# Dendrimers for Infectious Diseases

Functionalized and modified dendrimer platforms are capable of precise imaging and efficient treatment of tumors, providing solutions for combined monitoring and early treatment of cancers.

## 1. Introduction

Nanotechnology comprises a multidisciplinary approach at the nanometric level for characterization, manipulation and arrangement of molecules in a systematic way. It utilizes the diverse knowledge, concepts and novel ideas from different fields of sciences including engineering, physics and biological chemistry to design materials having 1–100 nm size range. The pharmaceutical nanotechnology aims to deliver the therapeutic moieties specifically at the site of disease to reduce unwanted and toxic effects of drugs to normal cells of organisms. The nanocarriers can alter the innate physicochemical, biological and pharmacokinetic properties of drug molecules for better therapeutic outcomes [1][2][3].

The recent advancements and innovations made in the field of molecular and polymer chemistry have led to a new domain called dendrimer chemistry. Dendritic nanoparticles have gained a lot of attention and interest from various research groups for biomedical and pharmaceutical applications. The word dendrimer originated from the Greek word Dendron meaning tree and the idea to synthesize such macromolecular, hyperbranched architectures originated from the numerous patterns observed in nature. The vascular system, tree branches, neuronal system, light patterns, tributary origination, explosions or erosions are a few examples found in nature [4][5].

The first attempts to characterize the architecture of dendrimers with a unique four-dimensional, core–shell with alterable surface groups were initiated by two research groups in 1978 and 1985 (Buhleier and Tomalia respectively). The dendrimers have multiple trees like branches originating from a central core molecule with various terminal functional groups giving them a unique and dense structure with more surface area for reaction. The control over synthesis steps of dendrimer result in unique biological properties by creation of various layers around a central core molecule. The efficient loading of therapeutics and imaging materials, specified desired delivery, versatile selection of administration route, monodispersed system, improved pharmacokinetic and pharmacodynamic profiling are some of the advantages of this unique drug delivery system [6].

## 2. Types of Dendrimers

Based on the method of synthesis, physicochemical properties, physical structure and shape, the dendrimer chemistry has been described for several types.

Polyamidoamine (PAMAM, now commercially available as StarburstTM) has been extensively investigated since 1997 for their excellent solubilizing capacity, biocompatibility and comparatively low toxicity [7]. These dendrimers have been prepared using five different methods utilizing divergent, convergent, click chemistry, self-assembling, LEGO chemistry synthesis method with Michael addition and some amidation reactions [8].

The transport of drug molecule, the surface charge, generation size and concentration of a particular dendrimer play an important role in evaluation of the safety of PAMAM dendrimers. The presence of strong positive charge on the surfaces of PAMAM dendrimers limits their clinical applications due to rapid clearance from the systemic circulation and cytototoxicity. PAMAM succinamic acid dendrimers, synthesized with the reaction of succinic anhydride molecules with amine-terminated PAMAM dendrimers, are full generation dendrimers with less polydispersity compared to half generation carboxylate terminated dendrimers. These types of dendrimers can be better candidates for the transport of pharmacologically active guest molecules as compared to standard half generations [9].

Polypropylene imine dendrimers are the oldest dendrimers first synthesized by Voegtle et al., 1978 [10]. The divergent method finds its implication with diamino butane (DAB) or EDA as core. The surface of PPI dendrimers contains cationic groups that facilitate the interaction between their positive charge and membrane negative charge [11]. Currently up to five generations of PPI dendrimers have been prepared for applications in drug delivery and a theranostic [12].

Since the discovery of the family of marketed PAMAM dendrimers, various attempts have been made to modify the physicochemical and biological properties of dendrimers. Discovery of several defects of single generation dendrimers such as limited drug loading capacity or gene transfection efficiency of lower generation dendrimers, and complexity, cost and time consuming synthesis and toxicities related to higher generations led to search for more effective alternatives to overcome these limitations. The higher generations using as core and lower generations as a shell surface covalently linked to a core led to the synthesis of a new type of dendrimer with advantages over conventional dendrimers [13]. They attached β-cyclodextrins to G5 PAMAM amine-terminated dendrimers as a core and adamantane or benzimidazole modified G3 dendrimers as shells that can be a promising vehicle for gene transfection applications.

The racemic active ingredients require enantioselective synthesis methods or direct chiral separations to resolve the enantiomers that are pharmacologically active from the rest that may be inactive or even toxic. The chiral resolutions and analysis time could be regulated by critical control over size and concentration of chiral dendrimers utilized [14][15]. These types of dendrimers are being extensively investigated as chiral selectors in modern supercritical fluid chromatographic systems that are relatively newer and promising in terms of ease, economics and speed of analysis [16]. The highly selective biological actions of chiral molecules due to specific enzymatic associations offer countless applications in drug delivery systems.

These were synthesized by Hawker and Frechet [17]. They contain poly-benzyl ether as a hyperbranched skeleton with carboxylic groups as terminal groups that facilitate further reactions.

A new class of dendrimer with a liquid crystal nature organized to form lamellar or globular architecture has been widely explored. The calamitic (rod-like) and discotic (disc-like) molecules form a skeleton called mesophage, which is liquid crystalline in nature [18][19]. The mesogenic liquid crystalline type of monomers facilitate formation of an interfacial layer. This liquid crystalline alignment can be spatially controlled by irradiation with light of different wavelengths [20].

These dendrimers are radial or wedge type in shape with a peptide core that is synthesized frequently by both convergent and divergent methods. These dendrimers have peptide bonds in their structure and are formed by polymerization of amino acids. These types of dendrimers have been extensively utilized as surface active agents and gene and drug carriers. Several reports supporting extended therapeutic activity of loaded therapeutics have been published recently [21] [22].

Linear types of polymers combine with dendritic types to form a dense, compact and globular structure, The dendrimers are combined with other drug delivery systems to form novel constructs with superior characteristics [23]. Albumin nanoparticles stabilized by dendrimers were presented as a unique platform for sustained release of therapeutic moieties, genes, siRNA and miRNA. Supramolecular nano constructs were established with electrostatic controlled gelation of G4 PAMAM dendrimer by encapsulation of paclitaxel [24].

## 3. Application of Dendrimers in Treatment of Infectious Diseases

Due to their unique structural features, dendrimers are likely to be used in many fields of science and industry in the future. Much attention is now paid to research into the use of these polymers in medicine, chemistry, genetic engineering and environmental protection. The greatest interest of scientists has arisen from applications in medicine, which satisfy the need for better and more effective forms of therapy, especially in the case of diseases for which so far there is no cure. Trends in research on the use of dendrimers in medicine are divided.

Until recently, infectious diseases caused by pathogenic microorganisms, including bacteria, viruses, parasites and fungi, were rationally controlled by a wide range of antimicrobials. There was no doubt that there was a need for new compounds with a broad spectrum of actions. Biofilm formation is inhibited and used to active compounds mimicking the action of detergents and antimicrobial peptides [25]. Antimicrobial dendrimers showing low cytotoxicity to eukaryotic cells are being investigated as new drugs for a variety infectious diseases, especially those which are highly lethal or incurable [26].

Currently a combination antiretroviral therapy (cART), with three or more drugs, is the most common and effective method of combating HIV infection. The downside of this therapy is the side effects associated with the administration of cART, including the risk of hyperlipidemia, adipose tissue redistribution and diabetes [27]. Recently, these limitations of cART

have been mitigated through the use of nanotechnology with targeted drug delivery and controlled drug release profiles in clinical trials. Currently, the most commonly used carriers for antiviral drugs are: dendrimers [28], nanosuspensions [29] and polymer micelles [30].

Currently, a preparation called VivaGel, based on the structure of dendrimers, produced by the Australian company Starpharma, has passed Phase III clinical trials and is in the process of obtaining FDA approval. This carbomer gel contains a fourth-generation poly-l-lysine dendrimer containing naphthalene disulfonate surface groups and a benzhydrylamine amide center (SPL7013). The strongly polyanionic surfaces of the dendrimers are believed to bind gp120 proteins on the surface of the virus. The VivaGel preparation has the ability to absorb HIV into the dendrimer, preventing it from spreading throughout the body [28].

The same antiviral mechanism that blocks the gp120/CD4 interaction (shown in Figure 3 [31]) is also utilized by the G2-S16 polyanionic carbosilane dendrimer with a silica core and 16 sulfonate end groups. In vivo results showed inhibition of HIV-1 transmission at an early stage of replication [32]. The G2-S16 dendrimer was also combined with the tenofovir reverse transcriptase (TFV) inhibitor or the CCR5 entry inhibitor maraviroc (MRV). The results obtained confirmed the synergistic effect of dendrimers and inhibitors, which confirmed that the developed combination is a good candidate as an antiviral agent for HIV prophylaxis, due to its stability at low pH

In comparative studies, two second-generation carbosilane dendrimers (G2-NN16 and G2-03NN24) with the same quaternized amino terminal groups, but different core groups, were tested for their safety and efficiency in CD4 + siNef T cell transfection [33]. They reduced the expression of the helper Nef gene that enhances viral replication and spread by increasing viral titer. The G2-03NN24 dendrimer derived from the polyphenol core was stiffer, while the Si-core G2-NN16 was more flexible, resulting in increased cellular uptake by CD4 + T cells. As in PAMAM dendrimers, the efficiency of transfection increased with their flexibility [34].

In the development of anti-HIV therapy, PAMAM generation five dendrimers with a triethanolamine core and 96 amino terminal groups have also been used to provide siRNA combinations for CD4, TNPO3 and tat/rev proteins [35]. HIV tat/rev proteins are viral regulatory molecules that are essential in the HIV life cycle. PAMAM dendrimers were shown to systemically deliver a combination of functional siRNA. In vivo treatment of HIV-1 infected, viremic humanized mice provided effective protection against HIV-1 mediated T-cell loss with no apparent toxicity [36][37].

Coronaviruses are a family of highly infectious viruses that cause severe respiratory disease, with a possible fatal outcome. Currently a worldwide pandemic of coronavirus disease (COVID19) caused by severe acute respiratory syndrome coronavirus 2 is affecting global health and the economy. Major symptoms of COVID-19, include acute respiratory disorder, excessive inflammation and an exaggerated immune response, which leads to a cytokine storm and progression to acute lung injury and often death.

The spike protein is most important for virus–cell receptor binding and virus–cell membrane fusion, which then becomes an effective target for CoV vaccine design. These types of vaccine may also potentially be delivered by dendrimers. These recent findings suggest that dendrimers have potential to be mRNA vaccine delivery vehicles. The advantage of using dendrimers as a vaccine against coronaviruses is that their structures provide high density of surface modifiable functional groups.

Recently dendrimers were also used as the antiviral agents themselves against MERS-CoV. Antiviral activity of three types of dendrimers, including polyanionic dendrimers comprising the terminal groups sodium carboxylate (generations 1.5, 2.5, 3.5, and 4.5), hydroxyl (generations 2, 3, 4, and 5), and succinamic acid (generations 2, 3, 4, and 5) and polycationic dendrimers containing primary amine (generations 2, 3, 4, and 5) were investigated. µM were able inhibit activity in plaque formation. These dendrimers proved to be a basis for further research as an antiviral therapy [38]. Recent studies also showed that topical application by inhalation of peptide dendrimer carrying SARS-CoV-2-specific modified siRNA

These receptors are considered a potential gateway of infection for this virus, and hence, a strategy of blocking these receptors was used to block the entry of the Ebola virus [39][40]. The Boltron dendritic polymer used as a core when combined with 32 mannose groups on the surface, showed increased antiviral activity [41][42]. A modified multivalent version of this dendrimer showed increased antiviral activity in the nanomolar concentration range in a pseudotyped Ebola virus infection model. The results obtained indicate that the use of a glycosylated form of dendrimers may be a good strategy for the development of antiviral drugs [43].

Another strategy to fight Ebola virus is to prevent infection by vaccine usage. The platform created was used to carry and successfully deliver RNA, which results in antibody production and antigen-specific CD8+ T-cell responses towards the encoded protein antigen. The dendrimers delivered artificial polyepitope T-cell immunogens in the form of a DNA. Due to relatively low immunogenicity, this approach needs more research [44].

For example, sialodendrimers can inhibit the process of hemagglutination of human erythrocytes induced by influenza virus. The attachment of a-sialic acid fragments to the surface of the dendrimer increases the therapeutic effect and allows the polymer molecule to achieve greater inhibitory activity during influenza infection. dendrimers conjugated with either 3′-sialyllactose (3SL) or 6′-sialyllactose (6SL) were synthesized as host-specific inhibitors of influenza virus infection and showed promising activity [45]. Carbosilane dendrimers with hemagglutinin binding peptide against influenza virus types H1N1 and H3N2 were also prepared and showed strong inhibitory activity against them [46].

In the case of herpes simplex virus, HSV, both polycationic (polyarginine and polylysine [47]) and polyanionic [48] dendrimers, have been used to prevent the virus from adsorbing to the cell surface. However, an advantage of polyanionic dendrimers over polycationic dendrimers is their lower cytotoxicity. In addition, peptide dendrimers and their derivatives (SB105 and SB105-A10) were also used. Dendrimer derivatives in combination with acyclovir showed a synergistic effect in vitro [49].

The developed dendrimer carriers showed antiviral activity and were non-toxic to cells in the range of concentrations used [50][51]. Some of the dendrimers acted by direct binding to HSV-2, thereby inactivating, while others adhered to host cell surface proteins. As with peptide dendrimers, carbosilane dendrimers were synergistic with acyclovir and tenofovir. The mechanism of action of peptide-derivatized dendrimers, carbosilane dendrimers, galactose polysulfate-functional glycodendrimers, and PAMAM dendrimers used as germicides against sexually transmitted diseases is based on blocking a viral particle that binds to heparan sulfate on the cell surface or binds to cellular coreceptors [52].

Dendrimers are also used as a carriers or treatment itself for other viral infections. In Table 2 we summarized the other dendrimer applications for antiviral treatment.

Unlike dendrimer, antiviral drugs, antimicrobial dendrimers contain cationic surfaces typically modified with amino groups or with tetraalkyl ammonium groups. Generally, these compounds adhere to the anionic cell wall of bacteria, causing damage followed by decomposition of the whole bacterium. An example of an antibacterial dendrimer is the PPI-based dendrimer modified with tertiary alkyl ammonium groups, which has been shown to be a potent antibacterial agent against both Gram positive and Gram negative bacteria [53].

Dendrimer-glucosamine conjugate (PETIM-DG) created by Shaunak's team was tested in a broad spectrum of infectious diarrheal diseases caused by E. coli, Shigella and Salmonella. The authors showed that the PETIM-DG conjugate was an inhibitor of the genus Shigella, inhibiting damage to the intestinal epithelial wall in rabbits. At the same time, it minimizes the invasion of bacteria and limits the expression of local cytokines [54][55].

Lysine-based dendrimers containing surface mannose molecules also showed high antimicrobial activity against E. coli strains [56]. They have been used to prevent premature labor due to E. coli infection in the guinea pig membranes and placenta models. The hydroxyl-terminated PAMAM dendrimers found their way into the cervix, thereby preventing E. coli from entering the uterus, reaching the fetus, and thus preventing premature labor [57]. It is well known that silver nanoparticles and silver complexes exhibit antimicrobial properties that last a long time.

Dendrimers can also be used as a preventive medicine for Vibrio cholera, another Gram-negative bacterium, which causes cholera. It is a life-threatening disease due to extensive loss of electrolytes. The mechanism of action of this protein is to form the pore on the cell surface after recognition of GM1 ganglioside. Finally, water and ions are released from the cells [58].

One of the strategies used to prevent infection was with dendrimers with a core of 3,5-bis (2-aminoethoxy) benzoic acid and a GM1-mimic ligand Unfortunately, both of the dendrimers were not investigated in the in vitro model. The affinity of dendrimers to cholera toxin was evaluated by ELISA and fluorescent spectroscopy. These dendrimers prevented B subunit of cholera toxin attachment to the cell surface [59].

Another approach used a dendrimer as a carrier for the known antimicrobial drug vancomycin. Serri et al. used G3 and G5 NH2-PAMAM dendrimers to encapsulate the vancomycin hydrochloride. As a result the delivery system reduced minimum inhibitory concentration MIC values by up to 64 times in E. coli, K. pneumonia, S. typhimurium and P. aeruginosa by increasing the permeation through the bacterial membrane [60].

This opportunistic pathogen is especially dangerous for people with chronic conditions, a compromised immune system or people who have had surgery and those who used a catheter (e.g., dialysis patients) [61][62]. Usage of maltose-modified PPI G4 dendrimers against Gram-positive S. aureus provided efficient antibacterial activity and selectivity. At the same time, these nanoparticles showed little toxicity to eukaryotic cells [63]. Another type of G4 dendrimer modified with boronic acid and its antibacterial recognition properties were evaluated in S. aureus.

The growth of S. aureus can be also inhibited by G1 polyphenolic carbosilane dendrimers functionalized with caffeic and gallic acids. The mechanism of action of these dendrimers is based on their antioxidant abilities, which corresponds to the number of hydroxyl groups in polyphenol structure [64]. Carbosilane dendrimers can be used as a scaffold for metal ions to help fight against Gram-positive bacteria as shown in Figure 5.

Copper (II) and ruthenium (II) in combination with G0, G1 and G2 carbosilane dendrimers were effective biocidal agents for S. aureus biofilms. It is desirable to inhibit bacteria's growing as a biofilm since chronic and recurring infections are much related to bacteria's ability to produce a biofilm structure [65], which make them resistant to the antibiotic's treatment. Dendrimers can be used to increase the antimicrobial effect of the drug, as it happened in the case of DAB-core G0 PAMAM-dendrimer and ciprofloxacin conjugate. The observed synergistic effect of the dendrimer and ciprofloxacin conjugate is believed to be related to ciprofloxacin mode of action by primarily stabilizing the complex of topoisomerase IV, leading to DNA fragmentation in Gram-positive bacteria, since the control dendrimer did not demonstrate any antibacterial activity itself [66].

Out of the five types of Plasmodium that infect humans Plasmodium falciparum is considered the most lethal one causing malaria. The parasite is transferred from person to person through blood transfusion, organ transplant, sharing of needles and also by the bite of a female Anopheles mosquito acting as a carrier [67]. Tropical and the subtropical regions have the highest number of malaria cases in the world. Symptoms of the disease include, vomiting, headache and fever but severe cases may cause anemia, severe pains and coma [68].

Children under the age of 5 were at the highest risk of malaria transmission as they were 67% of malaria deaths worldwide. Antimalarial drugs such as chloroquine, primaquine and artemisinin and its derivatives are used to treat malaria, but they produce severe toxicities and drug resistance [69]. Development of new delivery systems to treat malaria is needed. These types of dendrimers can be considered as selective antimicrobial drug candidates, since they do not show cytotoxic effects in the healthy cells, but strong antimalarial activity [70].

The symptoms for cutaneous forms include skin sores whereas symptoms for visceral form include weight loss, fever, enlarged liver and spleen [71]. Annually about 2 million cases are detected worldwide [72]. However, these drugs promote development of resistance and severe toxicities such as cardiotoxicity and pancreatitis [73][74]. However, these drugs produce severe toxicities and are expensive.

Dendrimers are a good choice as delivery vehicles due to their biocompatibility and their ability to solubilize the drug and thereby reduce toxicity [75]. dendrimers and have noticed that the formulation had a lowered toxicity profile in comparison to the marketed amphotericin B toxicity while remaining active against the parasitic infection observed in the macrophage cell lines and in mice studies. This formulation had an improved ability to target macrophages, unlike amphotericin B alone, and hence has immunomodulatory and antileishmanial activity [76]. These formulations have also shown reduced toxicity towards human erythrocytes and macrophages [77][78].

Toxoplasmosis is caused by the parasite Toxoplasma gondii, which infects roughly an estimated two billion people worldwide annually, which causes both morbidity and mortality [79]. Drugs such as pyrimethamine and sulfadoxine are used in the treatment of toxoplasmosis that led to potential toxicities and hypersensitivity. The problem with the traditional forms of therapy is the drugs fail to pass the membranes of the host cells to reach the bradyzoites of Toxoplasma gondii [80][81]. Dendrimers such as the transductive peptide dendrimers can act as an efficient drug delivery tool to deliver the drugs across the several membranes of tachyzoite and encysted bradyzoite, effectively increasing the efficacy of the drug and its toxicity to the parasite [81][82].

In vitro cytotoxicity experiments showed concentrations of these dendrimers from 0.03 to 33 nM of sulfadoxine. Anionic dendrimers showed higher cytotoxicity at higher concentrations while cationic dendrimers have shown increased toxicity at lower concentrations. It can be concluded that lower doses of sulfadoxine in cationic dendrimers act as a good drug delivery tool with significant antitoxoplasmic effect. The antiparasitic effect of dendrimers can be attributed to both surficial activity and endosmolytic effect [83].

## 4. Use of Dendrimers as Diagnostics

Infectious diseases, especially viruses and bacteria caused diseases, are directly related to the occurrence and development of various kinds of cancers. According to a survey, about 70–80% of liver cancer developed from hepatitis B. Human papillomavirus (HPV) is associated with cervical cancer [84]. It is not only related to nasopharyngeal carcinoma and lymphatic carcinoma, but also possesses connections to gastric cancer, lung cancer, breast cancer and cervical cancer [85][86]. Since there is a deep connection between infectious diseases and cancer, and the direct application of dendrimers in the diagnosis of infectious diseases is rarely reported, we reviewed the application of dendrimers in the diagnosis of cancer caused by infectious diseases.

By linking to biocompatible NPs, proteins or polymers by stimulus-responsive chemical bonds, lower-generation dendrimers temporarily produce hybrid materials with relatively high charge density that are capable of efficient, nontoxic gene delivery while enabling the NPs to function as diagnostic agents. The introduction of inorganic NPs (such as Au, iron oxide and quantum dots) endows these hybrid gene carries with new functions. The unique cavity structure of dendrimers can encapsulate or stabilize metal NPs for cancer imaging. In addition, owing to their hydrophobic internal environment, dendrimers can effectively encapsulate anticancer drug molecules and, with the surface modified with a targeting agent, can be used for targeted diagnosis and therapy of cancers.

SPECT is an imaging technology that obtains the morphology, position and functionality of tissues and organs by collecting and displaying the distribution density and flow of radioisotopes in the human body. More than just the imaging of anatomical structures, SPECT can detect functional changes of organs or systems and effectively support disease diagnosis. However, the clinical application of this technology is limited by the less-than-desirable properties of the available radioisotopes (such as short half-lives, lack of tissue-specificity and other disadvantages).

Owing to their good physiochemical properties, dendrimers can be used as nanoplatforms to carry radioisotopes for SPECT imaging. [87] reacted a partially acetylated generation-5 PAMAM (G5-Ac) with biotin and 2-(p-isothiocyanatobenzyl)-6-methyl-diethylenetria minepentaacetic acid (1B4M-DTPA) successively. The resulting complex, Bt-G5-Ac-1B4M, was subsequently covalently bonded with avidin. In vitro cellular uptake tests confirmed that the avidin-bonded carrier was remarkably effective in targeting HeLa cells.

[88] surface-modified a partially acetylated G5 dendrimer (G5.NH2) with folic acid (FA)-containing polyethylene glycol (PEG) and diethylenetriaminepentaacetic acid (DTPA) chelator and subsequently radiolabeled the resulting conjugate with 99mTc. In vivo micro-SPECT imaging results showed that the nanomaterials accumulated mainly in the kidney, liver and tumors, without marked accumulation in other tissues and organs. In addition, mouse tumor models treated with 99mTc-G5-Ac-peg FA-DTPA yielded stronger SPECT imaging signals than those treated with 99mTc-G5-Ac-FA-DTPA or 99mTc-G5-Ac-DTPA. Therefore, 99mTc-G5-Ac-peg FA-DTPA was more effective in targeted SPECT imaging of tumors.

X-ray CT is based on the principle that tissues and organs have different compositions and densities and thus attenuate the passing X-ray beam at different degrees. In other words, CT images are obtained by measuring the intensity of the passed X-ray beam. Thus, more accurate diagnostic information can be obtained [89]. In the case of emergency disease control, chest CT provides a rapid and effective method to early recognize suspicious cases [90], especially for patients with COVID-like symptoms with a negative result for RT-PCR [91].

Yordanov et al. PAMAM dendrimer as the carrier and bonded an iodine compound, 3-N-[(N′,N′-dimethylaminoacetyl)amino]-α-ethyl-2,4,6-triiodobenzenepropanoic acid (DMAA-IPA), to the surface to obtain a iodinated imaging agent G4-(DMAA-IPA), which had a high iodine content of 33.1%. This was the first successful attempt to bind a small-molecule iodine compound and a dendrimer for CT imaging.

In addition to iodine, many other heavy-metal NPs have received increasing attention in medicine, particularly imaging diagnostics of diseases, due to their excellent properties in optics and quantum size. Because of their high X-ray attenuation coefficient, Au NPs are a good CT imaging agent. Dendrimers loaded with CT imaging and chemotherapeutic agents can realize effective targeted CT imaging and chemotherapy of tumors. Functionalized and modified dendrimer platforms are capable of precise imaging and efficient treatment of tumors, providing solutions for combined monitoring and early treatment of cancers.

The resulting theranostic nanomaterial α-TOS-Au DENPs had an average particle size of 3.3 nm and 9.8 α-TOS molecules per dendrimer and were fairly stable under different pH, temperature and solvent conditions. Compared with pure α-TOS, the RGD-targeting α-TOS-Au DENPs induced tumor cells to generate a higher level of reactive oxygen

species, thereby enhancing cancer cell apoptosis. The target specificity of FA enabled the theranostic nano agent to bind specifically with cancer cells overexpressing FA receptors, thereby increasing the uptake of the nano agent into these cancer cells. In addition, the therapeutic effect of MTX enabled specific inhibition of the growth of these cancer cells.

MR uses externally applied magnetic field gradients to detect electromagnetic signals from the human body, which are then computed to reconstruct anatomical information [92]. MR imaging is similar to other tomographic imaging techniques. However, MR imaging can obtain the tomographic and three-dimensional images in any direction. However, to improve the detection sensitivity, image definition and diagnostic accuracy of MR imaging, the assistance of imaging agents is necessary.

Small-molecule metal agents commonly used at present for MR imaging have the following disadvantages that limit their clinical application: (1) short residence in and quick removal from the blood circulation system; (2) lack of targeting capability; (3) small signal-to-noise ratio. Dendrimers have an exceptional macromolecular structure that contains unique internal cavities and many modifiable surface functional groups. Therefore, MR imaging agents can be bound to dendrimers. In addition, MR imaging nano agents with stable properties, good biocompatibility, high relaxivity, long blood circulation time and targeting capability can be obtained through functional modification of the dendrimer surface [93][94][95].

Mohamadi et al. [96] synthesized a new MR imaging agent by attaching Gd molecules to a dendrimer and evaluated the hepatic uptake and cytotoxicity of the synthesized agent by performing in vitro and in vivo imaging tests. The results showed that the binding of Gd and the dendrimer produced a safer, more efficient imaging agent.

Mustafa et al. [97] proposed a facile approach for synthesizing dendrimer-functionalized, Gd-loaded LAPONITE® (LAP) nano disks for in vitro and in vivo T1-weighted MR imaging. Cell viability assays showed that the synthesized LM-G2-DTPA (Gd) nanocomposite was non-cytotoxic in the given concentration range, had a high r1 relaxivity and was an efficient contrast agent for T1-weighted MR imaging of cancer cells in vitro and animal organs/tumor models in vivo.

Gadolinium-containing G4 dendrimer was also used as a biomarker for sepsis-induced acute renal failure (ARF). This approach helps to detect renal injury at an early stage, and provide information about the cause, response to therapy and prognosis [98]. To replace gadolinium dendrimers as contrast agents, G0- and G1-OEG-PROXYL radical dendrimers were created as a safer option. These dendrimers can be considered potential candidates as alternatives to Gd-based contrast agents currently used in MRI applications such as in follow-ups of infectious diseases [99].

The PAMAM-G8 dendrimers were also used as a MR imaging contrast agents in a mouse model. The purpose of this study was to visualize the lymphatic flow and lymph nodes to distinguish between the dilation of lymphatic vessels, proliferative or neoplastic lymph node swellings and changes in lymph nodes caused by infection/inflammation [100].

COOH)-modified ultrasmall The results of cell viability assays, cell morphological observations and hemolysis assays showed that the synthesized G5.NHAc-RGD-Fe3O4 NPs had good biocompatibility and hemocompatibility. In vivo tumor MR imaging tests showed that the RGD-mediated targeting increased the uptake of G5.NHAc-RGD-Fe3O4 NPs by tumor cells. These studies provided ideas for effective early diagnosis of cancers and showed the potential of these nanoplatforms for targeted MR imaging of various cancers.

A similar approach was used to prepare dendronized magnetic nanoparticles. + ions were bound to dendrons functionalized with carboxyl groups at the periphery. These carbosilane dendrimers can capture different HIV-1 isolates, due to electrostatic interactions between carboxylate groups and HIV-1 antibodies of the samples. The exact mechanism by which the dendrimers bind to HIV-1 is still not clear, but this research provides a new approach for faster HIV-1 detection, which reduces the waiting of 2–4 weeks required by current screening techniques [101].

Significant research on contrast agents for RT/MI bimodal imaging has been conducted. For example, with Au NPs functionalized with Gd ions [102][103], core–shell NPs [104][105][106] and dendrimer-based bimodal nanomaterials [107][108][109][110][111][112].

Fe3O4 NPs were assembled with multilayers of poly (γ-glutamic acid) (PGA)/poly(l-lysine)/PGA/folic acid (FA)-modified Au DNEPs using a layer-by-layer self-assembly technique. The synthesized nanomaterial exhibited a relatively high R2 relaxivity, good X-ray attenuation properties and good cytocompatibility and hemocompatibility in the tested concentration range. With the FA-mediated targeting, the NPs were specifically uptaken by cancer cells overexpressing FA receptors and were an efficient probe for targeted CT/MR bimodal imaging of a xenografted tumor model.

(RGD peptide) for targeted CT/MR bimodal imaging of tumors. The resulting multifunctional Au DENPs (symbolized as Gd-Au DENPs-RGD) were characterized using different techniques. The results showed that the multifunctional DENPs had an Au core size of 3.8 nm, had good water-dispersibility, were stable over a different pH range (5–8) and temperature

range (4–50 °C) conditions and had a low cytotoxicity at an Au concentration up to 100 µM. In addition, the synthesized Gd-Au DENPs-RGD had good X-ray attenuation properties and a high r1 relaxivity and was an efficient nanoprobe for targeted CT/MR bimodal imaging of a xenografted small tumor model overexpressing αvβ3 integrin.

Wen et al. The Au DENPs were synthesized using G5.NH2 surface-modified with Gd chelator and PEG monomethyl ether as the platform, followed by chelation of Gd(III) and acetylation of the dendrimer surface. The synthesized contrast agent (Gd-Au DENPs) was efficient for CT/MR bimodal imaging of the heart, liver, kidney and bladder of rat and mouse models. In addition, an in vivo biodistribution study showed that the Gd-Au DENPs had an extended blood circulation time that was cleared from the major organs in 24 h.

Functionalized and modified dendrimer platforms are capable of precise imaging and efficient treatment of infectious related tumors, providing solutions for combined monitoring and early treatment of cancers. However, currently available dendrimer-based theranostic agents have some deficiencies (Table 4). For example, the loading of hydrophobic agent affects the stability and water-solubility of Au DENPs, and these Au DENPs are prone to precipitation when stored for a long time. Therefore, synthesis of functionalized dendrimers that provide diagnostic and therapeutical effect while maintaining good stability and water-solubility is at the present a pressing problem and a direction for future research of dendrimer-based theranostic agents.

Due to some limitation of conventional infectious disease diagnostics, including imaging, polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA), new diagnostic methods have been in demand. In South Korea, a dendrimer-based assay to detect malaria has been approved as a rapid and cheap diagnostic tool. The assay is based on fluorescence as shown in Figure 6 [113].

The created coumarin-derived dendrimer-based fluorescence-linked immunosorbent assay (FLISA) can detect two malaria-specific antigens: histidine-rich protein II (HRP2) and lactate dehydrogenase (LDH). The advantage of this method is that it provides higher sensitivity than traditional ELISA, which can be useful to detect asymptomatic cases [114].

Another dendrimer assay that detects Schistosoma circulating anodic antigen (CAA) is comprised of magnetic particles coated with G4-PAMAM-NH2. The principle of this assay involves the electrostatic interactions between the negatively-charged CAA biomarker and positively charged poly(amidoamine) (PAMAM) dendrimers modified with magnetic nanoparticles. The advantage of this method is that enables concentration of the sample, and thus becomes less time-consuming and waives the requirement of significant laboratory infrastructure with detection of the CAA antigen of 200-fold on a lateral flow assay when compared to currently used assays [115].

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