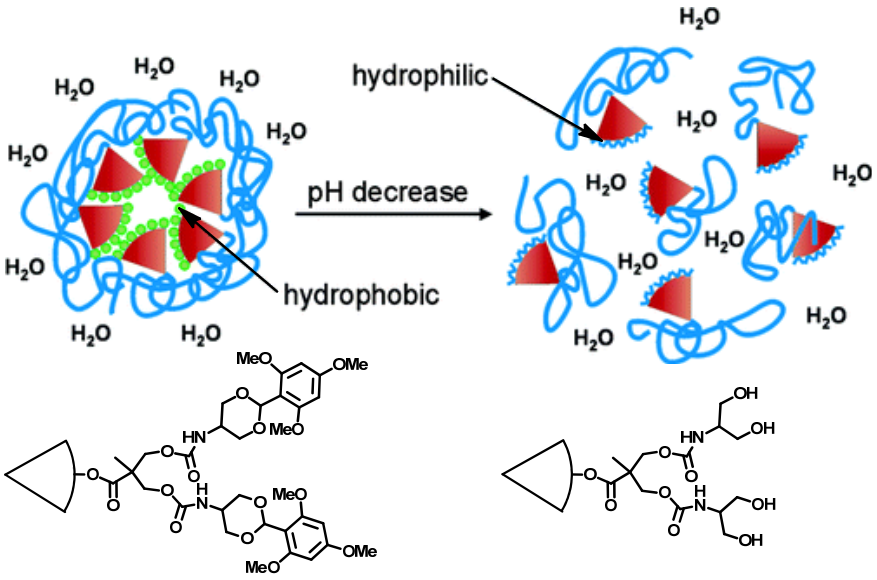


Figure 2. Schematic representation of pH-sensitive micelles prepared from PEG-dendritic (bis-MPA) block copolymers functionalized with peripheral hydrophobic groups using highly acid-sensitive acetal linkers. Reproduced with permission from ref. 23.

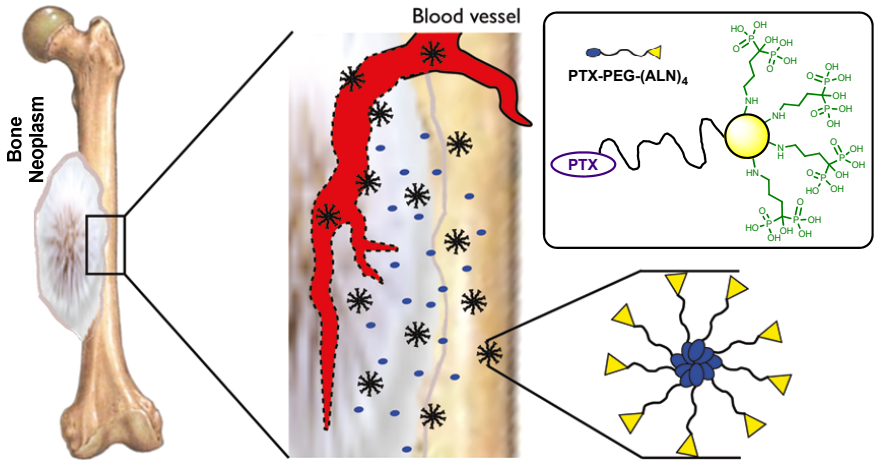


Figure 3. Micelles prepared by self-assembly of a PTX-PEG-(ALN)$_4$ copolymer have shown a great binding affinity for the bone mineral hydroxyapatite and cytotoxic activity against prostate cancer cells [PTX (paclitaxel); ALN (alendronate)]. Reproduced with permission from ref. 29.

PEG length, the structure and generation of the dendritic block, and the nature of the dendrimer-acetal linker. Shortly after, one of the copolymers based on a G3 bis-MPA dendron was employed for the encapsulation of doxorubicin (DOX).[24] *In vitro* toxicities revealed empty micelles to be relatively non-toxic, while those encapsulating DOX showed toxicity similar to that of the free drug. Interestingly, differences in the intracellular fate of encapsulated and free DOX were seen. Following a similar strategy, the group of Fréchet has also developed micelles from PEG-dendritic copolymers carrying peripheral diazonaphthoquinone residues (hydrophobic), which upon irradiation with near infrared (NIR) light, rearrange into more hydrophilic moieties and trigger the delivery of hydrophobic payloads (Nile Red).[25]

Related examples on the use of PEG-dendritic block copolymers (AB and ABA) for the preparation of micelles have been reported by the group of Dong.[26] Copolymers hydrophobically functionalized with poly(ε-caprolactone) (PCL) or poly(γ-benzyl-L-glutamate) (PBLG) chains at the terminal amino groups of PAMAM dendrons were prepared by a combination of Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) and ROP. These copolymers were able to aggregate into micelles where DOX was encapsulated with high loading efficiency. The resulting system displayed a sustained release profile. The group of Malkoch has prepared analogous PEG-dendritic copolymers decorated with PCL chains at the periphery of bis-MPA dendrons, which revealed useful in the production of micelles and honeycomb membranes.[27] Their results indicate lower CMC for these copolymers compared to linear PEG-PCL copolymers of similar molecular weight.

Luo, Lam, and coworkers have also described well-defined micelles from PEG-dendritic block copolymers hydrophobically functionalized with cholic acid at the periphery of PLL dendrons.[28] The resulting copolymers were used for the encapsulation of paclitaxel and studied for the treatment of ovarian cancer in mice [paclitaxel (PTX) is a potent cytotoxic agent approved as a first line of therapy for metastatic breast cancer and tested in the clinic for the treatment of metastatic prostate cancer]. A NIR dye was also encapsulated to allow a real-time study of micelle distribution and targeting *in vivo*. PTX loaded micelles with size 17-60 nm showed prolonged circulation times and preferential accumulation in ovarian cancer murine models *via* EPR effect, which resulted in enhanced therapeutic efficacy compared to FDA-approved Taxol® and Abraxane®.

In a complementary approach designed to treat bone metastases derived from breast and prostate cancers, Pasut and coworkers have covalently linked PTX at the end of the PEG chain in a PEG-dendritic block copolymer (based on β-glutamic acid repetition units) decorated with four alendronate (ALN) molecules at the dendritic surface (Fig. 3).[29] ALN is a bisphosphonate with high affinity for the bone mineral hydroxyapatite which is used as ligand for bone targeting. ALN also shows an effective antiangiogenic activity. The resulting PTX-PEG-(ALN)$_4$ dendritic conjugate aggregated into micelles with PTX at the core and the hydrophilic ALN molecules exposed on the surface to confer enhanced solubility and bone targeting properties. These micelles demonstrated a great binding affinity for hydroxyapatite *in vitro* and an IC$_{50}$ comparable to that of the free drugs combination in human adenocarcinoma of the prostate (PC3) cells. In addition, the conjugate exhibited an improved pharmacokinetic profile compared with the free drugs owed to the marked increase in their half-life.

Polyion complex (PIC) micelles constitute another promising type of DD system that can be prepared from PEG-dendritic block copolymers. PIC micelles are formed by electrostatic interaction between oppositely charged polyions and, similarly to classical polymeric micelles, are characterized by a core-shell structure.[30] Properties such as their small size, electrical neutrality, and narrow size distribution make these systems highly attractive for DD applications. Our research group has reported the preparation of remarkably stable PIC micelles (25 nm) from an anionic PEG-dendritic block copolymer of the GATG family (decorated with 27 peripheral sulfates) and an oppositely charged poly(amino acid).[31] Notably, these micelles displayed enhanced stability against dilution and ionic strength compared to PIC micelles from linear PEGylated copolymers, which has been ascribed to the more rigid dendritic architecture. In a similar fashion, we have more recently developed related pH-sensitive PIC micelles with potential application in DD and cancer therapy.[32]

Applications in gene therapy

Gene therapy aims the transfer of nucleic acids into cells to correct genetic defects or confer new functions.

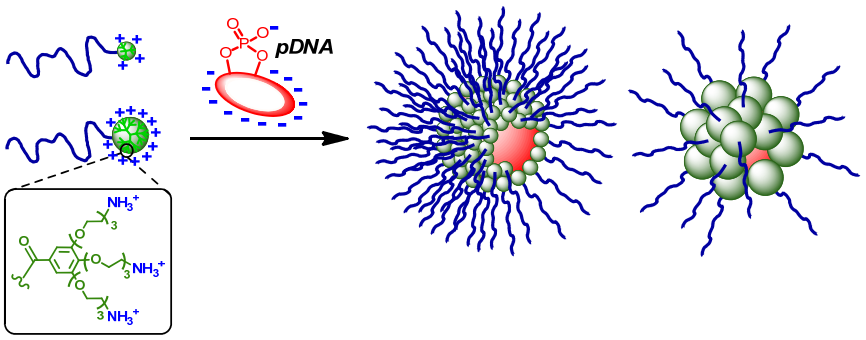


Figure 4. Schematic representation of dendriplexes prepared from a plasmid DNA (pDNA) and two generations of PEG-dendritic (GATG) block copolymers as nanostructures with core-shell stoichiometry determined by steric reasons. Reproduced with permission from ref. 39.

Although with an enormous potential for the treatment of inherited and acquired diseases, the clinical application of nucleic acids is hampered by their low stability under physiological conditions and poor internalization efficiency. As a result, vectors capable of delivering nucleic acids have been developed. They were firstly based on modified viruses, and more recently on cationic synthetic carriers which electrostatically interact with negatively charged nucleic acids.[33] Among the latter, dendrimers have received special attention, with PAMAM and poly(propylene imine) being by far those most frequently referred.[34] Unfortunately, some limitations of cationic delivery vectors relate to aggregation with blood components and cytotoxicity. In the case of dendrimers, PEGylation has been explored as a way to mask the positive charge of the resulting complexes (dendriplexes).[34] When PEGylation is performed at the focal point, the resulting PEG-dendritic block copolymers lead to sterically stabilized dendriplexes with lower ξ potential, reduced cytotoxicity, and increased circulation times.

Some of the most relevant contributions of PEG-dendritic block copolymers to gene therapy have been described by the group of Park. In a series of pioneering works, they prepared AB and ABA PEG-dendritic block copolymers based on PAMAM and PLL dendrons, which after incubation with plasmid DNA (pDNA) resulted in compact dendriplexes with enhanced water solubility and reduced toxicity.[35] In these examples, higher dendrimer generations led to more effective complexation to pDNA and protection towards degradation by DNAse I. Although PAMAM dendrons granted somewhat higher transfection efficiency (TE) than PLL (endosome buffering effect), low levels of TE were typically observed as a result of PEG limiting interaction with cell surfaces. Interestingly, in a more recent contribution, a G5 PAMAM-PEG-PAMAM copolymer was peripherally decorated with arginine residues which afforded dendriplexes displaying 30 times higher TE than the native dendriplex. This has been interpreted as arginine ligands benefiting from an extended repertoire of uptake pathways.[36]

Langer, Hammond, and coworkers have exploited the incorporation of carbohydrates as ligands at the end of PEG in PEG-PAMAM block copolymers as a means for targeting pDNA to cells bearing carbohydrate receptors.[37] Interestingly, these authors showed dendriplex size to be relatively insensitive to dendron G and nitrogen to phosphate ratio (N/P), suggesting that dendriplexes consist of a single pDNA. Application of the same concept to peptide ligands has been adapted by the same authors and other groups for targeting cancer cells overexpressing clinically relevant tumor antigens.[38]

More recently, in a joint effort of our group with that of Alonso, the ability of amino-fuctionalized GATG dendrimers and their block copolymers with PEG to complex pDNA has been evaluated.[39] Based on the variation of the dendriplex size and ξ potential with G, N/P, and the presence of PEG, dendriplexes have been described as core-shell nanostructures with sterically induced stoichiometry. A single pDNA condensed at the core is surrounded by a shell of dendrimers with a stoichiometry determined by the core/dendrimer relative size: the higher the dendrimer G, the fewer dendrimers can be accommodated on the dendriplex surface (Fig. 4). Interestingly, in the case of PEG-dendritic block copolymers, this results in the possibility to tune the PEG density on the surface, and hence in a means to control the steric stabilization of the dendriplex.

Other biomedical applications

In addition to the above supramolecular nanostructures, PEG-dendritic block copolymers have also found application in DD as macromolecular scaffolds and containers for drugs, imaging agents, targeting ligands, and other biologically relevant molecules. In this context it is worth mentioning the seminal work by Fréchet, Szoka, and coworkers who prepared A_3B_3 star-shaped polymers carrying G2 bis-MPA dendrons for the delivery of DOX.[40] To achieve a selective drug release, acid-labile hydrazone linkages were selected for attaching DOX on the dendritic surface. The resulting water-soluble, non-toxic structure showed little accumulation in vital organs and enhanced serum half-live compared to free drug. Similar strategies have later been adapted by other groups for alternative drugs, either covalently bound or encapsulated within the dendritic block of AB and ABA copolymers (cisplatin, 10-hydroxycamptothecin) with promising *in vitro* and *in vivo* results.[41]

In a more recent contribution, Albertazzi, Hawker, and coworkers have reported the preparation of ABA copolymers carrying dendrons internally functionalized with hydroxyl groups that were envisioned as handles for hydrophobic molecules.[42] Multiple units of a coumarin, selected as model hydrophobic agent, were attached at the dendrimer interior through ester bonds that were enzymatically hydrolysed at the endosome (B16 mouse melanoma cells).

Another interesting application of PEG-dendritic block copolymers is the

preparation of biocompatible hydrogels for DD, tissue engineering, and wound healing. The group of Grinstaff has achieved significant success in this field by crosslinking PEG-dendritic copolymers as ocular sealants.[9,43] Photocrosslinkable ABA copolymers carrying poly(glycerol−succinic acid) dendrons were functionalized with terminal methacrylate groups and studied as sealants for corneal lacerations with better results than conventional sutures. Application of these and related PEG-dendritic hydrogels to cartilage and osteochondral repair have also been reported by the same group.[44]

In recent years, PEG-dendritic block copolymers carrying paramagnetic ions have found application as contrast agents (CA) in magnetic resonance imaging (MRI). Particularly interesting is the use of these macromolecular CA in quantitative studies of microvessels and for prolonged angiographies, both of great interest in cancer imaging evaluation. Brasch and coworkers have prepared copolymers of the type ABA with PLL dendrons (various generations and PEG molecular weights) functionalized with peripheral Gd chelates.[45] A copolymer with a high molecular weight PEG chain (20000 Da, large hydrodynamic radius) was identified in dynamic MRI assays as a promising CA in diagnosis since it leaks from microvessels in cancer tissue, but remains in circulation in benign soft tissues. In a related work, Shih and coworkers employed an ABA copolymer carrying G3 bis-MPA dendrons functionalized with peripheral folate ligands and Gd chelates in the diagnosis of folate receptor-positive tumors in mice.[46]

From a synthetic point of view, one of the major difficulties in the preparation of dendritic CA for MRI is their complete surface functionalization with metal chelates, which often leads to mixtures of compounds with varying degrees of substitution. This way, not only the advantage of starting from monodisperse materials is lost, but the final products become strongly batch-dependent. In this regard, our research group has recently reported the advantage of using CuAAC for this goal by allowing the complete incorporation of preformed Gd chelates onto the dendritic surface of PEG-GATG block copolymers in very high yields.[47] The analysis of the physical and pharmacokinetic properties *in vitro* and *in vivo* of this new family of PEG-dendritic CA (contrast enhancements similar to Gadomer-17) revealed them as a promising platform for the development of CA for MRI.

Finally, emerging niches for biomedical application of PEG-dendritic block copolymers include CA for computed tomography[48] and their use as scaffolds for *in vivo* antibody suppression.[49]

Conclusions

PEG-dendritic block copolymers have consolidated as a customizable multivalent platform for the design of materials for specific applications in the biomedical field. The careful selection of the PEG length, the structure and generation of the dendritic block, and the nature of the peripheral groups has allowed fine-tuning their solubility, assembly properties, and supramolecular interactions. In addition, the monodisperse dendritic block facilitates the controlled incorporation of biologically relevant molecules at specific positions with unprecedented selectivity in the polymer field. This way, effective systems for drug delivery, targeting, and diagnosis have been produced during the last decade, including micelles, polymer-drug conjugates, contrast agents, and hydrogels. Despite this success, however, challenges are still ahead awaiting imaginative solutions. Thus, the costly stepwise synthesis of dendritic structures warrants further efforts to develop accelerated procedures for their preparation. In addition, although PEG-dendritic copolymers have revealed distinct advantages over their PEG-linear analogs in the biomedical field, precise comparative studies are required to identify innovative functions associated to the branched dendritic architecture.

Acknowledgements

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Graphical abstract

The incorporation of poly(ethylene glycol) (PEG) chains at the focal point of dendrimers results in customizable platforms for the design of materials for specific applications in the biomedical field. In this focus article, the synthesis, properties, and biomedical applications of PEG-dendritic block copolymers are discussed with examples in drug and gene delivery, tissue repair, and diagnosis.