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Carbosilane Dendrimers: Drug and Gene Delivery Applications

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Abstract

Carbosilane dendrimers are a particular type of dendrimer structure that has been used as delivery vehicles for drugs and nucleic acids. They have a defined structure according to their generation number, and their terminal groups can be rendered cationic or anionic. The cationic charges can address the limitation of electrostatic repulsion between the negatively charged phosphate groups of nucleic acids and negatively charged cell membranes. Specific drugs can be loaded into the central part of the dendrimer or attached at the exterior, and the overall positive charge may improve the efficacy of anti-inflammatory drugs. One promising feature of dendrimers is their non-toxicity both *in vitro* and *in vivo* up to therapeutic concentrations. Carbosilane dendrimers display good biocompatibility and can be used for anti-HIV, anti-viral, and anti-inflammatory applications, as well as for delivery of nucleic acids for anti-cancer therapy.

Graphical abstract

Keywords

Carbosilane dendrimers, Drug delivery, Gene delivery, Topical antivirals, Nanomedicine, Immunotherapy

1. Introduction

Dendrimers are nanosized branched molecules composed of a central core with dendrons extending outward, similar to tree branches. The dendrimer molecules are designed to have a uniform molecular weight and size according to their generation number. The terminal groups on the exterior can be chemically modified or tailored according to the desired application [1]. Dendrimers can encapsulate cargos or be chemically attached to different molecules according to the size, surface properties, and functional groups present, and thereby protect these molecules against the adverse effects of external factors. Furthermore, they can release these molecules within their targeted environment [[2], [3], [4]].

Poly(propylene imine) (PPI) and Poly(amido amine) (PAMAM) dendrimers are the two most studied dendrimers, according to their commercial accessibility [5]. However, poly(L-Lysine) (PLL) [6], phosphorous dendrimers (P-dendrimers) [7], and carbosilane dendrimers [8], are widely discovered. These various groups of dendrimers were studied for their usage in different applications such as drug and gene delivery systems, and antiviral and antibacterial agents [9].

Carbosilanes are compounds with elements silicon and carbon in the molecular skeleton. With the use of silicon chemistry, various types of carbosilane dendrimers which have hydrophobic scaffolds and high thermal stability have been developed [10]. The benefits of carbosilane dendrimers is related with high energy of the C–Si bond, and also hydrophobicity. Although they can be changed into hydrophilic materials by surface functionalization with polar moieties. Groups such as Si–Cl, Si–H, and Si–CH₂CH=CH₂ can introduce various intriguing organic and inorganic substituents, and causes the increasing use in biomedical fields [11].

Based on nature of the periphery, carbosilane dendrimer is divided into two types of cationic and anionic dendrimers. The cytotoxicity of carbosilane dendrimers depends on the nature and number of functional surface groups. Cationic carbosilane dendrimers show high toxicity, while anionic dendrimers demonstrate low toxicity effects [12]. PAMAM dendrimer have terminal amines are considered by toxicity based on generation, and carbosilane dendrimers terminated with neutral or anionic groups show low toxicity [13]. Therefore, modification of the surface of the cationic dendrimer with negatively charged or neutral moieties decreases its cytotoxicity.

In recent years, carbosilane dendrimers have demonstrated the potential for many applications such as delivery of drugs and nucleic acid into cells, and treatment of diseases due to their good properties [14,15]. Drug delivery systems are therapeutic carriers which suggestion various benefits than conventional drugs applied for the treatment of infectious diseases and cancers. Different types of delivery system used in biomedical application, such as nanoparticle, lipid-based materials, micelles, dendrimers, etc. [16,17]. The good properties of dendrimers make them appropriated for the treatment of infectious diseases and cancers. Reduced toxicity and side effects of drugs, increased bioavailability, and increased half-life resulting in reduced kidney clearance are advantages of using

dendrimers as drug carriers [9]. However, carbosilane dendrimer can have antiviral activity in combination with antiviral drugs and used as therapeutic agents in therapy of combination [18,19].

Cationic dendrimers have emerged as powerful platforms for the formation of dendriplexes due to the electrostatic interaction with nucleic acids, including small interfering RNA (siRNA) and oligonucleotides [20]. Cationic dendrimers including are increasingly being used in cell transfection protocols. The water solubility of cationic carbosilane dendrimers allows them to be used as non-viral carriers for drug and gene therapy, owing to their powerful amphiphilic behavior. However, evidence suggests that the ammonium end groups of these carbosilane dendrimers need to be carefully controlled to prevent toxicity. This intrinsic toxicity can possibly be addressed by binding to polyethylene glycol (PEG). Cationic phosphorus dendrimers complexed with nucleic acids have been shown to be able to serve as vehicles for siRNA and DNA delivery *in vitro* [[21], [22], [23], [24]].

Additionally, water-stable nanocarriers such as anionic carbosilane dendrimers have received considerable attention, and their 1st to 3rd generation analogues can be synthesized to contain sulfonate and carboxylate groups [25,26]. Second-generation carbosilane dendrimer functionalized with sulfated (G2-S16) is an example of a second-generation anionic dendrimer that bears sulfonate groups on the exterior with a silica-based core [27,28]. High biocompatibility is an important feature of the G2-S16 anionic carbosilane dendrimer with 16 sulfonate groups. This polyanionic carbosilane dendrimer has shown anti-HIV viral activity, thus addressing a major health concern. The biocompatibility, low toxicity, and high inhibitory capacity are advantages for HIV inhibition. Maraviroc is a chemokine receptor antagonist that has been designed to act against HIV by interfering with the interaction between HIV and chemokine receptor type 5 (CCR5), and thereby blocking HIV from entering human cells. The combination of polyanionic carbosilane dendrimer with naphthyl sulfonated (G2-NF16) –and G3-S16 with maraviroc increased the antiviral potency against HIV [[29], [30], [31], [32]].

In this review, we describe some applications of carbosilane dendrimers in biomedical fields and nanomedicine, especially for anti-cancer therapy, immunotherapy, drug delivery, and gene therapy, and highlight their importance in the treatment of the dread diseases, cancer and HIV/AIDS.

2. Chemistry of carbosilane dendrimers

Dendrimers are usually synthesized by one of two methods. The divergent method begins with the core and proceeds radially outwards in defined generations, each of which adds an additional layer. The second method was designed by Hawker, called the convergent method, starts by the synthesis and connection of the outermost parts, and eventually adding a central core that connects all the branches together. Other approaches that have been investigated for dendrimer synthesis include click chemistry, total synthesis routes, double exponential, and hypercore and branched monomers [[33], [34], [35], [36]].

The preparation of hybrid carbosilane-based dendrimers containing viologen and phosphorus-based groups has been described using a convergent strategy based on the double alkylation of 4,4-bipyridine units. The interaction of these hybrid dendrimer molecules with plasma proteins, such as human serum albumin (HSA) and the impact of this on the hemotoxicity and cytotoxicity was investigated [37]. Hydrophilic dendrimers generally have different overall sizes, and show different reactions with HSA.

This is probably due to the size, rather than the number of positive charges according to zeta-potential data. Measurement of the HSA fluorescence intensity and the Stern-Volmer quenching constant (K_{sv}) revealed that the larger dendrimer interacted with the secondary structure of HSA to a greater extent than the smaller dendrimer. The effects of these dendrimers on cell viability was evaluated using eukaryotic cells (mouse fibroblasts). The cytotoxicity of these carbosilane viologen-phosphorus dendrimers was associated with the outer positive charge, rather than internal charges; therefore they may be suited to act as antibacterial compounds, or non-viral carriers for nucleic acids [37,38].

Biodegradable cationic carbosilane dendrimers can be prepared using two different approaches. The first one uses a reaction with amine dendrons where the hydroxyl group is located at the focal point and the dendrimers have Si-Cl peripheral bonds. The second method exploits the reaction of dendrimers that have acidic peripheral groups to produce first alcohols then amines, and finally adding MeI for quaternization of the neutral compounds to form cationic ones. However, the aryl groups attached to the oxygen atoms (Si-OR) result in a reduced hydrolysis rate compared to compounds with alkyl chains attached to oxygen atoms. Dendrimers with Si-O bonds are unstable in aqueous conditions and hence these compounds are not appropriate for biomedical applications. Dendrimers that show higher water stability are better suited as carriers for gene and drug delivery [[39], [40], [41], [42]].

Recent synthetic methods have been introduced involving hydrosilylation reactions via Cu-catalyzed cycloaddition of azide-alkyne derivatives. This method enables the preparation of novel anionic water-soluble carbosilane dendrimers possessing carboxylate, phosphonate, naphthalenesulfonate and sulfate terminal groups. One of the positive benefits of these anionic dendrimers is their non-toxicity in both *in vitro* cell culture up to 20 μ M concentration, and also *in vivo*. These dendrimers exhibited inhibition of HIV infection *in vitro* in peripheral blood mononuclear cells (PBMCs) due to the presence of anionic groups (carboxylate, naphthylsulfonate, and sulfate) [[43], [44], [45]]. Researchers have used *in vitro* experiments and computer modeling to show that carboxylate-terminated carbosilane dendrimers had the most significant interaction with proteins at acidic pH values, in comparison to basic and neutral pH conditions. At acidic and neutral pH, carboxylate dendrimers can form a stable complex with some proteins. This approach can be used for the purification of proteins from complex mixtures at acidic pH, using carboxylate-terminated carbosilane dendrimers to carry out selective protein enrichment [[46], [47], [48], [49]].

The click chemistry reaction has been used to prepare cationic carbosilane complexes by conjugating azide-terminated carbosilane dendrimers to propargyl amines, followed by the subsequent addition of methyl iodide for quaternization. Dendrimers have been developed as nanoparticles bound to plasmid DNA, and the ensuing DNA dendritic nanoparticles (dendriplexes) demonstrate a good transfection ability both *in vivo* and *in vitro*. Two different families of cationic carbosilane dendrimers have been developed, where the first family possesses ammonium group on segments and can be first to third generations. The second family contains two different atoms with positive charges. The second generation of the first family (F1G2 5/1($\pm$)) has been developed and evaluated for plasmid-mediated gene transfer in HePG2 cells [[50], [51], [52], [53]].

Anionic carbosilane dendrimers with sulfonate or carboxylate groups have also been synthesized via thiol-ene chemistry. The advantages of this method are more facile purification and shorter reaction times, as compared with Michael-type hydrosilylation or the click chemistry with azide-alkyne linkages.

A comparison of silicone-core dendrimers and polyphenoxo-core dendrimers revealed that the silicone-core second generation dendrimers 2 and 12 exhibited 85–90% HIV inhibition without any inflammation or vaginal irritation in female mice. The poly-phenoxo-core dendrimers showed lower biocompatibility. The silicone-core dendrimers could be promising candidates as topically applied microbicides against HIV [31,[54], [55], [56]].

A new class of cationic carbosilane dendrimers that were functionalized with varying peripheral phosphonium groups were synthesized, and their toxicity was evaluated using CV and MTT assays in cell lines (NRK, BRL, B14 cells). The cytotoxicity of carbosilane dendrimers bearing methyl groups displayed enhanced toxicity compared to dendrimers bearing different alkyl substituents (PBU_3 and $\text{P}(\text{Et}_2)_2(\text{CH}_2)_3\text{OH}$). $\text{P}(\text{C}_6\text{H}_4\text{-OMe})_3$ dendrimers demonstrated very low toxicity towards the range of cell lines. Overall, phosphonium-substituted carbosilane dendrimers could be a potential alternative to ammonium-substituted dendrimers for gene therapy applications [[57], [58], [59], [60]].

The multivalency of carbosilane dendrimers plays an important role in the antimicrobial activity of these compounds. Quaternary ammonium (QA)-functionalized carbosilane dendrimers showed higher microbicidal activity compared to monofunctional carbosilane dendrimers, as illustrated by ammonium-terminated hyperbranched polycarbosilane (PC) dendrimers [61]. Poly(propyleneimine) (PPI) dendrimers showed only a low antimicrobial activity, whereas ammonium-terminated Poly(propyleneimine) (PPI) dendrimers had higher antimicrobial activities [62]. Anionic carbosilane dendrimers bearing carboxyl and sulfonate groups have demonstrated anti-HIV activity. These compounds showed 100% viral inhibition and could act as antiretroviral drugs in TZM-bl cells [[62], [63], [64]].

3. Application of carbosilane dendrimers in biology and nanomedicine

Carbosilane dendrimers, which are hyperbranched macromolecules, have attracted researchers' attention over the last two decades due to their various characteristics, in the fields of biology and nanomedicine such as anticancer therapy, immunotherapy, and drug/gene delivery [8,65,66]. The existence of cationic groups on carbosilane dendrimers renders them water-soluble. The amphiphilic characteristics of carbosilane dendrimer make them important drug carriers. Thanks to the abundance of end groups, a high loading of drug or nucleic acid molecules can be attached by covalent bonds and/or by electrostatic interactions, thus making them a suitable choice for drug and gene delivery [30,[67], [68], [69]]. In the following sections, different application of carbosilane dendrimers have been introduced.

3.1. Application of carbosilane dendrimers in anticancer therapy and immunotherapy

Cancer patients often need high dosages of chemotherapeutic drugs, which tend to have unacceptably high toxicity. Moreover, these drugs have no specificity for tumors, and will cause serious damage to normal tissues such as heart, liver and lungs. The low molecular weight of many cytotoxic drugs and their lack of specificity, have led to searches for better ways to deliver them in a more selective manner. Dendrimer can be a good choice as anticancer agent, and some studies have been conducted on the role of carbosilane dendrimers in cancer therapy and immunotherapy [[70], [71], [72]] (see Fig. 1).

Carbosilane dendrimers that have been functionalized with *N*-, NH₂-donor monodendate ligands and *N,N*-chelating ruthenium complexes are a new approach in anticancer therapy. The ruthenium-terminated carbosilane dendrimers (CRD27 and CRD13) showed the most homogenous formulation. The cytotoxicity of CRDs towards cancer cells and normal cells, hemolytic activity, and biophysical characterization were examined. The zero generation metallodendrimers were effective drugs, because they were non-toxic to normal cells, but were still cytotoxic to cancer cells. CRDs were found to be effective against an acute promyelocytic leukemia cell line (HL60) [65] (Fig. 2).

Fig. 1. Synthesis of carbosilane dendrons (generations 1–3) [15].

Fig. 2. Structures of 3 newly synthesized classes of CRDs with imine-pyridine groups (CDR5, CRD14 and CRD28), pyridine-imine groups (CRD7, CRD13andCRD27), and ANH2 groups (CDR34 and CRD32) [65].

Dendritic cells (DCs) are an important class of antigen-presenting cells (APC), because they can activate adaptive immune cells (T-cells and B-cells) to recognize tumor antigens [73]. Innate immune cells, including many subsets of monocytes, macrophages and DCs can mediate the non-specific immune response against microbial invaders, but DCs in particular can stimulate the adaptive immune response through antigen presentation [74].

In one study, dendrimers were designed as a vehicle for HIV-1 specific peptides. The goal was to trigger an adaptive immune response against HIV-1 by delivering the peptides to DCs. The cationic carbosilane dendrimer (G2-NN16) was loaded with several HIV derived-peptides (p24/gp160/NEF or p24/gp160). The G2-NN16/peptide complex alone showed better uptake by immature DCs compared to mature DCs. The peptides did not affect the ability of DCs to migrate to draining lymph nodes. Molecular dynamic simulations revealed that the peptides inhibited the cell uptake of other peptides, for example NEF peptide prevented the binding of gp160 to G2-NN16. This showed that G2-NN16 could not act as a vehicle for delivery of two or more HIV-derived peptides to DCs [[75], [76], [77]].

Tumor-associated macrophages (TAMs) are found within tumors. TAMs with a M2 polarization express immunosuppressive chemokines, cytokines, and proteases including MMPs. These macrophages play an important role in the processes of angiogenesis and tumor metastasis, and are considered to be target prevent tumor progression [[78], [79], [80], [81]]. Carboxylate-functionalized dendrimers could have a role in restricting the signaling pathways and reducing TAM function. To investigate the potential role of dendrimers in tumor immunotherapy, the effect of $G_3O_3(SiONN)_{24}$ (2G-03NN24) on M2 macrophage polarization was studied. It was claimed that the 2G-03NN24 dendrimer reduced the LPS-induced 1L-10 production from monocyte-derived M2 macrophages. Moreover 2G-03NN24 could switch the gene expression profile towards the M1 polarization pattern, by increasing markers such as 1NHBA, FLT1, SERPINE1 and EGLN3, and decrease markers of M2 polarization, such as IGF2, EMR1, SLC40A1 and FOLR2. It was shown that the 2G-03NN24 dendrimer decreased STAT3 activation. Overall, the results showed that the 2G-03NN24 dendrimer could be used for antitumor therapy owing to its ability to reduce the M2 polarization state of TAMs [66,[82], [83], [84]] (Fig. 3).

Fig. 3. Schematic illustration of the decrease in the function of M2 macrophages and switching gene expression of M2 macrophages to M1 polarization state by 2G-03NN24 dendrimer [66].

3.2. Application of carbosilane dendrimers in drug and peptid delivery

Carbosilane dendrimers can be used as carriers in drug delivery by attaching chemical groups to the surface of the macromolecules. Drug delivery systems are probable therapeutic vehicles which suggest various benefits than conventional drugs applied for the treatment of diseases. A best drug delivery system must be capable to decreases drug toxicity, and enhanced biocompatibility, bioavailability and drug solubility [16]. Dendrimers are synthetic polymers with branched macromolecules and made up of the interior and exterior layers. Encapsulation of drugs occurs in the interior layers, decreasing toxicity and control release of drugs; and the exterior layer is composed of functional groups which are suitable for conjugation of drugs. Therefore, this properties of dendrimers make them beneficial as a drug delivery systems and they are being studied by many scientists [9].

Ibuprofen-modified dendrimers and dendrons (including cationic-ibuprofen dendrimer and dendrons) can improve the performance of the anti-inflammatory drug, ibuprofen by improving its uptake by cells. Cationic carbosilane dendrimers and dendrons can be loaded with ibuprofen, either within the

central core or by attachment to the outer reactive groups. Ibuprofen can be attached via ester bonds, which can be cleaved to release the anti-inflammatory drug. Cationic ibuprofen-conjugated dendrimers/dendrons demonstrated higher anti-inflammatory responses compared to free ibuprofen. The ibuprofen-conjugated dendrons (IboCO₂G₃(NMe⁺₃)₈) decreased inflammatory responses and lowered the secretion of several inflammatory cytokines, including IL-1 β , TNF α , IL-6, and CCL3 and decreased the LPS-induced expression of COX-2 [14,21,22,85,86] (Fig. 4).

Fig. 4. Schematic illustration of ibuprofen-conjugated cationic carbosilane dendrimers/dendrons and their impact on the anti-inflammatory function of ibuprofen [14].

Peptides and proteins are delivered as complexes with carbosilane dendrimers or dendriplexes. In dendriplexes, a cargo can be bound by electrostatic interactions and protected by dendrimer structure. Ionov et al. showed the complexation of HIV-derived peptides (Gp160, P24, and Nef) with cationic carbosilane dendrimers (CBD-OS and CBD-CS). This formulation was ready in molar ratio (2.5–3):1 of dendrimer: peptide with size range of 180–275 nm. The dendrimers were terminated with amino groups that are appropriate for binding the HIV derived peptides with negatively charge and for the delivery of HIV peptides to DCs [87].

Dendriplexes were formed by interactions between HIV-derived peptides and two different types of positively charged carbosilane dendrimers. The researchers then investigated the interactions that occurred between these dendriplexes and model lipid bilayer membranes that formed negatively charged vesicles. Negatively charged vesicles composed of a mixture of DMPC/DPPG showed the strongest interaction accompanied by an increase in fluorescence anisotropy of a probe localized in the polar domain of the lipid bilayer. There was also an increase in the surface pressure of the lipid monolayers. Carbosilane dendrimers could be used for delivery of HIV derived peptides into cells for vaccine purposes [88] (Fig. 5).

Fig. 5. The formation of HIV-peptide/dendrimer complexes to deliver HIV-peptides into cells [88].

3.3. Application of carboxilane dendrimers in the treatment of viral infection

Many studies have been conducted to assess the effect of carboxylated dendrimers on viral infections such as HIV, herpes simplex virus (HSV) infections and influenza [19,89]. Polyanionic carboxilane dendrimers (PCDs) used alone could be improved microbicides to prevent HIV transmission. Moreover, PCDs could also be used as drug-delivery vehicles for anti-viral drugs such as maraviroc (MRV) or tenofovir (TFV), and their combinations could show a synergistic anti-HIV activity. The synergistic combination provided greater efficacy than monotherapy with drugs or dendrimers alone. Combinations of PCD generations 1 or 2 plus MRV or TFV were investigated for preventing viral transmission of HIV and HSV-2. According to the results, the best candidate to prevent sexual transmission of HIV-1 was the dendrimer plus MRV, and the dendrimer combination with TFV was best to suppress HSV-2 [19].

Another study used CalcuSyn software to analyze the combination of dendrimers and TFV complexes. The inhibition of HIV-2 infection under different *in vitro* conditions was probed, including virus inactivation, reduced cell fusion, reduced internalization by PBMCs, and inhibition of attachment. The results revealed that the second and third-generation carboxilane dendrimers with a silicon atom core and 16 sulfonate (G2-S16), naphthylsulfonate (G2-NS16), and sulfate (G3-sh16) dendrimers inhibited HIV-2 viral proliferation *in vitro*. The synergistic interaction of the triple combination, dendrimers plus tenofovir plus raltegravir, led to increased anti-HIV-2 activity. *In vivo* studies in female BALB/C mice, using vaginal application of 3% G2-s16 for 2 days, showed there was no vaginal irritation. According to these results, anti-HIV-1 and anti-HIV-2 activities were demonstrated by the G2-S16, G2-NS16, and G3-sh16 dendrimers. G2 and G3 indicate the 2nd and 3rd generation dendrimers, while Sh16, NS16, S16 possessed sulfate, naphthylsulfonate and sulfonate terminal groups respectively [90].

One obstacle against the effectiveness of topical vaginal gels that have been employed *in vivo* to inhibit HIV-1 infection is the existence of amyloid fibrils within semen. Human semen contains peptides capable of forming amyloid fibrils called semen-derived enhancer of viral infection (SEVI) that can greatly increase HIV infection rates. In the presence of SEVI added to TZM-bl cells in culture, the HIV infection rate was increased, and although the IC50 values were both increased for 2nd and third-generation polyanionic carboxilane dendrimers functionalized with 16 sulphonated end groups (G2-STE16 and G3-S16), nevertheless the protective rate was maintained up to 90%. When the dendrimers were combined with TDF/MVC the anti-HIV-1 effects were improved by up to 7-fold in the presence of SEVI. These results showed a synergistic effect between polyanionic carboxilane dendrimers and antiviral drugs to overcome the undesirable effects of amyloid fibrils [[91], [92], [93]].

The combination of polyanionic carboxilane dendrimers with antiretroviral (ARV) drugs could act as novel microbicides against HIV. Double or triple-combinations of dendrimers and ARVs could inhibit HIV-1 in the early stages of replication. This activity is preserved in seminal fluid or in acidic environments, without causing any inflammatory response. The most effective combination was observed with the G2-STE16 dendrimer. Moreover, no irritation was found in female mice after vaginal administration [94].

Anionic carboxilane dendrimers functionalized with sulfonate (G3-S16) or naphthyl sulfonate (G2-NF16) terminal groups in combination with different ARVs have been tested for HIV-1 prophylaxis. G3-S16/EFV and G2-NF16/TFN achieved the best profile against the X4 and R5-HIV-1 strains. Experiments

were conducted in human cell lines that were tropic for R5 and X4 HIV-1 strains, revealed that G2-NF16 and G3-S16 dendrimers had synergistic or additive effects with efavirenz, tenofovir, and zidovudine (EFV, TFV, AZT) in the composite system. The combination of polyanionic carbosilane dendrimer with EFV, TFV, AZT showed better antiviral activity compared to single components [[95], [96], [97]].

The 2G-S16 dendrimer could act as a safe and effective topical microbicide against HIV-1 and HIV-2. 2G-S16 protected the epithelial monolayer from cell disruption, consequently, it can block HIV entry. It can also create protection against X4, R5 and X4/R5 HIV strains infecting or co-infecting PBMCs. The combination of 2G-S16 with tenofovir or maraviroc resulted in 100% HIV-inhibition and showed a synergistic profile at low doses against a set of HIV strains. After administration of different daily concentrations of 2G-S16 over 7 days, there were no side effects or irritation in the female rabbit genital tract [[98], [99], [100]].

As mentioned, triple combinations can protect against HIV-1 infection in seminal fluid or in an acid environment more effectively than a single drug. The three-drug combination G2-STE16/G2-S16/maraviroc, G2-STE16/G2-S24P/tenofovir and G2-STE16/tenofovir/maraviroc at 10:10:1, 2:2:1 and 10:5:1 ratios, showed impressive antiviral potency. With a lack of inflammation or irritation in female mice, the triple combination (carbosilane dendrimer, TFN, MRV) could be a good candidate for topical application [101,102].

Blocking the interaction between gp120/CD4 and HIV is an important strategy to protect against HIV infection. The second-generation polyanionic carbosilane dendrimer G2-S16 with a silica core was designed for this purpose. *In vivo* studies revealed 84% inhibition of HIV-1 transmission in humanized (h)-BLT mice, without any detectable HIV-1 RNA and no vaginal lesions after topical vaginal administration of 3% G2-S16. Dendrimers can also inhibit cell-to-cell HIV-1 transmission, showing their multifunctional capability to block HIV-1. To maximize acceptability, safety, and activity the dendrimer could be administered in a novel formulation as a locally applied solid film. This novel dendrimer could be a promising solution to prevent transmission of HIV-1 [[103], [104], [105]].

The worldwide spread of hepatic C virus (HCV) has led to the development of new drugs that act as direct antiviral agents (DAAs), but owing to the advent of drug-resistant virus variants, and the difficulty of using these drugs in less developed countries, newer antiviral approaches are being sought. Polyanionic carbosilane dendrimers (PCD) can destabilize infectious virions. Anionic polymers like heparin have been shown to inhibit both HCV and HIV, mainly by interfering with the ability of the virus to gain entry to the cell. The anti-HCV second generation carbosilane dendrimer consisted of a polyphenolic core with 24 sulfonate groups on the surface [106].

A series of carbosilane dendrimers that had all been functionalized with hemagglutinin (HA) binding peptide (Ala-Arg-Leu-Pro-Arg) was systematically synthesized, and studied for their ability to inhibit influenza viruses. The peptide sequence acted as a sialic acid peptide mimetic. The carbosilane-based peptide dendrimers, unlike sialylated dendrimers, could not be digested by viral neuraminidases. The dumbbell-type of peptide dendrimer induced the best inhibitory activities against two human influenza viruses, A/Aichi/2/68 (H3N2) and A/PR/8/34 (H1N1). The dumbbell-type dendrimer peptide showed IC₅₀ values with the highest activity against both strains [107] (Fig. 6).

Fig. 6. Carbosilane dendrimers functionalized with HA-binding peptide and anti-influenza virus activity [107].

3.4. Application of carbosilane dendrimers in gene delivery

Gene therapy holds great promise for treatment of a wide range of diseases, such as cancer, viral infections and genetic disorders [108,109]. Carbosilane dendrimers are among the promising novel non-viral carriers that have been investigated for the safe and effective transfer of nucleic acids into cells or tissues. Amphiphilic dendrimers that possess both hydrophilic and hydrophobic groups could serve as a vector for gene transfer [110,111]. Carbosilane dendrimers have intrinsically hydrophobic sections and hydrophilic PEG-conjugated dendrons can be attached by efficient click chemistry. Alkyne PEG-based dendrons and azide carbosilane dendrons (generation 1 and 2) can be attached at the periphery with NHBoc protection to provide cationic dendrimers with 6 or 8 ammonium groups. The carbosilane dendrimer (generation 3) produced only a very low yield. These hybrid dendrimers were active in PBMC. As a consequence of the presence of PEG, the dendrimers showed lower cytotoxicity but weaker interactions with siRNA, as compared to the homodendrimer. The amount of PEG needs to be carefully optimized for application as a nucleic acid nanocarrier [15].

Three different types of cationic dendrimers (phosphorus, carbosilane, PAMAM) were investigated for the delivery of siRNAs for anti-cancer therapy, and also protects the siRNA from destruction by nucleases [20,112]. The siRNAs were designed to down-regulate the pro-survival and anti-apoptotic genes, siMcl-1, siBcl-xL, and siBcl-2. The dendrimer siRNA complexes were characterized using transmission electron microscopy (TEM), fluorescence, circular dichroism (CD), gel electrophoresis, dynamic light scattering and Zeta potential methods. All dendrimers could form complexes with siRNA and protected the siRNA from RNase A-mediated degradation. The results showed that the siRNA-dendrimers complex were more effective than only siRNAs, allowing one to reduction siRNAs concentration in the targeted cells. As shown in Fig. 7, siRNAs is maintained from destruction by enzyme in the presence of dendrimers, and duplex siRNA can be released from dendriplexes after heparin treatment. In fact, the carbosilane and PAMAM dendrimers were best in preserving the siRNA structure [113].

Fig. 7. Combination of dendrimers and siRNA form stable dendriplexes to protect siRNAs from nuclease degradation [113].

The administration of siRNA can also be used to down-regulate the expression of viral-associated genes. It has been shown that carbosilane dendrimers could deliver specific anti-viral siRNAs to astrocytes and block HIV expression. The siRNA carbosilane dendriplex could target HIV-1 infected cells within the CNS without causing cytotoxicity, and may have a role in treating neuro-AIDS and other neurological disorders [114].

Due to the difficulties encountered in transfecting CD4 T-lymphocytes using non-viral vectors, the second-generation carbosilane dendrimers 2G- $[\text{Si}\{\text{O}(\text{CH}_2)_2 \text{N}(\text{Me})_2^+(\text{CH}_2)_2\text{NMe}_3^+(\text{I}^-)_2\}]_8$ (2G-NN16) and $[\text{G}_2\text{O}_3(\text{SiONN})_{12}]^{24+}$ (2G-03NN24) were investigated for their ability to transfect CD4 T lymphocytes with siRNA against the Nef HIV-1 gene. Dendrimers were also tested on macrophages to determine whether they could modify macrophage phenotype and induce an inflammatory response. The studies showed the highest inhibition of HIV-1 replication was produced by the dendriplex formed by 2G-03NN24/siRNA-Nef. Dendriplexes did not trigger CD4 T lymphocyte proliferation and decreased $\text{TNF}\alpha$ and IL-12p40 release from macrophages. The specific ability of the 2G-03NN24 dendrimer to decrease CCR2 and CCL2 expression in macrophages confirmed their utility. Both 2G-NN16 and 2G-03NN24 carbosilane dendrimers could be used as siRNA carriers against HIV infection [115].

The delivery of siRNA can be facilitated by the use of micelle-forming amphiphilic carbosilane dendrons as delivery vehicles. To characterize the binding between cationic dendrons and siRNA molecules, the pro-apoptotic siRNA called MC1-1 was used as a model compound. In this study, siRNA binding through dendrons is the product of micelle formation. Carbosilane dendrons with generation 1–3 were modified with hexanoic acid or palmitic acid groups. The binding of siRNA modified was similar between the two different fatty acids, but did depend on the dendrimer generation ($\text{G1} < \text{G2} < \text{G3}$) [116].

The nanoparticles -based hybrid materials have been characterised and their properties as gene delivery carriers, displaying a higher DNA adsorption ability and transfection efficiency. Functionalized of the nanomaterials such as inorganic and polymeric nanoparticles with the various generation of a

dendron presented good DNA binding properties [117,118]. Mesoporous silica nanoparticles (MSNs) is pretty candidate to be applied in nanomedicine, due to probability of controlling their size, their tuneable pore diameter, and easy functionalization of the nanoparticles surface [119]. Carbosilane dendrimers are applied as nontoxic materials to decorate nanoparticles in the search of drug/gene delivery systems. The presence of a pore network inside the silica matrix can be applied to house various agent into the mesopores with the purpose of reaching a multiple delivery [117]. Mesoporous silica nanoparticle (MSNs) that have been decorated by carbosilane $\text{H}_3\text{N}^+\text{G}_2(\text{N}^+\text{Me}_3)_4$ (8 or G2+) and $(\text{EtO})_3\text{SiG}_3(\text{NMe}_2)_8$ (10 or G3) dendrons could transport single-stranded oligonucleotides into cells, while at the same time having the potential to deliver other drugs incorporated into the silica mesopores (Fig. 8). The cationic charge overcomes the problem of electrostatic repulsion between the negatively charged nucleic acid strands and the negatively charged cell membrane. By using a human osteoblast-like cell line as an *in vitro* model, the hybrid dendrimers were found to be non-cytotoxic, and could efficiently deliver oligonucleotide DNA into the cells [117] (Fig. 8).

Fig. 8. Schematic illustration of functionalization of MSNs with carbosilane dendrons [117].

Another type of hybrid nanoparticle could be constructed by covalently attaching carbosilane dendrimers to polymeric nanoparticles. Poly(D,L-lactide-co-glycolide) acid (PLGA) nanoparticles were prepared with a controlled size using nano-emulsion templating and low-energy emulsification methods. A carbodiimide-mediated coupling reaction was used to functionalize the nanoparticles with a cationic carbosilane dendrimer. Antisense oligonucleotides could be complexed to the nanoparticle surface by electrostatic interactions. These complexes were non-toxic and non-hemolytic at the required concentrations, and allowed efficient antisense-mediated gene silencing [118] (Fig. 9).

Fig. 9. Schematic illustration of formation of nanoparticles by nano-emulsion and functionalization with dendrimers as a non-viral gene delivery vectors [118].

Biodistribution studies are more accurate when the dendrimers are modified with fluorescent labels. In one study, fluorescein-labeled cationic carbosilane dendrimers were developed that could form a stable dendriplex with siRNA Nef and also possessed the ability to cross the blood brain barrier in a mouse model. To label the dendrimer with fluorescein, first thiol groups were attached to vinyl-terminated dendrimers. Next the thiol groups were converted to -NH_3 groups and -NMe_2 groups. These were reacted with FITC followed by quaternization with Mel. Dendriplexes were then formed with siRNA Nef that had been labeled with a second fluorescent reporter dye, Cy5.5. These dendriplexes were characterized by electrophoresis and found to be non-toxic *in vitro*. Fluorescent imaging showed that the dendriplexes were able to deliver siRNA Nef to the kidney, liver and lymph nodes, compared to siRNA alone [120] (Fig. 10).

Fig. 10. Formation of dendriplexes with siRNA Nef and testing in a BALB/c mouse model [120].

3.5. Application of carbosilane dendrimers for other biomedical applications

Dendrimers have been investigated for the treatment or prevention of neurological and degenerative brain diseases. One major problem in the treatment and/or prevention of central nervous system diseases is the poor penetration of drugs through the blood-brain barrier. These problems can be circumvented by the use of nanocarriers such as dendrimers [121]. Carbosilane dendrimers were investigated for their potential to treat or prevent processes linked to Parkinson's disease. One study used the mouse hippocampal cell line (MHippOE-18) to test whether carbosilane dendrimers could protect the cells from rotenone-induced damage, and to prevent the fibril formation of α -synuclein (ASN). Carbosilane dendrimers could prevent ASN fibril formation by interacting with the soluble protein. When MHippOE-18 cells were pre-incubated with carbosilane dendrimers before adding rotenone, the mitochondrial membrane potential was maintained, the levels of cellular ROS cells were reduced, and the viability was enhanced. The different surface functional groups carbosilane dendrimer did not make any significance different. Carbosilane dendrimers could be a valuable pharmacological strategy to combat neurodegenerative disorders [122] (Fig. 11).

Fig. 11. Role of carbosilane dendrimers to prevent the formation of ASN fibrils and prevent cells from rotenone-induced damage [122].

In view of the good water-solubility of cationic and anionic carbosilane dendrimers (generation 1–3), they could be formulated as eye drops, containing a mucoadhesive polymer preparation. Anionic carbosilane dendrimers terminated by carboxylate groups, and cationic carbosilane dendrimers with ammonium groups have been investigated. To investigate the hypotensive effects of carbosilane dendrimers loaded with acetazolamide (ACZ, a poorly water-soluble drug with low biological permeation) an eye drop formulation was evaluated after intraocular installation in normotensive rabbits. Both cationic and anionic carbosilane dendrimers demonstrated non-toxicity, and were tolerated in a concentration range between 5 and 10 μM . The generation 3 positively charged carbosilane dendrimer showed a good interaction with ocular mucins, using a biosensor evaluation. Carbosilane dendrimers could increase the bioavailability of topical drugs administered in the eye at a safe concentration level. Shortening the onset time and increasing the duration of the hypotensive effects of acetazolamide were notable advantages of this approach [123].

4. Conclusions

Considering all of the above evidence, it appears that carbosilane dendrimers could be suitable candidates for antiviral therapy, antitumor therapy, immunotherapy, and for gene and drug delivery. Dendrimers can be tailored to have different generation numbers, and therefore different molecular weights and sizes. The core and the periphery of the dendrimers are very different environments, and hydrophobic molecules can be incorporated inside the core. The periphery can be functionalized with either cationic or anionic groups to provide water-solubility, and very different biological properties depending on the surface charge. Various molecules can be attached to the peripheral groups using either charge-mediated electrostatic interaction to form complexes, or else covalent chemical bond formation to form conjugates. One of the best examples of complex formation is that between cationic carbosilane dendrimers and negatively charged nucleic acids such as DNA oligonucleotides or antisense or small interfering RNA molecules. These complexes are called dendriplexes, and can protect the nucleic acids against degradation and markedly increase the cell uptake. Several studies have

investigated the dendrimers as topical anti-HIV virucidal preparations for intravaginal application, either alone or combined with anti-retroviral drugs. Anti-cancer applications, and routes to improve vaccine delivery have also been studied. Despite the fact that there are several other dendrimer backbones now available with different chemical structures, we believe that carbosilane dendrimers may have advantages over these other compositions, that will be made clearer with further research in the future.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MRH declares the following potential conflicts of interest. Scientific Advisory Boards: Transdermal Cap Inc, Cleveland, OH; BeWell Global Inc, Wan Chai, Hong Kong; Hologenix Inc. Santa Monica, CA; LumiThera Inc, Poulsbo, WA; Vielight, Toronto, Canada; Bright Photomedicine, Sao Paulo, Brazil; Quantum Dynamics LLC, Cambridge, MA; Global Photon Inc, Bee Cave, TX; Medical Coherence, Boston MA; NeuroThera, Newark DE; JOOVV Inc, Minneapolis-St. Paul MN; AIRx Medical, Pleasanton CA; FIR Industries, Inc. Ramsey, NJ; UVLRx Therapeutics, Oldsmar, FL; Ultralux UV Inc, Lansing MI; Illumiheal & Petthera, Shoreline, WA; MB Lasertherapy, Houston, TX; ARRC LED, San Clemente, CA; Varuna Biomedical Corp. Incline Village, NV; Niraxx Light Therapeutics, Inc, Boston, MA. Consulting; Lexington Int, Boca Raton, FL; USHIO Corp, Japan; Merck KGaA, Darmstadt, Germany; Philips Electronics Nederland B.V. Eindhoven, Netherlands; Johnson & Johnson Inc, Philadelphia, PA; Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany. Stockholdings: Global Photon Inc, Bee Cave, TX; Mitonix, Newark, DE.

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