Life Sciences 233 (2019) 116754

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Peptide dendrimers as valuable biomaterials in medical sciences

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ARTICLE INFO

Keywords:
Peptide
Dendrimer
Bioactivity
Therapeutic
Diagnostic

ABSTRACT

Peptides are oligomers of amino acids, which have been used in a wide range of applications, particularly in medical and pharmaceutical sciences. Linear peptides have been extensively developed in various fields of medicine as therapeutics or targeting agents. The branched structure of peptide dendrimers with peptide (commonly, poly L-Lysine) or non-peptide (commonly poly-amidoamine) core, often exhibits valuable novel features, improves stability and enhances the functionality of peptide in comparison with small linear peptides. The potential applications of Branched and hyper-branched peptidic structures which are known as peptide dendrimers in biomedical sciences have been approved vastly. A peptide dendrimer contains three distinct parts including core, building blocks and branching units or surface functional groups. These structures provide a lot of opportunities in the pharmaceutical field, particularly for novel drug development. In this review, a brief summary of different biomedical applications of peptide dendrimers is presented, and peptide dendrimers as active pharmaceutical ingredients and drug delivery carriers are discussed. Applications of peptide dendrimers in vaccines and diagnostic tools are also presented, in brief. Generally, peptide dendrimers are promising biomaterials with high evolution rate for clinical and non-clinical applications in medicine.

1. Introduction

Dendrimers are hyper-branched structures with a central core and flexible surface functionality that are able to entrap, complex and/or conjugate with therapeutic agents, and they are attractive carriers for drugs. Nowadays, there are a number of established chemical approaches to synthesize dendrimers, as well as, various methods for enhancing their physicochemical features and biocompatibility. Different types of monomers can be used to generate spherical dendrimers, but a vast range of them led to the cytotoxic products, basically due to their high charge. Besides, they had limited half-life and rapid clearance through their *in vivo* applications. Coating and functionalization of dendrimers can rectify these limitations as well as induce site-specificity and targeting property to spherical dendrimers [1,2]. Dendrimers prepared from amino acids residues, are called peptide dendrimers. Peptide dendrimers are spherical hyper-branched biomacromolecules with a peptidyl core, building blocks or branching units, containing respectable surface functional units for covalent attachment of other chemo/biomolecules [3,4]. Most of recently synthesized peptide dendrimers have been prepared without core, which are characterized with branching unit and highly functional surface. Dendrimer roots in a Greek word of 'Dendron' that means 'tree-like', in combination with the 'mer' that means 'part' [4,5]. In this review, a brief illustration of structure and synthesis of peptide dendrimers is presented. Then, different reported modifications on peptide dendrimers are discussed. Finally, their promising application in therapeutic and analytical fields of biomedicine are summarized.

2. Structure of peptide dendrimer

Peptide dendrimers can be prepared through polymerization of amino acids or small peptide units. In other words, peptide dendrimers generally are the dendrimers with peptide bonds in their structures (Fig. 1) [6]. Scientists classified peptide dendrimers in three categories, according to position of amino acids in the dendrimer structure. Types I and II are the covalent peptide dendrimers, prepared from natural or un-natural amino acids, incorporated into the dendrimer core, building blocks, or branching units. Type III is non-covalent peptide dendrimers, in which amino acids or peptides residues complex non-covalently with a non- peptidic framework at surface [7]. One of the most common

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https://doi.org/10.1016/j.lfs.2019.116754
Received 28 May 2019; Received in revised form 31 July 2019; Accepted 11 August 2019
Available online 12 August 2019
0024-3205/

applied and commercially available polymeric cores for synthesis of peptide dendrimers is poly-amidoamine (PAMAM) core. Peptides or proteins can be attached to this structure which results in various functional peptide dendrimers. A wide range of molecular weights have been reported for peptide dendrimers from low molecular weight structures (about 2KDa) to large structures with more than 100 KDa molecular weight [4]. Peptide dendrimers like other dendrimers may be presented in different generations based on the layer of branching from G_0 to G_n, in which n represented the number of branching cycles during synthesis. Higher generations have more functional or branching unites at their surface [7]. One of the common structures of peptide dendrimers is poly-L-Lysine dendrimeric structures. These structures consist of two classes, α-poly-lysine and ε-poly-lysine, which the former is more toxic and artificially synthesized, however, the naturally occurring ε-poly-lysine has exhibited more promising chemical and biological properties and improved safety profile [8].

Rather than classical peptide dendrimers with symmetric branching structure containing constant length of branching units, some of peptide dendrimers have been asymmetrically synthesized, which have different length in branching units radiated from core. Presence of different spacers in central core or branches of dendrimers would make a particular asymmetry in structure that changes the conformational and physicochemical features of asymmetric peptide dendrimers. In general, asymmetric peptide dendrimers may have particular properties regarding self-assembly or complexing with other moieties [9].

A recent study introduced a novel bioreducible fluorinated peptide dendrimers from low generation peptide dendrimers, in which the chemical modification improved the cellular uptake, endosomal escape, cytoplasmic trafficking and nuclear entry of dendrimeric structure. Therefore, this type of peptide dendrimers was reported as a proper carrier for therapeutic oligonucleotides delivery [10].

With regards to an *in-silico* study on structural features of peptide dendrimers, it was reported that the presence of positively charged amino acids had influence on the structural properties including the number and placement of charged amino acids in the dendrimeric structure. Peptide dendrimers with high content of charged residues have more structural plasticity, and reduced content of charged residues can increase the structural rigidity [11].

3. Conjugation/combination of peptide dendrimers with other moieties

3.1. Self-assembly of dendrimeric peptides

The large size and controllable functionalities of dendrimers make them an ideal choice for being assembled into supra-molecular structures in solutions. Polar dendrimers such as peptide dendrimers might be aggregated in less polar solvents which is dependent on the reaction condition and temperature [12]. Self-assembly of dendrimeric peptides, forced by inter- or intra- molecular non-covalent interactions, such as electrostatic, hydrophobic or hydrogen bonding can result in the formation of supramolecular structures of peptide dendrimers, emerging novel physicochemical features [13]. Similarly, it was showed that the introduction of urea or urea-triazole at the core of peptide dendrimer could result in the self-assembly of these structures and resulted in a fibrillar morphology. These supra-molecular structures form gel in the presence of organic solvents, which has great importance in the pharmaceutical applications [14]. Regarding the self-assembly of surface functional groups, peptidesomes were introduced, which have nanoparticulated structure. They mimic viral capsid and have promising functions in gene transfection and can be applied as non-viral vectors for gene therapy. A type of peptidosome were built through a two-step self-assembly of globular peptide dendrimers with lysine residues at ends of branches and poly (L-leucine) carrying one glutamic acid residue [15]. Self-assembly of Zn-mesoporphyrin as a chromophore to peptide dendrimers, especially cationic peptide dendrimers, can result

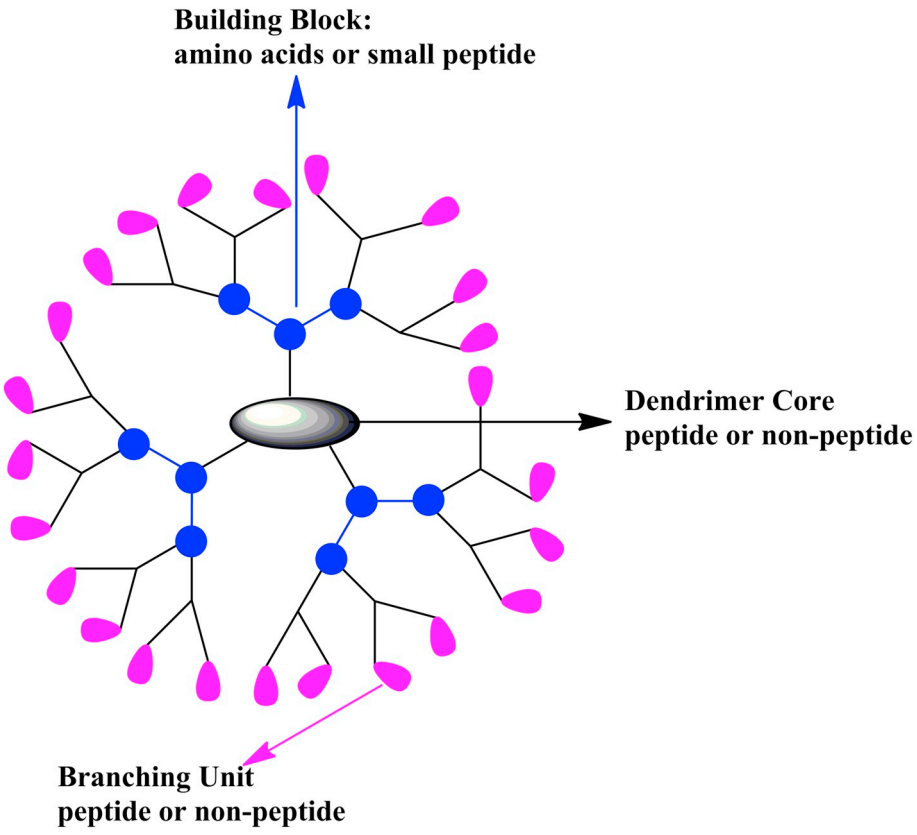

Fig. 1. Typical structure of a peptide dendrimer; three types (I-II-III) of peptide dendrimers are produced according to the position of amino acids or peptides.

Table 1
Several examples of peptide dendrimer decorated nanoparticles.

Nano-composite structure	Application	Ref.
Ternary nanoparticles of [poly(carboxybetaine methacrylate) (pCBMA)(peptide dendrimer-modified carbon dots (CD-D)/doxorubicin (DOX))]	pH responsive tumor-specific drug delivery and highly efficient cancer therapy	Ma et al. [30]
Magnetic mesoporous silica nanoparticles coated with polyglutamic acid peptide dendrimer (G3),attached to arginine-glycine-aspartic peptide (RGD); with or without Nottokinase	Dual targeted thrombolysis	Huang et al. [31]
Glutamic acid-modified iron oxide nanoparticles modified EDA-KR2 peptide dendrimer (arginine branching unit)	Improved cancer therapy by combining chemotherapy with magnetic hyperthermia.	Nigam and Bahadur [32]

in light-harvesting nano-structures with an efficient biomimetic functionality, similar to photosynthetic systems [16–18].

Lipidated peptide dendrimers are amphiphilic structures that can self-assemble in to micellar particles. Therefore, these type of modified peptide dendrimers are good candidates for the delivery of low soluble therapeutic agents. For example, decanoic acid addition onto the core peptide dendrimer with 4 positively charged arginine residues at branching unit led to an amphiphilic molecule, which could quickly assemble into micelles at/above the critical micelle concentration. Therefore, this structure was able to encapsulate the negatively charged bufalin, as an anti-cancer steroidal structure and therefore, improved the bufalin solubility [19].

3.2. Conjugation with bio macromolecules

Peptides, proteins, lipids and polysaccharides can be attached to the peptide dendrimeric structures for various purposes. Peptide dendrimers can be constructed as multiple antigenic peptides (MAPs), anchoring peptidic antigens with the aim of improving the immunogenicity [20]. Reports showed that the conjugation of peptide epitope to sequential oligopeptide carrier, consisting of repetitive linkage of Lys–Ala–Gly moieties with favored spatial orientation can lead to an effective presentation of epitope without steric hindrance [21].

Conjugation with lipidic structures has been also extensively studied. Peptide dendrimer-lipid conjugates have been mostly known for their great effect on the efficiency of DNA and siRNA transfection [22,23]. The attachment of asymmetric peptide dendrimer to lipids, such as colic acid and decanoic acid, was investigated to design a self-assembly micellar structure in the delivery of therapeutic oligonucleotides. Results confirmed that the cholic acid-conjugated asymmetric dendrimers, significantly, had a superior efficacy in oligonucleotide delivery [24]. Considering other bioactivities, lipid (C6-C24) conjugation to second generation peptide dendrimer of lysine-leucine dipeptide repeats (G2KL) showed broad activity against MDR strains of *P. aeruginosa* and *A. baumannii* and MRSA strain of *Staphylococcus aureus*. However, the authors found that elongation of lipid chain more than C18 strongly elevated the hemolytic effect as an adverse effect [25].

In addition, attachment of polysaccharide moieties to peptide dendrimeric structures can introduce novel features. Glycopeptide dendrimers containing fucosyl or galactosyl groups had designed to develop lectin-targeted anti-biofilm peptide dendrimers [26].

3.3. Conjugation with small chemicals

Small molecules or drugs can be conjugated to the large 3D structure of peptide dendrimers in order to enhance their delivery or bioactivity. In this regard, a series of peptide dendrimers containing lysine residues attached with multiple redox-active p-aminobenzoic acid (PABA) were designed and synthesized for their antioxidant property. Results confirmed that these large structures had significant radical scavenging capacity, especially for radical cations, due to the carrying multiple copies of PABA. Enhanced antioxidant activity of PABA-functionalized peptide dendrimers might be donated to indole residue or their 3D structure, which is called dendrimeric effect. However, some of structures showed unexpected high cellular toxicity. It was suggested that the structure of dendrimer could significantly affect the chemical interaction with target [27].

Attachment of a chemical moiety to a peptide dendrimeric structure can introduce the ability of complexation with other chemicals, such as radiolabel agent to peptide dendrimers. In this regard, monomeric, dimeric and tetrameric c[RGDfK] dendrimers were synthesized through a microwave-assisted addition of cyclo[Arg-Gly-Asp-D-Phe-Lys] to dendrimeric alkynes. This cyclopeptide was aVb3 integrin antagonists. In addition, the RGD dendrimers were conjugated with a 1,4,7,10-tetraazadodecane-*N,N′,N″,N‴*-tetraacetic acid (DOTA) moiety, which made the complex with ^{111}In as a diagnostic radioactive chemical. These radiolabeled structures had efficient tumor targeting features. Among these structures, tetrameric RGD-dendrimer showed superior tumor targeting compared with dimeric and monomeric structures [28].

3.4. Peptide dendrimer decorated nanoparticles

More than self-assembled peptide dendrimeric nanostructures [29], peptide dendrimers have been applied as surface coating or bioactive agents accompanying nanostructures. Solubility and drug loading capacity of peptide dendrimers are of great importance in this regard. Three of successful examples are presented in Table 1.

4. Biochemical activity of peptide dendrimers

4.1. Peptide dendrimers with catalytic/enzyme activity

Generally, combinatorial chemistry has been used for the discovery, screening and optimization of peptide catalyzers [33]. The first use of dendrimers as catalysts was reported in 1994 by Van Koten et al. who synthesized silane dendrimers catalyzing the reaction of kharasch addition. In 1995, Bruner firstly used the term “Dendrizyme” for enantioselective dendrimer catalysts with a chelate core [34–36]. Lots of efforts have been made to synthesize different dendrimeric structures catalyzing various reactions, such as oxidation, alkylation, polymerization and others [37]. Among them, the first peptide dendrimer with catalytic activity was introduced in 2003 [38]. Peptide dendrimers do not undergo folding, and their globular or disk-shaped structure can mimic enzymes, due to their topology. Reymound et al. in 2003 prepared the first catalytic dendrimeric peptide with the sequence of ((CapCONH-A3)2(Branch)A2)2-(Branch)-Cys-A1-NH2, where serine, aspartate and histidine were utilized at A1, A2 and A3 positions, and B was an achiral diamino acid (1,3-diaminoisopropyloxy)acetic acid, as the branching point. The use of cysteine residue resulted in the formation of dimeric structure through disulfide-bridge. Among 21 synthesized structures, three of them showed greater esterase activity than others, in which histidine settled in A3 position and introduced the functionality at branching ends, not in the core. These 3 structures catalyzed the relative reactions in a pH dependent and modestly enantioselective manner. pH dependency was related to the pKa of histidine residues, which was reduced following the cooperativity of other side chains. In addition their catalyzing activity obeyed Michaelis–Menten kinetics [38]. In the next study, in order to increase the

chiral discrimination ability of peptide dendrimers, Reymound group altered the branching unit to 3,5-diaminobenzoic acid that led to an opener structure in comparison with the compact dendrimeric structure made by (1,3-diaminoisopropyloxy)acetic acid in the previous study, which resulted in limited contact of substrate with core. They made G1-G4 generation number of His-Ser-Asp peptide dendrimer [39], in which higher generation number had His-Ser consensus sequence in all branches, and then evaluated and compared their catalytical kinetic features. It was found that the higher the size of dendrimer and the higher number of histidine residues led to the higher catalytic rate and substrate binding constants (K_{cat} and $1/K_m$). Furthermore, relative substrate binding/product binding capacity was high, and raised up in higher generation numbers. As a result, this study demonstrated a strong dendritic effects in peptide dendrime-catalyzed ester hydrolysis reaction. However, the yield of synthesis was low for higher generation number (4.6% for G4). Therefore, in the following study, they used multivalent ClAc-ligation to prepare bigger dendrimers, a method that has been used for the attachment of peptides to PAMAM dendrimers. This mechanism is a convergent thioether ligation, consisting a reaction between the cysteine of G2 or G3 peptide dendrimers and the chloroacetylated N-termini of a peptide dendrimer. Using this approach, their group has made G5 and G6 peptide dendrimers. This method also can be applicable for the synthesis of peptide dendrimers with different cores and branch sequences [39–43].

Not all the catalytic sites are at the branches of peptide dendrimers. Catalytic peptide dendrimer with esterase activity containing catalytic site at the core has also been reported. In these artificial esterases, the structure of the best catalyst was comparable to previously reported catalysts with catalytic sites at the branches. Histidine residue has the principal role of catalysis in the core and branches made of aromatic amino acids (Tyr and Trp) together with the later structure improved the catalyzing effect [44].

Reported catalytic activities of peptide dendrimers are not limited to ester hydrolysis. Peptide dendrimers with aldolase and peroxidase activities were also reported by Reymound group [42,45,46]. The pyrrolidine ring of proline and N-termini or side chain of lysine play the significant role in catalysis efficiency for acetone aldolization and cyclohexane aldolization, respectively [45]. Dendrimeric enzyme model of peroxidase was the first metallopeptide dendrimer example of aqueous catalysis. Two identical G2 or G3-peptide denderimers rich in glutamate residues were bound to head and end of 5,5′-Bis(bromomethyl)-2,2′-bipyridine by thioether bond. At acidic pH 4, tri-coordinated complex [FeII (BP1)3] was formed following the addition of Fe(II). At pH 6.5, due to anionic side chains of glutamate residues, a mono-coordinated complex [FeII (BP1)] was formed. [FeII (BP1)]-metallopeptide dendrimer complex catalyzed oxidation with kinetics similar to oxidation by H_2O_2. Considering that Fe(II) and [FeII(BP1)3] could not catalyze the reaction by itself [46].

4.2. Peptide dendrimers as receptor inhibitors

Peptide dendrimers have been proven to be useful as an inhibitor for essential proteins and enzymes of pathogens, tumor cells and immune system, as well as for the inhibition of protein aggregations, due to their controllable structures and multi-valence structure. Freund et al. constructed a multivalent dendritic polyglycerol scaffold, which has seven peptides with the sequence of WPPPPRVPR, to inhibit the proline-rich sequence at the recognition site of formin-binding protein 21 (FBP21), which is an important protein for the splicing of pre-mRNA in eukaryotic cells. They reported that these peptide dendrimer displayed a *circa* 10-fold enhanced affinity towards the WW domains of FBP21 protein as compared to the monovalent peptide [47].

5. Therapeutic applications of peptide dendrimers

Biocompatibility and low toxicity of peptide dendrimers have made them an attractive material for clinical applications. Peptide dendrimers can be considered as bioactive ingredients, as well as biocompatible carriers. One of the most studied activities of these biomaterials is their activity as potent antimicrobial agents. Besides, they can be good architecture for presenting peptide antigens as they are able to present multiple antigens, simultaneously. They can also be designed as specific protein agonists or antagonists. The following sections illustrate the bioactivities of peptide dendrimers.

5.1. Antimicrobial activity of peptide dendrimers

An interesting class of peptide dendrimers is those with effective antimicrobial properties, which are called antimicrobial peptide dendrimers (AMPD). Common antimicrobial peptides (AMP) are commonly produced *via* defense system of multicellular organisms, and have a wide spectrum of antimicrobial activity against bacteria, viruses, fungi and some other pathogenic organisms [48]. AMPDs activity is mostly contributed to their positively charged amino acids, which give them the ability to attach the membrane and also to hydrophobic residues for membrane anchoring and disintegration [49]. It has been demonstrated that AMPDs, compared with AMPs, were more resistant to proteolysis, due to their molten globule-like structure. In addition, they led to fewer hemolysis. Commonly, AMPDs was designed based on a dendritic poly (lysine) tree as backbone for adding AMP sequences, but in a study, a combination of topology and sequence design was applied to introduce a potent antimicrobial agent against *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The designed AMPDs consisted of Lys (K) and Leu (L) residues, $((KL)_8(KKL)_4(KKL)_2KKL$, named as G3KL, including multiple short dipeptides in connection to a lysine branching structure [50]. Moreover, Pires et al. demonstrated the biological activity of G3KL against a number of different worldwide clinical isolates of *Acinetobacter baumannii* and also, *P. aeruginosa* (including antibiotic resistant species). This study presented that G3KL peptide dendrimer was an efficient antibiotic compared to standard therapeutics against multidrug-resistant, particularly drug-resistant *A. baumannii* and *P. aeruginosa* isolates. G3KL is a third-generation AMPD, which act as a membrane disrupting agent. The *in vitro* study of G3KL activity confirmed that G3KL could be a novel drug candidate, which had low minimum inhibitory concentration (MIC)/minimum bactericidal concentration (MBC) values compared to other AMPDs, and it had little toxicity for red blood cells [51]. Antimicrobial peptide dendrimers with preferred selectivity have been also designed. For example, Lind et al. synthesized a new amphiphilic peptide dendrimer, named BALY, which was effective on multi-resistant bacteria. Although the results exhibited that the MIC of this peptide was near 1 mM for gram-positive bacteria (e.g. *S. aureus*), through cell lysis mechanism, however, it showed 10 times more selectivity for gram negative species [52].

With regard to the therapeutic challenges of biofilm (resulted from bacterial lectins, LecA and LecB) which formed by the human pathogen *P. aeruginosa* and make a barrier against antibiotics activity, peptide dendrimers had been reported that could inhibit biofilm construction, due to the potentials of being multivalent and having high dispersion activity. Since the fucosyl groups are targeted to LecB and the galactosyl groups, they preferably bind to LecA, and therefore, glycopeptide dendrimers which had targeted to the lectin, can exert a significant inhibition against biofilm formation [26]. The high affinity multivalent fucosyl-peptide dendrimers bind to lecB that is responsible for tissue attachment and the formation of *P. aeruginosa* biofilms. Reymond et al. reported that two fucosyl-peptide dendrimers, including FD2 $(C\text{-}Fuc\text{-}Lys\text{-}Pro\text{-}Leu)_4$ $(Lys\text{-}Phe\text{-}Lys\text{-}Ile)_2$ Lys-His-Ile-NH_2 and PA8 $(OFuc\text{-}Lys\text{-}Ala\text{-}Asp)_4$ $(Lys\text{-}Ser\text{-}Gly\text{-}Ala)_2$ Lys-His-Ile-NH_2, strongly bind to lecB, thereby inhibit and disrupt the *P. aeruginosa* biofilm establishment. It has been proved that fucose-specific lectin (LecA), which has similar function to LecB, could be inhibited by specific glycopeptide dendrimers, named GalAG2 and GalBG2 [53]. Recently, this research group improved the previously reported structure by exploiting the

multivalent chloroacetyl cysteine thioether (ClAc) ligation. They reported that the attachment of four copies of Lewis antigen, as the natural LecB ligand to the dendrimeric structure, could result in a slightly stronger binding capacity compared to other structures and exhibited good biofilm inhibition. This study showed that the additional positive charges could increase biofilm inhibition and anti-bacterial or bactericidal effect. It was notable that biofilm inhibition and dispersion would be better acquired through simultaneous application of dendrimer and traditional antibiotics, as seen in co-administration of FD2 peptide dendrimer and tobramycin. It was suggested that combination therapy with this peptide dendrimer synergistically improved the antibiotic effects [54].

Peptide dendrimers have also shown antiviral activity, in some cases. Antiviral activities of an antimicrobial peptide dendrimer, SB105-A10, synthetized on a lysine core with four 9-mer peptide chains on surface [55], against human papillomaviruses [56], human respiratory syncytial virus (RSV) [57] and human immunodeficiency virus type 1 (HIV-1) [58] were reported. It was suggested that this structure could block the viral attachment and entry to target cells. Moreover, Roy et al. reported the synthesis of a peptide dendrimer containing sialic acids coated on a core of poly-lysine. This peptide dendrimer could cross-link and precipitate *Limax flavus* lectin [59], in addition to inhibiting the influenza virus hemagglutinins of various strains [60]. Novel peptide dendrimers against Herpes viruses have been also reported, which prevent HSV-1 and HSV-2 attachment to target cells [61].

5.2. Peptide dendrimers as an anti-thrombotic agent

It was shown that some peptide dendrimers could exhibit anti-thrombotic effect. For example, PEGylated polyglutamic acid peptide dendrimer (G3-PEG-G3) [62] could exert respectable thrombolytic effect. In addition, loading of nottokinase as a thrombolytic enzyme on peptide dendrimer could improve thrombolytic activity. Nottokinase (NK) loaded polylysine dendrimer (PLLD G4) [63] was designed that showing promising anti-thromobtic effect. The main point was the fact that the loading of NK with positive charges on polyglutamic acid peptide dendrimers with negative charges is a simple electrostatic interaction. In this way, the enzyme activity of NK was conserved, and the anti-thrombotic effect of G3-PEG-G3 was also added. Furthermore, the presence of PEG increased the size of the dendritic macromolecules and therefore, prolonged blood circulation time, which resulted in an improved dissolution of thrombus. Since the loading efficiency of this approach is relatively low, so through another approach, a series of multiarm-polyethylene glycol-polyglutamic acid peptide dendrimers (x-PEG(G3)x, x 5 2, 4, 6, 8) was designed as NK carrier through another approach. Results showed that 4-PEG$(G_3)_4$ with 4 armed PEG had a higher loading efficiency and excellent potential in dissolving thrombus using *in vitro* and *in vivo* studies [64].

5.3. Peptide dendrimers with anti-cancer activity

Gu et al. were designed tryptophan-rich peptide dendrimers (TRPDs) as a novel dendritic peptide drug candidate for efficient tumor therapy. It has been shown that molecular structure of TRPDs could create supramolecular aggregates by significant interactions between DNA and tryptophan residue (indole rings and amino groups), which led to the disruption of tumor cell cycle and acceleration of cell apoptosis at tumor sites [65]. In another study, Kojima and Kondo et al. developed several peptide dendrimers, CPP44-linked p16INK4a (tandem linked dendrimer), CPP44 and p16INK4a (parallel linked dendrimer), for acute myelogenous leukemia (AML) and reported their tumor targeting activities *via* CPP44 peptide and their antitumor effects due to the antitumor p16INK4a peptide. They suggested that the conjugation strategy was important for preparing highly active peptide-conjugated dendrimers with dual functionality [66].

5.4. Peptide dendrimers as antigen presenting agent

5.4.1. Peptide dendrimers as vaccines

Peptide dendrimers have been considered as immune responses inducers, including the production of antibodies with high sensitivity [67,68]. In this regard, multiple antigenic peptides with dendrimeric structure were introduced that were able to present multiple copy of an antigen or multiple antigens to the immune system, simultaneously. Therefore, MAPs can be promising vaccines towards various cancers and viral infections [67,69]. Tam et al. used poly L-lysine dendrimer as a peptide carrier for multiple copy of antigenic peptides, and introduced MAPs as a suitable carrier structure for various antigens that could induce strong immune response. These structures were applied to design and generate vaccines against *Aphtae epizooticae*, AIDS and malaria [70]. Various studies on the development of effective vaccines based on peptide dendrimers, against sever life threatening infections, such as malaria and HIV, have been progressed during last decades [67,71]. In a more recent study, a synthetic “star” nanostructure was designed for immunization against HIV that is based on a biocompatible polymer on a PAMAM dendrimeric core, which is covalently attached to Envelop variable loop 3 (V3) and T-helper glycol-peptides at branching units. Using *in vivo* studies, these star-shaped nanoparticles showed efficient targeting property towards lymph nodes, specially towards sub-capsular macrophages and resident dendritic cells. This strategy improved the immunogenicity response and antibody titers [72]. In these studies, co-administration of T-cell activator antigens has an important role in design of effective vaccines.

Applications of MAP dendrimers as vaccine for influenza (type A) [73], hepatitis virus (A and C) [74,75], swine fever virus [76,77], Foot-and-mouth disease virus (FMDV) [78,79] and HIV [80] have been reported. However, dendrimer vaccine has some restrictions in delivery, neutralization and bio-stability [67]. Sato et al. synthesized a series of carbosilane dendrimers uniformly functionalized with hemagglutinin (HA)-binding peptide (sialic acid-mimic peptide; Ala-Arg-Leu-Pro-Arg), then evaluated the activity of this vaccine against two human influenza viruses (H1N1 and H3N2). The results showed that biological activities of peptide dendrimer depended on the form of their core frame, as the dumbbell-type carbosilane-based dendrimer displayed the strongest inhibitory activity [81].

Using different epitopes simultaneously is one of the main advantages of peptide dendrimers as vaccines. Hague et al. synthetized hetero-multimeric peptide constructs, which could stimulate B-cell and T_h cell immune responses. These martial display enhanced binding, avidity and specificity towards an established HIV-neutralizing human antibody Mab b12. They suggested that these hetero-multimeric peptide constructs had potential to be applied as HIV-1 vaccine candidate [82]. In a recent study, dendrimeric structure was used to enhance immune response to weak antigenic epitopes. Attachment of multiple copies of *Candida albicans*' glycopeptidic epitopes simultaneously in a dendrimeric structure improved antigen uptake by antigen presenting cells and therefore, the following immune response. β1,3 hexaglucan ligand as a dectin-1 (dendritic cell receptor) specific ligand and T-cell/B-cell epitopes peptide were covalently attached to the opposite sides of dendritic vaccine core, which resulted in a asymmetric peptide dendrimer with multiple antigenic sites (Fig. 2). Activity assay of this construct in mice showed that it could be a promising glycopeptide vaccine against *Candida albicans*, but more optimization should be performed [83].

This strategy was also applied for immunization against foot-and-mouth-disease virus (FMDV). Balnco et al. designed a bi and tetra-valent B-cell and T-cell epitope dendrimeric vaccine against FMDV using different linkers and were evaluated in swine. Results confirmed that bivalent dendrimeric vaccine was more promising and cost-effective candidate for FMDV vaccine than tetra-valent dendrimers [84]. T-cell and B-cell binding site of the viral capsid protein were also considered in designing another dendrimeric peptide vaccine against FMDV

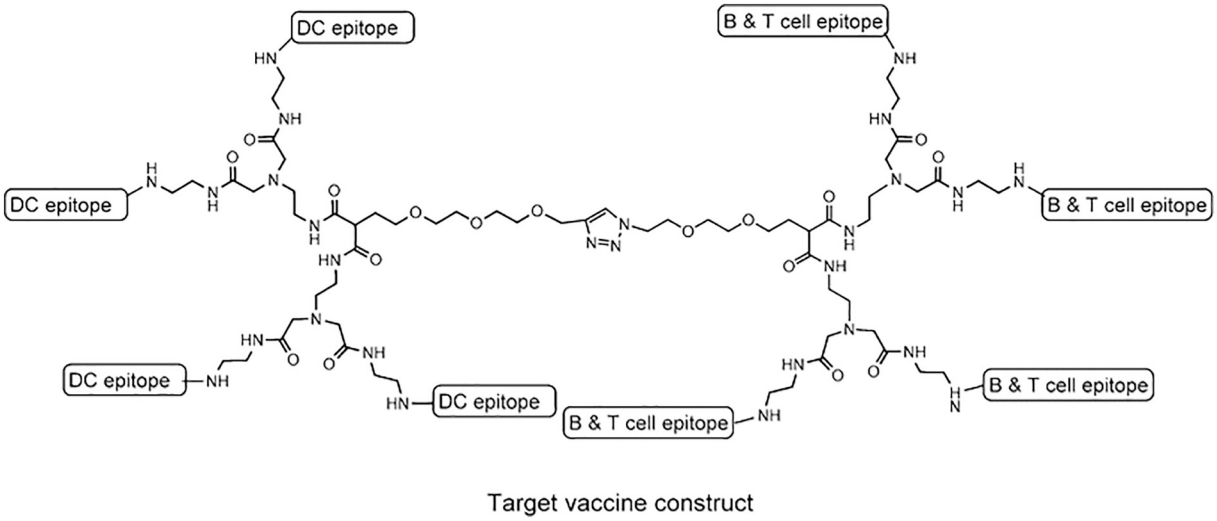

Fig. 2. Schematic presentation of asymmetric dendrimeric structure as a potential vaccine, designed for immunity development against *Candida albicans*. DC epitope: dendritic cell epitope [83].

(Fig. 3). All the designed vaccines could partially promote inter-serotype/intraserotype protection rather than humeral immunity against FMDV in cattle, which was a challenge in FMDV immunity produced after traditional vaccines [85].

5.4.2. Peptide dendrimer in diagnosis

Synthetic peptides are one of the attractive diagnostic tools especially for life threatening viral diseases [67]. Due to low coating efficiency, constrained orientation and flexibility of short synthetic peptides, they can be used as antigens in sero-diagnosis of bacterial or viral infections. Researchers have focused on the development of highly branched peptides to overcome the limitations in immunoassays and sero-diagnosis [86]. More than their application as vaccine, MAPs can be used as a sensor to detect pathogen- specific- antibodies in serum or other biological samples by colorimetric, enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance (SPR) methods (Table 2) [67].

6. Peptide dendrimers in drug delivery

Since dendrimers have a small and designable structure, they can be designed to mimic the action of a variety of biomolecules in addition to acting as a drug carrier [90]. Peptide dendrimers have been also considered for controlled drug delivery. Kojima et al. synthesized and characterized the fully elastin-mimetic dendrimers with different peptide lengths, which belong to different dendrimer generations, to control the dependency of delivery system on temperature. They reported that temperature dependency of the elastin-mimetic dendrimers was similar to the elastin-like peptides, and they could aggregate by phase transition, in which the related phase transition temperature was affected by the peptide length, dendrimer generation, salt concentration and pH [91].

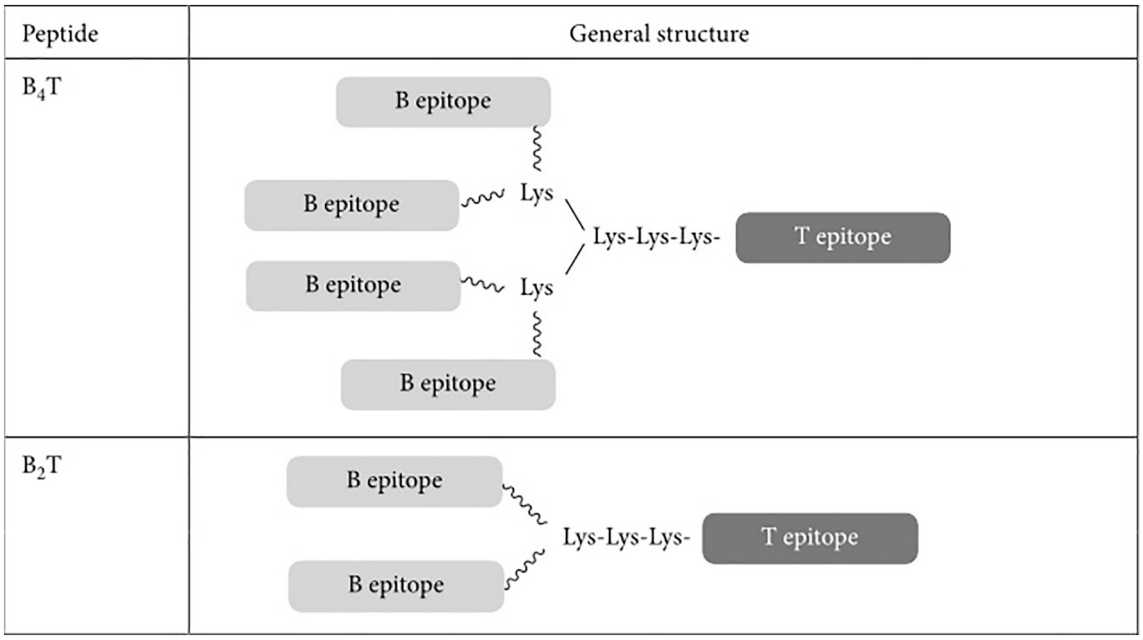

Fig. 3. Schematic presentation of dendrimeric peptide vaccines designed for FMDV [85].

Table 2
Some examples of peptide dendrimers as diagnostic tools.

Target	Specific feature	Application	Ref.
Hepatitis G virus type C	Tetrameric branched peptides containing structural and nonstructural proteins tags of for the diagnosis of GBV-C infection	Prognostic marker for unusual clinical manifestation in patients with HCV/HIV co-infection	Gómara [87]
Plasmodium malariae	Octameric MAP, carrying 6 repeats of tandem repeated sequence of the immunodominant region of the circumsporozoite (CS) protein	Detecting antibodies in sera from naturally immunized individuals	Habluetzel [88]
HIV	Four-branch MAP derived from the V3-loop of HIV-1 gp120 as antigen	High sensitive immunoassay for HIV antibodies	Kin and Pau [86]
Bursal disease virus (IBDV)	MAPs containing VP2 protein	ELISA test for IBDV detection	Saravanan [89]

Dextran conjugated peptide dendrimers recently have been studied for its potential intracellular drug delivery. To synthesize this structures, poly L-Lysine peptide dendrimers were pre-fluorinated, which resulted in more hydrophobic branches. Having this feature gave the advantage of self-assembling of peptide dendrimers and hydrophobic drugs through hydrophobic interaction. Connection of this peptide dendrimers to hydrophilic dextran shell through acid-sensitive hydrozone bond led to a structure that was dis-assembled inside lysosomes following the fusion of endosomes to lysosome [92].

Another controlled released drug delivery system based on peptide dendrimer was designed to deliver gemcitabine to the tumors. The GFLG peptide is an enzyme cleavable linker that was applied to conjugate gemcitabine to a dendrimeric peptide structure. GFLG peptide is the substrate of Cathepsin B and cleavage of this peptide can lead to intra-lysosomaly drug release. PEGylated peptide dendrimer was reacted with GFLP-gemcitabine to produce a final nanostructure with improved cancer targeting, as well as intracellular drug release. Results of *in vitro*, *ex vivo* and *in vivo* cytotoxicity studies confirmed that it can be considered as a promising anticancer agent in breast cancer therapy [93].

Study on the application of peptide dendrimers in controlled drug delivery systems is an attractive field of pharmaceutical studies, which is progressing extensively.

6.1. Gene delivery

Application of peptide dendrimers in gene delivery has been another attractive filed for pharmaceuticals scientists. For example, a combination of peptide dendrimer and Lipofectin was developed for delivery of splice-switching oligonucleotide [94]. Also, a flexible strategy had been developed including cooperative two-step hierarchical self-assembly of globular poly (L-lysine) dendrimers with a linear poly (L-leucine) into nano-architectures that mimics viral capsids [15]. It was reported that this capsid-like nanostructures as non-viral gene vectors, had high gene-transfection efficiency.

Over the past three decades, due to the unique characteristics such as controllable three-dimensional molecular architecture (shape and size), low polydispersity, highly adjustable surface chemistry, biocompatibility, high cellular uptake and endosomal scape, many researchers have tested peptide dendrimers as candidates for non-viral nucleic acid delivery [95].

Among different types of dendrimers, polypropylene imine (PEI) and PAMAM derivatives have been widely studied as gene delivery vehicle [96,97]. Although PAMAM derivatives showed an ideal structure for nucleic acid transfer, along with the increase of PAMAM generations and transfection efficacy, its cytotoxicity raise [98]. Therefore, researchers have tried to modulate the structure of aforementioned polymer in order to achieve the appropriate dendrimers for gene transfection with high efficacy and low toxicity. Choi et al. made arginine and lysine functionalized PAMAM, and analyzed them in comparison with the regular PAMAM and PEI. The results showed that gene transfer by PAMAM-Arg was better than the regular PAMAM and PAMAM-Lys. Nonetheless, PAMAM-Arg showed low transfection efficacy and cytotoxicity as compared to PEI [99]. With the aim of gene delivery across the blood-brain barrier, Zarebkohan et al. developed the 4th-generation PAMAM dendrimers functionalized with SRL (serine-arginine-leucine), and compared them with PAMAM-Arg and PAMAM-DNA particle. The result demonstrated that SRL-PAMMA dendrimers exhibited a better penetration to the brain compared to the others [100]. It was reported that increase in the generation of dendrimer could affect the gene transfection, as the 5th generation-peptide dendrimers functionalized with arginine are more promising in gene transfection, and also had lower cytotoxicity compared with 6th generation, [101].

The type of dendrimer core can affect the transfection efficiency. Yiyun Cheng et al. developed PAMAM-cored dendrimers, including Diaminododecane-cored generation 4 (C12G4), diaminoethane-cored generation 4 (C2G4) and diaminohexane-cored generation 4 (C6G4) and then, evaluated their gene transfer efficacy. Among these peptide dendrimers, C12G4 showed dramatically higher efficacy in gene transfection. Also, the transfection efficacy of modified C12G4 with arginine was significantly increased. Moreover, 2,4-diamino1,3,5-triazine and fluorine compounds were tested and resulted in efficacy enhancement. They reported that transfection efficacies of these modified C12G4 were higher than commercial gene transfection reagents, such as SuperFect and Lipofectamine 2000 [102].

Addition of lipid to the structure of peptide dendrimers has influenced on the toxicity and delivery efficiency. Kokil et al. synthesized a panel of low-generation cationic peptide asymmetric dendrimers with side arm lipid (cholic and decanoic acid) conjugation, and assessed their performance in the delivery of genes to a range of cells types. The result showed that these peptide dendrimers are non-cytotoxic in a broad concentration range. Furthermore, the cholic acid-conjugated asymmetric dendrimers possessed far superior delivery efficiency, compared with commercial Lipofectamine [24].

Peptide dendrimers have also been evaluated for siRNA delivery. Reversible crosslinking of G2-lysine peptide dendrimers in bioreducible fluorinated peptide dendrimers complexed with siRNA, not only resulted in efficient endocytosis and endosomal escape but also enhanced the physiologic stability. Gu et al. could improve the delivery of siRNA to cancer cells, using polyhedral oligomeric silsesquioxane (POSS) at the core of low generation peptide dendrimers together with some modifications, including crosslinking and fluorination [10,103,104].

6.2. Delivery of chemotherapeutics

Nowadays, new approaches are available to reduce toxicity and expand bioavailability of cancer therapeutics. In many studies, peptide dendrimers have been applied for drug delivery of anti-cancer agents (Table 3). Some interesting reports confirmed that the superficially combined carbohydrates with peptide dendrimers of aspartate, histidine and serine that form glycopeptide dendrimer, could be used for the delivery of antineoplastic drugs [105].

Active targeting through affinity ligands can be adapted with peptide dendrimer-based delivery systems. Aptamer conjugated peptide dendrimers have been studied for targeted delivery to lung adenocarcinoma cell line (A549). A549 cells with overexpressed mucin-1 on their membrane were investigated for the potential targeting ability of

Table 3
Several examples of using peptide dendrimers for delivery of anti-cancer chemotherapeutics.

Peptide dendrimer structure	Peptide functional group	Drug	Application	Ref.
Glycopeptide dendrimers with cysteine residue at the core	Ser, Thr, His, Asp, Glu, Leu, Val, Phe	Colchicine	-Increase targeted cellular uptake in to cancer cells -Decrease of toxicity compared to free colchicine	Lagnoux et al. [105]
PEGylated lysine peptide dendrimer	Gly-Phe-Leu-Gly (GFLG) as an enzyme-cleavable linker	Gemcitabine	-Self-assembling into nanoscale particles -Enhanced permeation and retention (EPR) effect -Low side effects to normal tissues -Safe antitumor agent for breast cancer therapy	Zhang et al. [93]
Peptide or PAMAM core	*e.g.* Gly-Phe-Leu-Gly peptide	Doxorubicin (DOX)	-Overcome DOX low selectivity and high toxicity -targeting cancer tissues	Burns and Delehanty [106], Kojima et al et al. [107], Li et al. [108], Liu et al. [109], Zhang et al. [110], Lee et al. [111]
Amphiphilic dendrimer oligopeptides	Pro-Val-Gly-Leu- Ile-Gly (PVGLIG)	DOX	-Oligopeptide substrate of metalloprotease-2 (MMP-2/9) -Exhibited fewer toxicity	Mendoza-Nava [112]
Octa(3-aminopropyl) silsesquioxane (OAS) core	Poly(L-glutamic acid) (PLGA)	DOX	-Biotin as targeting moiety for cancer targeting through biotin-specific receptors (BSR) -pH-sensitive hydrazone bonds with a faster cleavage in slightly acidic situation	Yuan et al. [113]
Poly(L-lysine)	Heparin	DOX	-High antitumor activity on breast cancer cell line (4T1), -induced apoptosis and anti-angiogenesis effects	Levine et al. [114]
PEGylated peptide dendrimer	Poly (L-lysine)	Diaminocyclohexyl-platinum (II) (Similar to oxaliplatin)	-Increase the concentration of the metal in the tumor tissue -Decreased the toxic effects -Treat ovarian cancer	Pan et al. [115]
PAMAM dendrimer	pH Low Insertion Peptide (pHLIP)	DOX	-pH-triggered system for direct cytosolic delivery -Bearing multiple numbers of DOX *via* disulfide linkages -Passive cancer targeted carrier	Burns and Delehanty [116]

anti-MUC aptamer conjugated to peptide dendrimer. The study confirmed the effective internalization of the conjugated peptide dendrimers [117].

Application of peptide dendrimers are extremely interested for skin and oral delivery of therapeutic agents:

6.2.1. Peptide dendrimer in skin delivery

Generally, conventional chemical and physical methods in dermal drug delivery are restricted because of the complexity of application, skin irritation and poor patient compliance. Hence, dendritic polymers have been verified regarding their ability in improving the dermal delivery of different molecules. Dendrimers have multiple advantages for drug delivery across the skin due to high drug loading capacity and minimal skin irritation potential. Dendrimers can help the therapeutic agents to penetrate into the skin, which is mostly rely on the molecular size, surface charge and terminal functional groups surrounding the dendrimers. Treatment of diseases such as skin cancer, psoriasis and other genetic disorders with origins in skin epidermal layers needs localized drug delivery, which dendritic polymers can play a significant role to achieve therapeutic goal. In addition, some dendrimers have antimicrobial properties, which were approved for vaginal application, and it can be used further in the treatment of skin infectious, such as acne vulgaris. Applications of dendrimers for skin-mediated delivery systems could be categorized in three groups. In the first one, peptide dendrimers with topical application on skin surface are gathered, and they are mostly achieved by the higher generation dendrimers (> G6). The second group has effect on the intradermal parts of skin *via* lower generation (G2–G5), neutral or cationic dendrimers, and the last group on transdermal area of skin which achieved by the lower generation of dendrimers (G1–G4) [118]. In numerous studies regarding skin delivery, researchers have employed peptide dendrimers, sometimes by collaboration of a physical transport mechanism such as the low-frequency ultrasound (sonophoresis) [118], which offered that acoustic cavitation, induced by means of the ultrasound waves led to greater penetration into the skin [119,120].

6.2.2. Peptide dendrimers in oral delivery

The oral route is the most convenient approach for drug administration. Novel drug delivery systems are in the spotlight of studies because of optimal gastrointestinal (GI) transit, site-specific drug delivery and high oral drug bioavailability. Peptide dendrimer as one of these novel delivery systems has been applied in this regard.

Through the study of anionic PAMAM dendrimer in oral delivery system, it was demonstrated that anionic PAMAM dendrimers generations 2.5 and 3.5 had principally rapid transfer rates and few tissue deposition, representing a very effectual transport pathway [121]. In practice, a peptide dendrimer containing vasoactive intestinal peptides, which was bound covalently to PAMAM dendrimers, showed promising results as a remarkable carrier for the intestinal delivery of peptide [122]. Accordingly, peptide dendrimeric structures with PAMAM core can be developed as an oral delivery vehicle.

An asymmetric amino acid-based peptide dendrimer with arginine terminal groups was also applied to encapsulate bufalin for intestinal delivery. The bufalin-peptide-dendrimer inclusion improved the intestinal permeability and therefore, bioavailability of bufalin as a bioactive ingredient [123].

6.3. Peptide dendrimers for targeted bone delivery

Some studies on peptide-dendrimer systems have been evaluated in bone drug delivery in order to treat bone cancer. Janus dendrimers have shown promising results in this regard. This type of dendrimers contains two different functionalized parts on opposite sides, and showed self-assembly properties in addition to specific thermal behavior, and they can be applied in drug delivery. Zhao et al. had previously synthesized lysine dendrimers conjugate with 5-fluorouracil (G1–G3), which could easily penetrate to the cells. This system showed less cell uptake in normal cells compared to cancerous cells, thus, led to a reduction in cytotoxicity while retaining a sensible anticancer property. Another special peptide dendrimer was designed for bone delivery, which consisted of two distinct parts: one is RGD dimer and the other is 5-fluorouracil dimer, which created the first-generation Janus-type dendrimer. *In vitro* assays showed that this conjugate could bind to the major inorganic component of bone, hydroxyapatite, and it had a potential to induce sustained-release delivery with minimum side-effects [124]. Furthermore, peptide dendrimers with glutamic or aspartic acids demonstrated great selectivity to bone tissue [125]. In a study, hepta-aspartic acid (DDDDDDD) was covalently attached to a dendrimeric structure containing naproxen. Resulted amphiphilic supermolecule self-assembled into a micellar structure that efficiently encapsulated curcumin, which is used to treat osteosarcoma. Curcumin extracted from the herb *Curcuma longa* is a natural product, and has many therapeutic effects, such as antioxidant, anti-inflammatory and antitumor activities, reported in osteosarcoma, breast and colon cancer. Synergistic antitumor effects was seen when curcumin is combined with naproxen. In this structure, curcumin dispersed in naproxen-dendrimers released rapidly from the micelles. Curcumin micelle displayed more cytotoxic effect on cancer cells than free curcumin and naproxen-dendrimer, which might be due to the induction of apoptosis through mitochondrial pathway. Micellar encapsulation improved the absorption of curcumin by the cancer cells with high selectivity [126].

7. Analytical application of peptide dendrimers

7.1. Protein A mimetic peptide dendrimers for antibody detection and purification

In 1996, Fassina et al. identified a peptide mimicking *Staphylococcus aureus* protein A when screened a library of synthetic multimeric peptides. Protein A is a surface protein in the cell wall of *S. aureus*, which plays an important role in pathogenesis of these bacteria. The protein A mimetic (PAM) peptides can similarly recognize the Fc portion of IgG immunoglobulin, and can be used for antibody purification and therapeutic approach in autoimmune diseases, such as *Lupus erythematosus*. In this regard, a 4-mer of the Arg-Thr-Tyr (L- and D- aminoacid) linked to an asymmetric polylysine core has been identified as a good affinity ligand for FC of IgG, which can be used in affinity column chromatography of IgGs. The immobilized peptide dendrimers were not affected by denaturants, detergents or other reagents commonly used in therapeutic protein development [127]. Dinon et al. reported a novel dendrimeric peptide ligand, D-PAM-Φ, which have high capacity for human IgG, and suggested that this ligand could be used as inhibitor of the Fcγ receptor. D-PAM-Φ was obtained *via* addition of a hydrophobic group, phenylacetyl, at the free N(alpha) position of the terminal arginine of D-PAM, which had improved its affinity towards antibodies [128]. Nowadays, PAM and its derivatives are interesting biomaterials in the purification of therapeutic monoclonal antibodies [129,130].

8. Conclusion

Peptide dendrimers are highly branched nano-bio-structures that can present multiple functionalities in biomedicine. Building blocks and surface branching unites of peptide dendrimers may consist of bioactive peptides, which result in pharmacologically active supramolecular structures. They have been confirmed for their potential applications in infections, thrombotic events and vaccination up to now. Moreover, promising physicochemical features of peptide dendrimers make them an interesting drug delivery vehicle, especially for gene delivery, cancer targeted delivery, skin and intestinal delivery of poorly soluble drugs and *etc*. It seems that peptide dendrimers will be developed to the pharmaceutical market in recent future, if the cost of their synthesis as one of the limiting factors is removed.

References

[1] R. Duncan, L. Izzo, Dendrimer biocompatibility and toxicity, Adv. Drug Deliv. Rev. 57 (15) (2005) 2215–2237.
[2] F. Vögtle, G. Richardt, N. Werner, Dendrimer Chemistry, Wiley-VCH Weinheim, 2009.
[3] Y. Kim, F. Zeng, S.C. Zimmerman, Peptide dendrimers from natural amino acids, Chem Eur J 5 (7) (1999) 2133–2138.
[4] K. Sadler, J.P. Tam, Peptide dendrimers: applications and synthesis, Rev. Mol. Biotechnol. 90 (3–4) (2002) 195–229.
[5] Nanjwade BK, Bechra HM, Derkar GK, Manvi FV, Nanjwade VK. Dendrimers: Emerging polymers for drug-delivery systems. Eur. J. Pharm. Sci.. 2009 2009/10/08/;38(3):185–96.
[6] T. Darbre, J.L. Reymond, Peptide dendrimers as artificial enzymes, receptors, and drug-delivery agents, Acc. Chem. Res. 39 (12) (2006) 925–934.
[7] L. Crespo, G. Sanclimens, M. Pons, E. Giralt, M. Royo, F. Albericio, Peptide and amide bond-containing dendrimers, Chem. Rev. 105 (5) (2005) 1663–1681.
[8] C. Shi, Y. He, X. Feng, D. Fu, ε-Polylysine and next-generation dendrigraft poly-L-lysine: chemistry, activity, and applications in biopharmaceuticals, J. Biomater. Sci. Polym. Ed. 26 (18) (2015) 1343–1356.
[9] B.M. Okrugin, I.M. Neelov, F.A.M. Leermakers, O.V. Borisov, Structure of asymmetrical peptide dendrimers: insights given by self-consistent field theory, Polymer 125 (2017) 292–302 2017/09/08.
[10] X. Cai, R. Jin, J. Wang, D. Yue, Q. Jiang, Y. Wu, et al., Bioreducible fluorinated peptide dendrimers capable of circumventing various physiological barriers for highly efficient and safe gene delivery, ACS Appl. Mater. Interfaces 8 (9) (2016) 5821–5832.
[11] L.C. Filipe, M. Machuqueiro, T. Darbre, A.N.M. Baptista, Exploring the structural properties of positively charged peptide dendrimers, J. Phys. Chem. B 120 (43) (2016) 11323–11330.
[12] T.K.K. Mong, A. Niu, H.F. Chow, C. Wu, L. Li, R. Chen, β-Alanine-based dendritic β-peptides: dendrimers possessing unusually strong binding ability towards protic solvents and their self-assembly into nanoscale aggregates through hydrogen-bond interactions, Chem. Eur. J. 7 (3) (2001) 686–699.
[13] W.-D. Jang, D.-L. Jiang, T. Aida, Dendritic physical gel: hierarchical self-organization of a peptide-core dendrimer to form a micrometer-scale fibrous assembly, J. Am. Chem. Soc. 122 (13) (2000) 3232–3233.
[14] R.P. Verma, A. Shandilya, V. Haridas, Peptide dendrimers with designer core for directed self-assembly, Tetrahedron 71 (46) (2015) 8758–8765.
[15] X. Xu, H. Yuan, J. Chang, B. He, Z. Gu, Cooperative hierarchical self-assembly of peptide dendrimers and linear polypeptides into nanoarchitectures mimicking viral capsids, Angew. Chem. 124 (13) (2012) 3184–3187.
[16] M. Sakamoto, T. Kamachi, I. Okura, A. Ueno, H. Mihara, Photoinduced hydrogen evolution with peptide dendrimer-multi-Zn(II)-porphyrin, viologen, and hydrogenase, Biopolymers 59 (2) (2001) 103–109.
[17] M. Sakamoto, A. Ueno, H. Mihara, Construction of α-helical peptide dendrimers conjugated with multi-metalloporphyrins: photoinduced electron transfer on dendrimer architecture, Chem. Commun. (18) (2000) 1741–1742.
[18] M. Sakamoto, A. Ueno, H. Mihara, Multipeptide-metalloporphyrin assembly on a dendrimer template and photoinduced electron transfer based on the dendrimer structure, Chem. Eur. J. 7 (11) (2001) 2449–2458.
[19] J. Jing, K.R. Tupally, G.R. Kokil, Z. Qu, S. Chen, H.S. Parekh, Development of a hybrid peptide dendrimer micellar carrier system and its application in the reformulation of a hydrophobic therapeutic agent derived from traditional Chinese medicine, RSC Adv. 9 (5) (2019) 2458–2463.
[20] L. Yi-An, P. Clavijo, M. Galantino, S. Zhi-Yi, L. Wen, J.P. Tam, Chemically unambiguous peptide immunogen: preparation, orientation and antigenicity of purified peptide conjugated to the multiple antigen peptide system, Mol. Immunol. 28 (6) (1991) 623–630.
[21] M. Sakarellos-Daitsiotis, V. Tsikaris, P.G. Vlachoyiannopoulos, A.G. Tzioufas, H.M. Moutsopoulos, C. Sakarellos, Peptide carriers: a helicoid-type sequential oligopeptide carrier (SOCn) for multiple anchoring of antigenic/immunogenic peptides, Methods 19 (1) (1999) 133–141.
[22] A. Kwok, G.A. Eggimann, M. Heitz, J.L. Reymond, F. Hollfelder, T. Darbre, Efficient transfection of siRNA by peptide dendrimer–lipid conjugates, ChemBioChem 17 (23) (2016) 2223–2229.
[23] M. Heitz, A. Kwok, G.A. Eggimann, F. Hollfelder, T. Darbre, J.-L. Reymond, Peptide dendrimer–lipid conjugates as DNA and siRNA transfection reagents: role of charge distribution across generations, CHIMIA International Journal for Chemistry 71 (4) (2017) 220–225.
[24] G.R. Kokil, R.N. Veedu, B.T. Le, G.A. Ramm, H.S. Parekh, Self-assembling asymmetric peptide-dendrimer micelles–a platform for effective and versatile in vitro nucleic acid delivery, Sci. Rep. 8 (1) (2018) 4832.
[25] T.N. Siriwardena, M. Stach, R. He, B.-H. Gan, S. Javor, M. Heitz, et al., Lipidated peptide dendrimers killing multidrug-resistant bacteria, J. Am. Chem. Soc. 140 (1) (2017) 423–432.
[26] J.-L. Reymond, M. Bergmann, T. Darbre, Glycopeptide dendrimers as Pseudomonas aeruginosa biofilm inhibitors, Chem. Soc. Rev. 42 (11) (2013) 4814–4822.
[27] M. Sowinska, M. Morawiak, M. Bochyńska-Czyż, A.W. Lipkowski, E. Ziemińska, B. Zabłocka, et al., Molecular antioxidant properties and in vitro cell toxicity of the p-aminobenzoic acid (PABA) functionalized peptide dendrimers, Biomolecules 9 (3) (2019) 89.
[28] I. Dijkgraaf, A.Y. Rijnders, A. Soede, A.C. Dechesne, G.W. Van Esse, A.J. Brouwer, et al., Synthesis of DOTA-conjugated multivalent cyclic-RGD peptide dendrimers via 1,3-dipolar cycloaddition and their biological evaluation: implications for tumor targeting and tumor imaging purposes, Org. Biomol. Chem. 5 (6) (2007) 935–944.
[29] P.P. Sharma, B. Rathi, J. Rodrigues, N.Y. Gorobets, Self-assembled peptide nanoarchitectures: applications and future aspects, Curr. Top. Med. Chem. 15 (13) (2015) 1268–1289.
[30] J. Ma, K. Kang, Y. Zhang, Q. Yi, Z. Gu, Detachable polyzwitterion-coated ternary nanoparticles based on peptide dendritic carbon dots for efficient drug delivery in Cancer therapy, ACS Appl. Mater. Interfaces 10 (50) (2018) 43923–43935.
[31] M. Huang, S.F. Zhang, S. Lü, T. Qi, J. Yan, C. Gao, et al., Synthesis of mesoporous silica/polyglutamic acid peptide dendrimer with dual targeting and its application in dissolving thrombus, J. Biomed. Mater. Res. A 107 (8) (2019) 1824–1831, https://doi.org/10.1002/jbm.a.36703.
[32] S. Nigam, D. Bahadur, Dendrimer-conjugated iron oxide nanoparticles as stimuli-responsive drug carriers for thermally-activated chemotherapy of cancer, Colloids Surf. B: Biointerfaces 155 (2017) 182–192 2017/07/01/;.
[33] A. Berkessel, The discovery of catalytically active peptides through combinatorial chemistry, Curr. Opin. Chem. Biol. 7 (3) (2003) 409–419.
[34] J.W. Knapen, A.W. van der Made, J.C. de Wilde, P.W. van Leeuwen, P. Wijkens, D.M. Grove, et al., Homogeneous catalysts based on silane dendrimers functionalized with arylnickel (II) complexes, Nature 372 (6507) (1994) 659.
[35] H. Brunner, Dendrizymes: expanded ligands for enantioselective catalysis, J. Organomet. Chem. 500 (1–2) (1995) 39–46.
[36] J. Kofoed, J.-L. Reymond, Dendrimers as artificial enzymes, Curr. Opin. Chem. Biol. 9 (6) (2005) 656–664.
[37] D. Wang, D. Astruc, Dendritic catalysis—basic concepts and recent trends, Coord. Chem. Rev. 257 (15–16) (2013) 2317–2334.
[38] A. Esposito, E. Delort, D. Lagnoux, F. Djojo, J.L. Reymond, Catalytic peptide dendrimers, Angewandte Chemie - International Edition 42 (12) (2003) 1381–1383.
[39] C. Douat-Casassus, T. Darbre, J.-L. Reymond, Selective catalysis with peptide dendrimers, J. Am. Chem. Soc. 126 (25) (2004) 7817–7826.
[40] A. Esposito, E. Delort, D. Lagnoux, F. Djojo, J.L. Reymond, Catalytic peptide dendrimers, Angew. Chem. 115 (12) (2003) 1419–1421.
[41] E. Delort, T. Darbre, J.-L. Reymond, A strong positive dendritic effect in a peptide dendrimer-catalyzed ester hydrolysis reaction, J. Am. Chem. Soc. 126 (48) (2004) 15642–15643.
[42] N.A. Uhlich, T. Darbre, J.-L. Reymond, Peptide dendrimer enzyme models for ester hydrolysis and aldolization prepared by convergent thioether ligation, Organic & biomolecular chemistry 9 (20) (2011) 7071–7084.
[43] J.-L. Reymond, T. Darbre, Peptide and glycopeptide dendrimer apple trees as enzyme models and for biomedical applications, Organic & biomolecular chemistry 10 (8) (2012) 1483–1492.
[44] S. Javor, E. Delort, T. Darbre, J.-L. Reymond, A peptide dendrimer enzyme model with a single catalytic site at the core, J. Am. Chem. Soc. 129 (43) (2007) 13238–13246.
[45] J. Kofoed, T. Darbre, J.-L. Reymond, Artificial aldolases from peptide dendrimer combinatorial libraries, Organic & biomolecular chemistry 4 (17) (2006) 3268–3281.
[46] P. Geotti-Bianchini, T. Darbre, J.-L. Reymond, pH-tuned metal coordination and peroxidase activity of a peptide dendrimer enzyme model with a Fe (ii) bipyridine at its core, Organic & biomolecular chemistry 11 (2) (2013) 344–352.
[47] L.M. Henning, S. Bhatia, M. Bertazzon, M. Marczynke, O. Seitz, R. Volkmer, et al., Exploring monovalent and multivalent peptides for the inhibition of FBP21-tWW, Beilstein J. Org. Chem. 11 (2015) 701.
[48] J.P. Tam, Y.A. Lu, J.L. Yang, Antimicrobial dendrimeric peptides, FEBS J. 269 (3) (2002) 923–932.
[49] M. Sowinska, A. Laskowska, A. Guśpiel, J. Solecka, M. Bochynska-Czyż, A.W. Lipkowski, et al., Bioinspired amphiphilic peptide dendrimers as specific and effective compounds against drug resistant clinical isolates of E. coli, Bioconjug. Chem. 29 (11) (2018) 3571–3585.
[50] M. Stach, T.N. Siriwardena, T. Köhler, C. Van Delden, T. Darbre, J.L. Reymond, Combining topology and sequence design for the discovery of potent antimicrobial peptide dendrimers against multidrug-resistant Pseudomonas aeruginosa, Angew. Chem. Int. Ed. 53 (47) (2014) 12827–12831.
[51] J. Pires, T.N. Siriwardena, M. Stach, R. Tinguely, S. Kasraian, F. Luzzaro, et al., In vitro activity of the novel antimicrobial peptide dendrimer G3KL against multidrug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa, Antimicrob. Agents Chemother. 59 (12) (2015) 7915–7918.
[52] Lehn JM. Bibliography and Notes. Supramolecular Chemistry: Concepts and Perspectives.207–58.
[53] E.M. Johansson, S.A. Crusz, E. Kolomiets, L. Buts, R.U. Kadam, M. Cacciarini, et al., Inhibition and dispersion of Pseudomonas aeruginosa biofilms by glycopeptide dendrimers targeting the fucose-specific lectin LecB, Chem. Biol. 15 (12) (2008) 1249–1257.
[54] G. Michaud, R. Visini, M. Bergmann, G. Salerno, R. Bosco, E. Gillon, et al., Overcoming antibiotic resistance in Pseudomonas aeruginosa biofilms using glycopeptide dendrimers, Chem. Sci. 7 (1) (2016) 166–182.
[55] A. Pini, A. Giuliani, C. Falciani, Y. Runci, C. Ricci, B. Lelli, et al., Antimicrobial activity of novel dendrimeric peptides obtained by phage display selection and rational modification, Antimicrob. Agents Chemother. 49 (7) (2005) 2665–2672.
[56] M. Donalisio, M. Rusnati, A. Civra, A. Bugatti, D. Allemand, G. Pirri, et al., Identification of a dendrimeric heparan sulfate-binding peptide that inhibits infectivity of genital types of human papillomaviruses, Antimicrob. Agents Chemother. 54 (10) (2010) 4290–4299.
[57] M. Donalisio, M. Rusnati, V. Cagno, A. Civra, A. Bugatti, A. Giuliani, et al.,

Inhibition of human respiratory syncytial virus infectivity by a dendrimeric heparan sulfate-binding peptide, Antimicrob. Agents Chemother. 56 (10) (2012) 5278–5288.
[58] I. Bon, D. Lembo, M. Rusnati, A. Clò, S. Morini, A. Miserocchi, et al., Peptide-derivatized SB105-A10 dendrimer inhibits the infectivity of R5 and X4 HIV-1 strains in primary PBMCs and cervicovaginal histocultures, PLoS One 8 (10) (2013).
[59] D. Zanini, R. Roy, Synthesis of new α-thiosialodendrimers and their binding properties to the sialic acid specific lectin from Limax flavus, J. Am. Chem. Soc. 119 (9) (1997) 2088–2095.
[60] R. Roy, D. Zanini, S. Meunier, A. Romanowska, Synthesis and antigenic properties of sialic acid based dendrimers, ChemInform 26 (3) (1995) (no-no).
[61] A. Luganini, S.F. Nicoletto, L. Pizzuto, G. Pirri, A. Giuliani, S. Landolfo, et al., Inhibition of herpes simplex virus type 1 and type 2 infections by peptide-derivatized dendrimers, Antimicrob. Agents Chemother. 55 (7) (2011) 3231–3239.
[62] S.-F. Zhang, C. Gao, S. Lü, J. He, M. Liu, C. Wu, et al., Synthesis of PEGylated polyglutamic acid peptide dendrimer and its application in dissolving thrombus, Colloids Surf. B: Biointerfaces 159 (2017) 284–292.
[63] C. Wu, C. Gao, S. Lü, X. Xu, N. Wen, S. Zhang, et al., Construction of polylysine dendrimer nanocomposites carrying nattokinase and their application in thrombolysis, J. Biomed. Mater. Res. A 106 (2) (2018) 440–449.
[64] S.F. Zhang, S. Lü, C. Gao, J. Yang, X. Yan, T. Li, et al., Multiarm-polyethylene glycol-polyglutamic acid peptide dendrimer: design, synthesis, and dissolving thrombus, Journal of Biomedical Materials Research - Part A 106 (6) (2018) 1687–1696.
[65] X. Zhang, Z. Zhang, X. Xu, Y. Li, Y. Li, Y. Jian, et al., Bioinspired therapeutic dendrimers as efficient peptide drugs based on supramolecular interactions for tumor inhibition, Angew. Chem. Int. Ed. 54 (14) (2015) 4289–4294.
[66] C. Kojima, K. Saito, E. Kondo, Design of peptide–dendrimer conjugates with tumor homing and antitumor effects, Res. Chem. Intermed. (2018) 1–11.
[67] V.G. Joshi, V.D. Dighe, D. Thakuria, Y.S. Malik, S. Kumar, Multiple antigenic peptide (MAP): a synthetic peptide dendrimer for diagnostic, antiviral and vaccine strategies for emerging and re-emerging viral diseases, Indian Journal of Virology 24 (3) (2013) 312–320.
[68] H. Dechamma, V. Dighe, C.A. Kumar, R. Singh, M. Jagadish, S. Kumar, Identification of T-helper and linear B epitope in the hypervariable region of nucleocapsid protein of PPRV and its use in the development of specific antibodies to detect viral antigen, Vet. Microbiol. 118 (3–4) (2006) 201–211.
[69] S. Ramesh, P. Cherkupally, T. Govender, H.G. Kruger, F. Albericio, B.G. De La Torre, Chemical platforms for peptide vaccine constructs, Advances in Protein Chemistry and Structural Biology (2015) 99–130.
[70] J.P. Tam, J.C. Spetzler, Synthesis and application of peptide dendrimers as protein mimetics, Curr. Protoc. Immunol. 34 (1) (1999) 9.6. 1–9.6. 36.
[71] H. Baigude, K. Katsuraya, K. Okuyama, N. Kariya, T. Uryu, Synthesis of HIV vaccine model based on lactose-functionalized poly(lysine) dendrimer scaffold, Journal of Fiber Science and Technology 60 (4) (2004) 118–124.
[72] J.R. Francica, R. Laga, G.M. Lynn, G. Mužíková, L. Androvič, B. Aussedat, et al., Star nanoparticles delivering HIV-1 peptide minimal immunogens elicit near-native envelope antibody responses in nonhuman primates, PLoS Biol. 17 (6) (2019) e3000328.
[73] W. Kowalczyk, B.G. De La Torre, D. Andreu, Strategies and limitations in dendrimeric immunogen synthesis. The influenza virus M2e epitope as a case study, Bioconjug. Chem. 21 (1) (2010) 102–110.
[74] T.H. Abdelhafez, N.G. Bader El Din, A.A. Tabll, M.M. Mashaly, R.M. Dawood, N.A. Yassin, et al., Mice antibody response to conserved Nonadjuvanted multiple antigenic peptides derived from E1/E2 regions of hepatitis C virus, Viral Immunol. 30 (5) (2017) 359–365.
[75] Haro I, Pérez S, García M, Chan WC, Ercilla G. Liposome entrapment and immunogenic studies of a synthetic lipophilic multiple antigenic peptide bearing VP1 and VP3 domains of the hepatitis A virus: a robust method for vaccine design. FEBS Lett.. 2003; 540(1–3):133–40.
[76] G.X. Li, Y.J. Zhou, H. Yu, L. Li, Y.X. Wang, W. Tong, et al., A novel dendrimeric peptide induces high level neutralizing antibodies against classical swine fever virus in rabbits, Vet. Microbiol. 156 (1–2) (2012) 200–204.
[77] M. Monsó, J. Tarradas, B.G. De La Torre, F. Sobrino, L. Ganges, D. Andreu, Peptide vaccine candidates against classical swine fever virus: T cell and neutralizing antibody responses of dendrimers displaying E2 and NS2-3 epitopes, J. Pept. Sci. 17 (1) (2011) 24–31.
[78] I. Soria, V. Quattrocchi, C. Langellotti, M. Gammella, S. Digiacomo, B. Garcia de la Torre, et al., Dendrimeric peptides can confer protection against foot-and-mouth disease virus in cattle, PLoS One 12 (9) (2017).
[79] C. Cubillos, B.G. De La Torre, A. Jakab, G. Clementi, E. Borrás, J. Bárcena, et al., Enhanced mucosal immunoglobulin A response and solid protection against foot-and-mouth disease virus challenge induced by a novel dendrimeric peptide, J. Virol. 82 (14) (2008) 7223–7230.
[80] L.J. Cruz, E. Iglesias, J.C. Aguilar, L.J. González, O. Reyes, F. Albericio, et al., A comparative study of different presentation strategies for an HIV peptide immunogen, Bioconjug. Chem. 15 (1) (2004) 112–120.
[81] K. Hatano, T. Matsubara, Y. Muramatsu, M. Ezure, T. Koyama, K. Matsuoka, et al., Synthesis and influenza virus inhibitory activities of carbosilane dendrimers peripherally functionalized with hemagglutinin-binding peptide, J. Med. Chem. 57 (20) (2014) 8332–8339.
[82] J.G. Schellinger, L.M. Danan-Leon, J.A. Hoch, A. Kassa, I. Srivastava, D. Davis, et al., Synthesis of a trimeric gp120 epitope mimic conjugated to a T-helper peptide to improve antigenicity, J. Am. Chem. Soc. 133 (10) (2011) 3230–3233.
[83] D. Bundle, E. Paszkiewicz, H. Elsaidi, S. Mandal, S. Sarkar, A three component synthetic vaccine containing a β-mannan T-cell peptide epitope and a β-glucan dendritic cell ligand, Molecules 23 (8) (2018) 1961.
[84] E. Blanco, B. Guerra, B.G. De La Torre, S. Defaus, A. Dekker, D. Andreu, et al., Full protection of swine against foot-and-mouth disease by a bivalent B-cell epitope dendrimer peptide, Antivir. Res. 129 (2016) 74–80.
[85] I. Soria, V. Quattrocchi, C. Langellotti, M. Pérez-Filgeira, J. Pega, V. Gnazzo, et al., Immune response and partial protection against heterologous foot-and-mouth disease virus induced by dendrimer peptides in cattle, J Immunol Res 2018 (2018).
[86] P. Kim, C.-P. Pau, Comparing tandem repeats and multiple antigenic peptides as the antigens to detect antibodies by enzyme immunoassay, J. Immunol. Methods 257 (1–2) (2001) 51–54.
[87] M.J. Gómara, L. Fernández, T. Pérez, G. Ercilla, I. Haro, Assessment of synthetic chimeric multiple antigenic peptides for diagnosis of GB virus C infection, Anal. Biochem. 396 (1) (2010) 51–58.
[88] A. Habluetzel, A. Pessi, E. Bianchi, G. Rotigliano, F. Esposito, Multiple antigen peptides for specific detection of antibodies to a malaria antigen in human sera, Immunol. Lett. 30 (1) (1991) 75–80.
[89] P. Saravanan, S. Kumar, J. Kataria, Use of multiple antigenic peptides related to antigenic determinants of infectious bursal disease virus (IBDV) for detection of anti-IBDV-specific antibody in ELISA—quantitative comparison with native antigen for their use in serodiagnosis, J. Immunol. Methods 293 (1–2) (2004) 61–70.
[90] J. Wan, P.F. Alewood, Peptide-decorated dendrimers and their bioapplications, Angew. Chem. Int. Ed. 55 (17) (2016) 5124–5134.
[91] C. Kojima, K. Irie, T. Tada, N. Tanaka, Temperature-sensitive elastin-mimetic dendrimers: effect of peptide length and dendrimer generation to temperature sensitivity, Biopolymers 101 (6) (2014) 603–612.
[92] S. Ma, J. Zhou, A.R.M. Wali, Y. He, X. Xu, J.Z. Tang, et al., Self-assembly of pH-sensitive fluorinated peptide dendron functionalized dextran nanoparticles for on-demand intracellular drug delivery, J. Mater. Sci. Mater. Med. 26 (8) (2015) 219.
[93] C. Zhang, D. Pan, J. Li, J. Hu, A. Bains, N. Guys, et al., Enzyme-responsive peptide dendrimer-gemcitabine conjugate as a controlled-release drug delivery vehicle with enhanced antitumor efficacy, Acta Biomater. 55 (2017) 153–162.
[94] O. Saher, C.S.J. Rocha, E.M. Zaghloul, O.P.B. Wiklander, S. Zamolo, M. Heitz, et al., Novel peptide-dendrimer/lipid/oligonucleotide ternary complexes for efficient cellular uptake and improved splice-switching activity, Eur. J. Pharm. Biopharm. 132 (2018) 29–40 2018/11/01/.
[95] S.S. Santos, R.V. Gonzaga, J.V. Silva, D.F. Savino, D. Prieto, J.M. Shikay, et al., Peptide dendrimers: drug/gene delivery and other approaches, Can. J. Chem. 95 (9) (2017) 907–916.
[96] W. Godbey, K.K. Wu, A.G. Mikos, Poly (ethylenimine) and its role in gene delivery, J. Control. Release 60 (2–3) (1999) 149–160.
[97] W. Godbey, K.K. Wu, A.G. Mikos, Size matters: molecular weight affects the efficiency of poly (ethyleneimine) as a gene delivery vehicle, J. Biomed. Mater. Res. 45 (3) (1999) 268–275.
[98] D. Luo, K. Haverstick, N. Belcheva, E. Han, W.M. Saltzman, Poly (ethylene glycol)-conjugated PAMAM dendrimer for biocompatible, high-efficiency DNA delivery, Macromolecules 35 (9) (2002) 3456–3462.
[99] J.S. Choi, K. Nam, Park J-y, J.-B. Kim, J.-K. Lee, Park J-s, Enhanced transfection efficiency of PAMAM dendrimer by surface modification with L-arginine, J. Control. Release 99 (3) (2004) 445–456.
[100] A. Zarebkohan, F. Najafi, H.R. Moghimi, M. Hemmati, M.R. Deevband, B. Kazemi, Synthesis and characterization of a PAMAM dendrimer nanocarrier functionalized by SRL peptide for targeted gene delivery to the brain, Eur. J. Pharm. Sci. 78 (2015) 19–30.
[101] K. Luo, C. Li, L. Li, W. She, G. Wang, Z. Gu, Arginine functionalized peptide dendrimers as potential gene delivery vehicles, Biomaterials 33 (19) (2012) 4917–4927.
[102] H. Chang, H. Wang, N. Shao, M. Wang, X. Wang, Y. Cheng, Surface-engineered dendrimers with a diaminododecane core achieve efficient gene transfection and low cytotoxicity, Bioconjug. Chem. 25 (2) (2014) 342–350.
[103] X. Cai, H. Zhu, H. Dong, Y. Li, J. Su, D. Shi, Suppression of VEGF by reversible-PEGylated histidylated polylysine in cancer therapy, Advanced healthcare materials 3 (11) (2014) 1818–1827.
[104] X. Cai, H. Zhu, Y. Zhang, Z. Gu, Highly efficient and safe delivery of VEGF siRNA by bioreducible fluorinated peptide dendrimers for cancer therapy, ACS Appl. Mater. Interfaces 9 (11) (2017) 9402–9415.
[105] D. Lagnoux, T. Darbre, M.L. Schmitz, J.L. Reymond, Inhibition of mitosis by glycopeptide dendrimer conjugates of colchicine, Chem Eur J 11 (13) (2005) 3941–3950.
[106] K.E. Burns, J.B. Delehanty, Cellular delivery of doxorubicin mediated by disulfide reduction of a peptide-dendrimer bioconjugate, Int. J. Pharm. 545 (1–2) (2018) 64–73.
[107] C. Kojima, T. Suehiro, K. Watanabe, M. Ogawa, A. Fukuhara, E. Nishisaka, et al., Doxorubicin-conjugated dendrimer/collagen hybrid gels for metastasis-associated drug delivery systems, Acta Biomater. 9 (3) (2013) 5673–5680.
[108] N. Li, N. Li, Q. Yi, K. Luo, C. Guo, D. Pan, et al., Amphiphilic peptide dendritic copolymer-doxorubicin nanoscale conjugate self-assembled to enzyme-responsive anti-cancer agent, Biomaterials 35 (35) (2014) 9529–9545.
[109] S. Liu, Y. Guo, R. Huang, J. Li, S. Huang, Y. Kuang, et al., Gene and doxorubicin co-delivery system for targeting therapy of glioma, Biomaterials 33 (19) (2012) 4907–4916.
[110] C. Zhang, D. Pan, K. Luo, W. She, C. Guo, Y. Yang, et al., Peptide dendrimer-doxorubicin conjugate-based nanoparticles as an enzyme-responsive drug delivery system for cancer therapy, Advanced Healthcare Materials 3 (8) (2014) 1299–1308.

[111] S.J. Lee, Y.I. Jeong, H.K. Park, D.H. Kang, J.S. Oh, S.G. Lee, et al., Enzyme-responsive doxorubicin release from dendrimer nanoparticles for anticancer drug delivery, Int. J. Nanomedicine 10 (2015) 5489–5503.
[112] H. Mendoza-Nava, G. Ferro-Flores, F. De María Ramírez, B. Ocampo-García, C. Santos-Cuevas, E. Azorín-Vega, et al., Fluorescent, plasmonic, and radiotherapeutic properties of the177Lu-dendrimer-AuNP-folate-bombesin nanoprobe located inside cancer cells, Mol. Imaging 16 (2017).
[113] H. Yuan, K. Luo, Y. Lai, Y. Pu, B. He, G. Wang, et al., A novel poly (L-glutamic acid) dendrimer based drug delivery system with both pH-sensitive and targeting functions, Mol. Pharm. 7 (4) (2010) 953–962.
[114] P.M. Levine, T.P. Carberry, J.M. Holub, K. Kirshenbaum, Crafting precise multivalent architectures, MedChemComm 4 (3) (2013) 493–509.
[115] D. Pan, C. Guo, K. Luo, Q. Yi, Z. Gu, PEGylated dendritic diaminocyclohexyl-platinum (II) conjugates as pH-responsive drug delivery vehicles with enhanced tumor accumulation and antitumor efficacy, Biomaterials 35 (38) (2014) 10080–10092.
[116] K.E. Burns, J.B. Delehanty, Cellular delivery of doxorubicin mediated by disulfide reduction of a peptide-dendrimer bioconjugate, Int. J. Pharm. 545 (1) (2018) 64–73 2018/07/10/;.
[117] M. Masuda, S. Kawakami, W. Wijagkanalan, T. Suga, Y. Fuchigami, F. Yamashita, et al., Anti-MUC1 aptamer/negatively charged amino acid dendrimer conjugates for targeted delivery to human lung adenocarcinoma A549 cells, Biol. Pharm. Bull. 39 (10) (2016) 1734–1738.
[118] A.R. Hegde, P.V. Rewatkar, J. Manikkath, K. Tupally, H.S. Parekh, S. Mutalik, Peptide dendrimer-conjugates of ketoprofen: synthesis and ex vivo and in vivo evaluations of passive diffusion, sonophoresis and iontophoresis for skin delivery, Eur. J. Pharm. Sci. 102 (2017) 237–249.
[119] J. Manikkath, A.R. Hegde, G. Kalthur, H.S. Parekh, S. Mutalik, Influence of peptide dendrimers and sonophoresis on the transdermal delivery of ketoprofen, Int. J. Pharm. 521 (1–2) (2017) 110–119.
[120] K. Dave, V.V. Krishna Venuganti, Dendritic polymers for dermal drug delivery, Ther. Deliv. 8 (12) (2017) 1077–1096.
[121] R. Wiwattanapatapee, B. Carreño-Gómez, N. Malik, R. Duncan, Anionic PAMAM dendrimers rapidly cross adult rat intestine in vitro: a potential oral delivery system? Pharm. Res. 17 (8) (2000) 991–998.
[122] M. Dribek, I. Le Potier, A. Rodrigues, A. Pallandre, E. Fattal, M. Taverna, Determination of binding constants of vasoactive intestinal peptide to poly (amidoamine) dendrimers designed for drug delivery using ACE, Electrophoresis 28 (13) (2007) 2191–2200.
[123] C.O. Chan, J. Jing, W. Xiao, Z. Tan, Q. Lv, J. Yang, et al., Enhanced intestinal permeability of bufalin by a novel bufalin-peptide-dendrimer inclusion through caco-2 cell monolayer, Molecules 22 (12) (2017).
[124] A.-M. Caminade, J.-P. Majoral, Bifunctional phosphorus dendrimers and their properties, Molecules 21 (4) (2016) 538.
[125] J. Pan, L. Ma, B. Li, Y. Li, L. Guo, Novel dendritic naproxen prodrugs with poly (aspartic acid) oligopeptide: synthesis and hydroxyapatite binding in vitro, Synth. Commun. 42 (23) (2012) 3441–3454.
[126] Y. Zhao, Q. Zeng, F. Wu, J. Li, Z. Pan, P. Shen, et al., Novel naproxen-peptide-conjugated amphiphilic dendrimer self-assembly micelles for targeting drug delivery to osteosarcoma cells, RSC Adv. 6 (65) (2016) 60327–60335.
[127] G. Fassina, A. Verdoliva, M.R. Odierna, M. Ruvo, G. Cassini, Protein A mimetic peptide ligand for affinity purification of antibodies, J. Mol. Recognit. 9 (5–6) (1996) 564–569.
[128] F. Dinon, M. Salvalaglio, A. Gallotta, L. Beneduce, P. Pengo, C. Cavallotti, et al., Structural refinement of protein A mimetic peptide, J. Mol. Recognit. 24 (6) (2011) 1087–1094.
[129] N. Kruljec, T. Bratkovič, Alternative affinity ligands for immunoglobulins, Bioconjug. Chem. 28 (8) (2017) 2009–2030.
[130] N. Kruljec, P. Molek, V. Hodnik, G. Anderluh, T. Bratkovič, Development and characterization of peptide ligands of immunoglobulin G Fc region, Bioconjug. Chem. 29 (8) (2018) 2763–2775.