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Review Article

Poly (amidoamine) Dendrimers in Cancer Therapy: Chemotherapy, Radiotherapy and Imaging Advances

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Abstract

Cancer is estimated to overtake cardiovascular diseases and take the top spot as the leading and most important cause of mortality globally in the near future. Given the importance of early diagnosis to reduce mortality, many efforts have been made to discover a theranostic system for simultaneous cancer diagnosis and treatment. So far, the use of nanotechnology has greatly contributed to the improvement and development of these systems. Meanwhile, dendrimer nanoparticles have attracted considerable attention in medical research due to their unique properties. Poly(amidoamine) (PAMAM) dendrimers have become the primary category of dendrimers and have been widely studied for their possible application in cancer treatments. These nanoparticles have features including interior cavities and peripheral functional groups that allow the encapsulation of diverse medications or diagnostic agents. As a result, these particles can function as efficient nanocarriers and vectors for medical applications. This capability allows for the resolution of the obstacles presented by the tumor microenvironment. The prospective use of multifunctional PAMAM holds promise in enabling thorough monitoring of different stages of treated cancer tissue, hence providing substantial support in the early detection and prediction of tumor response. The primary focus of this study will be to investigate the most recent developments of PAMAM dendrimers in the field of cancer theranostics. The employment of NPs in anticancer medicine administration for radiation treatment, chemotherapy, and diagnostic imaging is underscored due to its significant potential.

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1. INTRODUCTION

According to a recent report by the World Health Organization (WHO), it is anticipated that cancer will rank as the second most significant contributor to global mortality in the year 2020. This will result in an estimated 10 million deaths, or about one-sixth of all recorded mortalities (1). The timely identification and screening of cancer are paramount in providing optimal and efficacious therapy, hence significantly mitigating death rates. Early diagnosis has a pivotal role in augmenting the efficacy of cancer treatment and improving the prospects of patient recovery (2, 3). Despite the progress achieved in traditional modalities such as surgical interventions, chemotherapy, and radiation therapy, their effectiveness has been proven to be restricted to specific categories of malignant tumors. The observed phenomenon can be ascribed to the diverse origins of tumors and the complex and diverse character of individual components. As a result, recent advancements in the field have given rise to complementary approaches, including immunotherapy and nanotechnology (4, 5) . The use of nanotechnology in the field of oncology has attracted a lot of attention. It has shown its efficiency in selectively targeting cells and administering appropriate therapeutic and diagnostic substances (6). A new approach to cancer care has mainly emerged thanks to the use of nanoparticles as effective carriers. Early cancer detection, imaging, and drug delivery are just some of the many applications of this technique (7). The synthesis and design of nanoparticles have made significant progress, resulting in the creation of theranostic nanoparticles that exhibit exceptional efficacy. These nanoparticles have shown promising results in several cancer models, both in laboratory settings (*in vitro*) and living organisms (*in vivo*) (8). Recent advances in the fields of imaging and drug delivery have led to the introduction of dendrimer-based nanoparticles as a novel class of applied nanoparticles with impressive capabilities (9). Dendrimer-based NPs of various sorts have recently emerged as potential tools for imaging and treating cancerous cells. These NPs range in size from 1 to 15 nm and have a polymer globular branching and symmetrical structure that defines their morphology and specificity (10). Dendrimers made of Poly(amidoamine) (PAMAM) have been studied extensively and are widely known to be an important form of nanoparticles used in cancer therapy (11). Several studies have demonstrated the efficacy of PAMAM as a highly efficient nanocarrier and vector for drug targeting, gene delivery, and various biomedical applications. This effectiveness is primarily related to its capacity to overcome the challenges given by the tumor microenvironment (12). The manufacturing of PAMAM nanocarriers can be accomplished by the divergent approach, which is often utilized for synthesizing dendrimers. The approach employed in this technique entails a systematic and incremental process, commencing from the central core and advancing outward in a sequential manner, layer by layer until the ultimate dendrimer architecture is achieved (13). Nanoparticles possess internal cavities and external functional groups that offer the potential for medication encapsulation or the incorporation of diagnostic components. PAMAM has distinctive characteristics, such as its nanoscale dimensions, flexible surface features, and proficient guest molecule binding capabilities, rendering it a very promising nanocarrier for therapeutic and diagnostic pharmaceuticals (14). In terms of early diagnosis and prediction of tumor response, the multifunctional PAMAM is invaluable due to its capacity to permit monitoring of various phases of treatment for cancer tissue (9). This review will focus on the latest advancements in the field of cancer theranostic PAMAM dendrimer. The potential of these nanoparticles for the administration of anticancer drugs in chemotherapy, radiation therapy, and diagnostic imaging is underscored.

2. Different types of dendrimers

Dendrimers can be categorized into many groups based on their geometric configuration, central core, and surface constituents. The types of dendrimers that have been studied extensively in the field include PAMAM dendrimers, PPI dendrimers, Chiral Dendrimers, Phosphorus Dendrimers, PLL (Poly-lysine) dendrimers, Peptide Dendrimers, and Hybrid dendrimers (15, 16). In this context, we briefly introduce the two most prevalent forms of dendrimers, namely PAMAM and the polypropylene imine (PPI) dendrimers.

PAMAM dendrimers are considered to be the pioneering category of synthetic dendrimers. The divergent methodology is used in the synthesis of chemicals, whereby either ammonia or ethylene diamine is employed as the central core. The existence of multiple functional end groups is responsible for the high solubility and reactivity exhibited by molecules. The morphology of these structures exhibits a spherical or elliptical shape, and it is possible to acquire cost-effective samples up to the tenth generation (G10). Antibacterial, antiviral, and antioxidant capabilities of dendrimers, namely PAMAM dendrimers, are only a few of their many applications (17, 18).

Dendritic polymers belonging to the polypropylene imine (PPI) family are also known as polypropylene amine dendrimers. Their basic ingredients are ethylenediamine

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(EDA) and diaminobutane (DAB), and they are synthesized using a different approach. Currently, commercially available technology generations extend up to the fifth generation (G5). Efficient delivery of hydrophobic compounds may be achieved by using carriers with high water solubility. This solubility is increased by the inclusion of terminal amino groups. Due to having fewer bonds (four as opposed to seven), PPI dendrimers are smaller in size than PAMAM dendrimers (19, 20).

3. Synthesis of PAMAM dendrimer

To date, several methodologies have been put forth for the synthesis of PAMAM dendrimers, with divergent and convergent approaches being the primary tactics employed. The initial method of divergent synthesis was developed by Tomalia in 1985. This approach involves the sequential formation of nanoparticles, starting from the core and progressing toward the shell. The core material is ethylenediamine or NH3, which undergoes a Michael addition reaction and subsequent amidation reaction to produce the surface of the nanoparticles. The aforementioned procedure was iterated until the required production of PAMAM dendrimer was achieved (22, 23).

The convergent technique involves a reversal of the procedure. In contrast to the divergent process, the synthesis process proceeds from the surface towards the core. Poly(amidoamine) branches are synthesized initially, followed by their subsequent attachment to the core. Applying this particular strategy allows for greater control over the synthesis process, resulting in reduced production of faulty dendrimers compared to the divergent approach. An alternative technique known as hybrid convergent-divergent synthesis, commonly referred to as double exponential growth synthesis, was initially documented by Kawaguchi in 1994. The synthesis process is expedited by the simultaneous production of Poly(amidoamine) branches and core in this particular technique (24).

Click and Lego chemistry is two alternatives that can improve the speed and efficiency of both convergent and divergent approaches while also reducing costs and facilitating easier implementation (25).

4. Application of PAMAM dendrimer in cancer management

Recent years have witnessed a significant increase in research into polymeric drug delivery systems to create sustained-release medication delivery systems. Dendrimers, also known as dendritic polymers, have a nanosized structure that allows them to be used for the delivery of any medication, hydrophilic or lipophilic, via oral, injectable, pulmonary, or nasal administration routes (27).

4.1. Drug delivery

Chemotherapy has employed a range of NPs, including liposomes, nanotubes, and polymer-drug conjugates. Studies have also explored the utilization of diverse dendrimer variants, including PAMAM, PPI, PLL, and polyether, to deliver anticancer drugs. Inorganic NPs are confined within dendrimers because of their distinctive structure, which includes internal cavities and peripheral functional groups. Targeting ligands, medicines, and bioactive substances are covalently conjugated to dendrimers to deliver a variety of medications (28). Dendrimers are utilized in the treatment of serious medical conditions such as cancer owing to their distinctive characteristics. Several notable characteristics of these structures can be identified. Firstly, they consist of branched, tree-shaped repeating units composed of drug molecules. Secondly, their surface contains functional moieties that can bind to particular targeting moieties. These structures exhibit biocompatibility, resilience, and solubility in aqueous conditions. The majority of dendrimers utilized in biomedicine are PAMAM-based (29).

PAMAM dendrimers possess properties that render them suitable for employment as drug carriers in targeted therapy. These properties include the enhancement of hydrophobic drug solubility, the capacity to modulate molecular size, and the potential to affix specific ligands that exhibit recognition by receptors that are overexpressed in cancer cells (13).

The water solubility of PAMAM dendrimers renders them promising candidates for the field of oral medication administration. Also, it has been shown that PAMAM dendrimers are capable of crossing epithelial junctions by engaging both transcellular and paracellular pathways. Consequently, their transportation via paracellular routes is enhanced. However, it is important to note that these dendrimers possess some drawbacks attributable to their substantial size and elevated molecular weight (29, 30).

Dendrimers are employed to control the release of drugs because of their multivalent nature. As a result, several medications can be attached covalently to distinct dendrimer groups. It is possible that the pharmacological effects of medications might be improved by their interaction with dendritic polymers (27). For example, cisplatin can be covalently bonded to PAMAM dendrimers to increase its concentration in solid tumors

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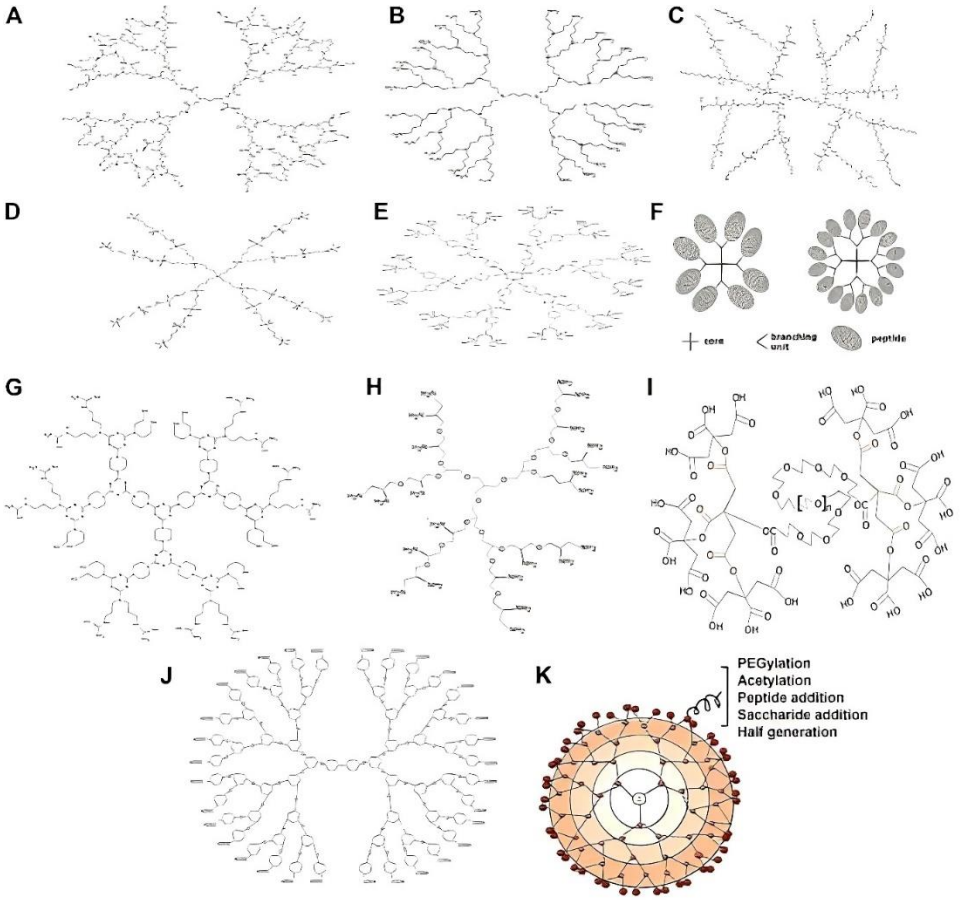

Figure 1. Types of dendrimers: **(A)** PAMAM Dendrimers; **(B)** PPI Dendrimers; **(C)** PLL Dendrimers; **(D)** Carbosilane Dendrimers; **(E)** Phosphorus Dendrimers; **(F)** Peptide dendrimers. Types of dendrimers: **(G)** Triazine dendrimers; **(H)** Polyglycerol dendrimers; **(I)** Citric acid dendrimer; **(J)** Polyether dendrimers; **(K)** Surface engineered dendrimers (adapted from Kaurav et al., 2023)(21).

while reducing its toxicity and extending its release time course (31). Hydrolysis of the release mechanism for cisplatin from the dendrimer occurs when anticancer prodrug complexes are formulated using carboxylated terminated PAMAM dendrimers of cisplatin, leading to an increased maximum tolerated dose, increased survival time in tumor-bearing mice, and a more sustained drug release over a longer period. The dendritic polymer can be given to the animal in several different routes in this procedure, including orally, intramuscularly, intravenously, subcutaneously, and topically for the treatment of malignant tumors (32).

Various generations of PAMAM dendrimers have been employed to deliver diverse chemotherapeutic agents to distinct cancer cell populations. The use of DOX-PAMAM G4 dendrimer in a lung cancer metastasis model, including B16-F10 melanoma cells, demonstrated that these dendrimers exhibited aggregation inside the lungs, reducing tumor burden (33). When employed for combination treatment (photothermal chemotherapy) of cancer cells (murine colon carcinoma), PEGylated-G4 PAMAM exhibited enhanced effectiveness compared to a single therapy module. It was attached through covalent bonding to mercaptohexadecanoic acid-functionalized gold nanorod and loaded with DOX (34).

The 5th generation (G5) modified polyethylene glycol-phenylboronic acid (PEG-PBA) PAMAM dendrimers (G5. NHAc-PEG-PBA @Cu) (II)/TPZ (GPPCT), which contain the Cu (II) chelate and the hypoxia-sensitive drug tirapazamine (TPZ), exhibit effective uptake by cancer cells that have an overexpression of sialic acid residues. This uptake produces reactive oxygen species (ROS) within the cells, depletion of glutathione (GSH), and significant elimination of hypoxic tumor cells. Furthermore, in the

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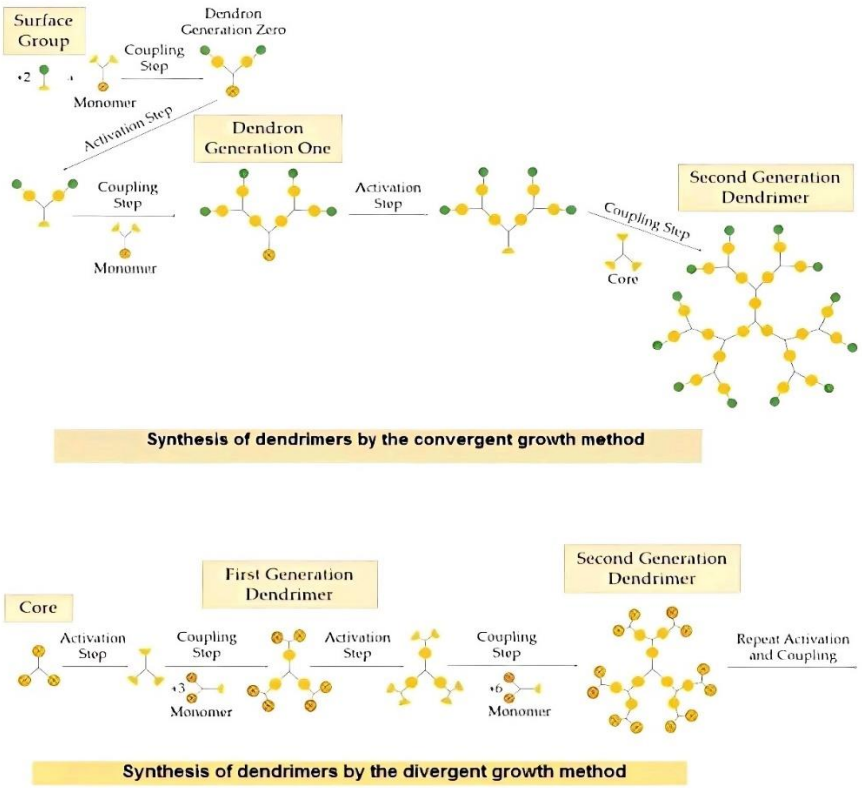

Figure 2. Schematic representation of divergent and convergent synthesis methods of dendrimers (adapted from Santos et al., 2020)(26).

In vivo experiment, it was observed that GPPCT accumulated at tumor sites during an extended circulation period. This accumulation effectively hindered the development and spread of 4T1 breast cancer. Importantly, the metabolism of GPPCT occurred without causing any systemic damage. Zhao et al. also reported on the utilization of a modified G0 PAMAM dendritic Schiff base in conjunction with platinum (II) and copper (II) for cancer treatment (12)

Certain PAMAM dendrimers exhibit notable selectivity in facilitating the drug delivery specifically to desired target cells. An instance of gemcitabine-loaded YIGSR-CMCht/PAMAM dendrimers, which are carboxymethyl chitosan/poly(amidoamine) (CMCht/PAMAM) dendrimer nanoparticles functionalized with YIGSR laminin receptor binding peptide, has been observed to result in significant mortality rates in HCT-116 cancer cells when co-cultured with L929 fibroblasts (a model of healthy cells) (35). The enhancement of molecular targeting can be achieved by the incorporation of additional ligands. An instance of this can be observed in the experiment conducted by Marcinkowska et al., where they successfully coupled PAMAM dendrimers with both the antibody trastuzumab (36) and Doxorubicin (DOX), resulting in the formation of DOX-TZ-PAMAM. This conjugation enhanced the targeted efficacy of the nanodrug against breast cancer cells (37). Furthermore, the use of paclitaxel (PTX)-biotinylated PAMAM complexes resulted in an enhanced internalization of nanomedicine by ovarian cancer cells (OVCAR-3) and human embryonic kidney cells (HEK293T) while concurrently reducing negative consequences (38).

A study was conducted in which ultrasound-targeted microbubble destruction (UTMD) technology was used to achieve adequate tumor accumulation and drug penetration. This approach involves creating several small holes on the surface of the cell membrane through the phenomenon of cavitation. The goal is to increase the transport of foreign macromolecules, facilitate gene transfer, accelerate the penetration of nanoparticles into tumors, and, as a result, improve the delivery of therapeutic drugs to tumor sites (39). The combined use of gold

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Table 1. An overview of the literature concerning the application of PAMAM dendrimer nanoparticles in chemotherapy drug delivery

Functional components	Applications	Tumor types	Ref
PEGylated-G4 PAMAM dendrimer, mercaptohexadecanoic acid, gold nanorod, DOX	Photothermal/ Chemotherapy	Mouse colon carcinoma	(34)
G5 modified polyethylene glycol-phenylboronic acid (PEG-PBA) PAMAM dendrimer, Cu(II) chelate, tirapazamine (TPZ), (G5.NHAc-PEG-PBA @Cu)(II)/TPZ (GPPCT))	Chemotherapy	4T1 breast tumors	(54)
YIGSR-CMCht/PAMAM dendrimers, Gemcitabine	Chemotherapy	HCT-116 cancer cells	(35)
PAMAM dendrimers, antibody trastuzumab, doxorubicin	Chemotherapy	Breast cancer cells	(37)
biotinylated PAMAM dendrimers, paclitaxel	Chemotherapy	Ovarian cancer cells (OVCAR-3) human embryonic kidney cells (HEK293T)	(38)
G5 PAMAM dendrimer, drug-efflux inhibitor TPGS, y-CDs, anticancer drug DOX	Fluorescence imaging and chemotherapy	Xenografted human breast MDR tumor model	(28)
G4 PAMAM dendrimer, folic acid		Head and neck cancer	(42)
G5 PAMAM dendrimer, folic acid, DOX		Glioma cells	(43)
PAMAM dendrimer, photothermally active polydopamine (PDA), polyethylene glycol (PEG), folic acid (FA), DOX	Chemo/photothermal therapy (with near-infrared laser irradiation)	Hepatocellular carcinoma cells	(44)
PAMAM dendrimers, DOX, angiopep-2	Chemotherapy	Glioma cells	(45)
G5 PAMAM dendrimer, arsenic trioxide	Chemotherapy	Rodent model of glioma	(46)
smaller PAMAM dendrimers (~5 nm in diameter), larger poly(ethylene glycol)-b-poly(D,L-lactide) (PEG–PLA) NPs (~70 nm)	Chemotherapy	Human epithelial carcinoma cells	(49)
half-generation anionic PAMAM dendrimer, cisplatin, platinum	Chemotherapy	A2780, A2780cisR, MCF-7, and CACO-2 cells and non-cancer cell line (BJ cells)	(50)
G5 PAMAM-glutaric acid dendrimers (G5-GA), cisplatin	Chemotherapy	MCF-7R Breast Cancer cells	(52)
G4 PAMAM dendrimer, capecitabine (CPB)	Chemotherapy	Colon cancer	(53)

nanoparticles (AuNPs), gemcitabine medication, and a microRNA-21 inhibitor has proven to be advantageous in augmenting combinational therapy for a pancreatic cancer model (40).

In a separate study, researchers employed (G5-TPGS@y-CDs)-DOX, a combination of generation 5 PAMAM dendrimers (G5) covalently bonded with the drug-efflux inhibitor TPGS, complexed with y-CDs through electrostatic interaction, and subsequently physically loaded with the anticancer drug DOX. This formulation was utilized for ultrasound (US)-enhanced fluorescence imaging and chemotherapy in a xenografted human breast MDR tumor model. In this experimental approach, the introduction of additional DOX and a P-gp (P-glycoprotein) inhibitor leads to a notable inhibition of cancer cells. This inhibition is achieved by the reduction of intracellular ATP levels and mitochondrial membrane potential, as well as the augmentation of ROS generation. Furthermore, using UTMD has been shown to enhance the effectiveness of chemotherapy in treating cancer cells in a subcutaneous tumor model with multidrug resistance by exploiting the sonoporation phenomenon (28).

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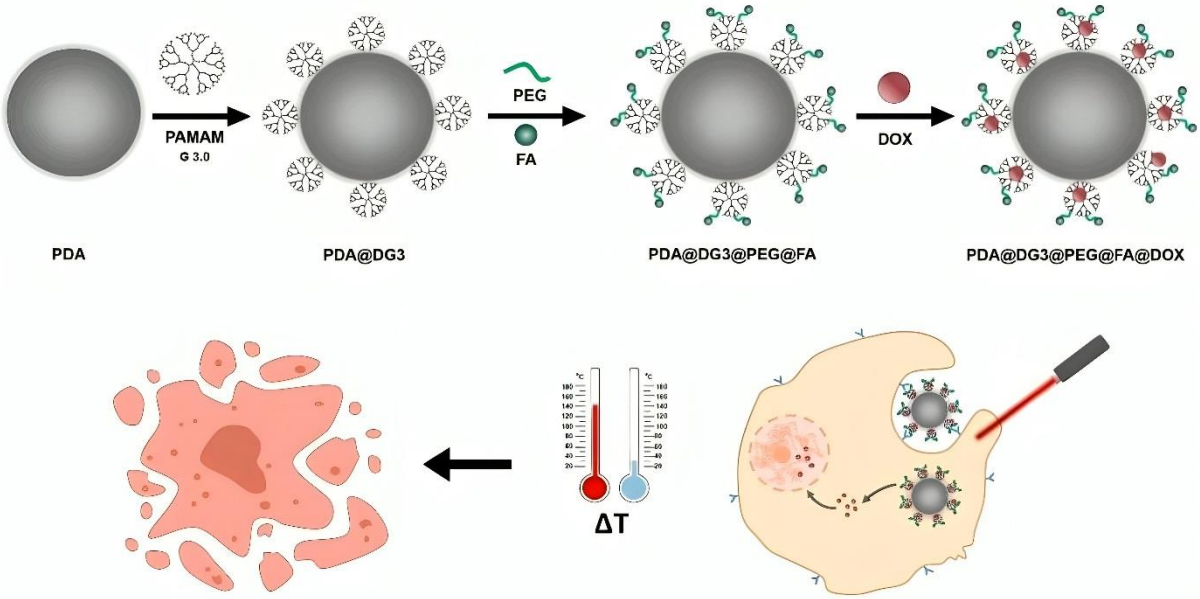

Figure 3. Schematic illustration of polydopamine (PDA)@PAMAM dendrimers G 3.0 NPs for targeted dual chemo and photothermal synergistic cancer therapy (adapted from Grześkowiak, et al., 2021)(44).

The use of folate ligands for targeted cancer therapy is possible as for the overexpression of folate receptors in several types of cancer cells, including kidney, breast, ovarian, and brain cancer cells. The solubility and affinity of this compound for receptor binding make it very compatible with dendrimers. Hence, the utilization of folate-conjugated dendrimers offers a promising avenue in the therapy of cancer (41). Folic acid and biotin have been identified as important elements that enhance the specific localization of dendrimers to brain tumors. The enhancement of the absorption of nanoparticles (NPs) by head and neck cancer cells was observed in an experiment by the conjugation of folic acid to G4 PAMAM dendrimers (42). The *in vitro* studies on glioma cells demonstrated that the presence of folic acid coupled with G5 PAMAM dendrimers, which were loaded with DOX, led to greater absorption by cancer cells than in cases where folic acid was not present (43). The efficacy of FA-FTIC-MTX-PAMAMG5, a G5 PAMAM dendrimer conjugated with folic acid (FA), fluorescein isothiocyanate (FITC), and methotrexate (MTX), a chemotherapeutic and immunosuppressive agent, is enhanced in the treatment of human epithelial carcinoma KB cell line, which exhibits elevated expression of folate receptors, compare to the administration of free MTX (33). The particle surfaces were coated with photothermally active polydopamine (PDA) that was functionalized with PAMAM dendrimers. Then, conjugated by PEG moieties and folic acid (FA) targeting ligands. Finally, the anticancer medication DOX was absorbed onto the surface of particles. The aforementioned nanoparticles were administered to cancer cells with precise targeting and effectively inhibited their proliferation. The manufactured nanoparticles were employed in a treatment approach that combined chemotherapy with photothermal therapy, employing near-infrared laser irradiation, to target hepatocellular cancer cells (44).

Glioblastoma is a malignant brain tumor that may be treatable using dendrimers (particularly PAMAM dendrimers), which can pass the blood-brain barrier (BBB) (33). PAMAM dendrimers loaded with DOX and angiopep-2 have the ability to selectively target tumor tissue by specifically binding to a protein that is overexpressed on both glioma cells and BBB (45). The *in vitro* and *in vivo* efficacy of G5 PAMAM dendrimers loaded with arsenic trioxide in promoting apoptosis in a mouse model of glioma has been shown (46).

The neutral form of PAMAM can go through the BBB and bind to microglia and other inflammatory cells. Improved site-specific targeting and distribution of therapeutic medicines can be reached by adding functional groups to PAMAM (47).

G5 PAMAM-NH2 dendrimers were shown to enhance cytotoxicity in a study of MCF-7 cell sublines with acquired

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Table 2. An overview of the literature concerning the application of PAMAM dendrimer nanoparticles in tumor radiosensitization.

Functional components	Applications	Tumor types	Ref
G5 PAMAM dendrimers,3-(4'-hydroxyphenyl)propionic acid-OSu (HPAO), PEG-linked FA, ^{131}I	Targeted radiotherapy and SPECT imaging	The glial cell line of a rat (C6 cells)	(57)
G5 PAMAM dendrimers, pol Chlorotoxin (CTX), ^{131}I	Targeted radiotherapy and SPECT imaging	Mice glioma model	(58)
G5 PAMAM dendrimer, (Fe3O4/Au DSNFs)	T1–weighted MR/CT/PA imaging and photothermal therapy/radiotherapy	Murine breast tumor model	(59)
G4 PAMAM dendrimer,2-(p-isothiocyanatobenzyl)-6-methyl-diethylene triamine penta-acetic acid (1B4M), OST7, ^{111}In or Gd (III)	Targeted radiotherapy	Human osteosarcoma xenograft tumor (KT005)	(60)
G4 PAMAM dendrimer, FA, bombesin-grafted, 177Lu	Targeted radiotherapy, fluorescence imaging, and photothermal therapy	Human breast cancer cell (T47D)	(61)

drug resistance. The charge of amine group of PAMAM is positive, and the negative charge of cell membranes leads to membrane degradation and eventual cell lysis (48).

Using larger NPs with diameters generally ranging from 50-200 nm in passive targeting leads to accumulating NPs within tumors by passive means. However, this approach hinders the effective penetration of NPs into the tumor tissue. On the other hand, smaller NPs with diameters below 20 nm, which are actively targeted, exhibit enhanced ability to enter the tumor mass. Nevertheless, their rapid systemic elimination poses a challenge. To address this constraint, Sunoqrot et al. developed a multi-scale hybrid NP platform that incorporates smaller poly(amidoamine) (PAMAM) dendrimers (~5 nm in diameter) into larger poly (ethylene glycol)-b-poly (D, L-lactide) (PEG–PLA) NPs (~70 nm). These larger NPs exhibit prolonged circulation in the bloodstream compared to free dendrimers. The study was conducted on BALB/c athymic nude mice with folate receptor (FR) expression. The KB (human epithelial carcinoma cells) xenograft is frequently observed to be overexpressed and then eliminated by liver and spleen macrophages (49).

The HER2 protein exhibits overexpression in several cancer types and serves as a focal point for immunotherapeutic interventions. past studies have shown the ability of G5 PAMAM dendrimers, when coupled with anti-HER2 monoclonal antibodies, to effectively target HER2 cell lines (48).

Multiple surveys have demonstrated the suitability of PAMAMs for the treatment of breast cancer. An instance of enhanced transport of docetaxel to breast cancer cells that overexpress the HER2+ receptor and subsequent apoptosis induction in MDA-MB-453 cancer cells may be observed with the aid of PAMAM dendrimers coupled with Trastuzumab. Additionally, G5 PAMAM dendrimers hydrophobically modified by lipid-like myristic acid (My) tail grafting improve tamoxifen transport to breast cancer cells. Additionally, the cytotoxic activity of the compound is increased in MCF-7 breast cancer cells when DOX is delivered using a glucose-modified PAMAM dendrimer (13).

Cisplatin, a chemotherapeutic agent, is associated with significant consequences, including nephrotoxicity, ototoxicity, and cardiotoxicity, hence imposing constraints on the maximum permissible dosage for safe administration. To mitigate the complexities associated with cisplatin, Camacho et al. conducted a study where they chemically linked cisplatin with anionic PAMAM dendrimers of half-generation. This linkage was gained through the coordination of the terminal functional groups of the dendrimers with platinum. Subsequently, the researchers investigated the potential cytotoxic effects of these conjugates on various cancer cell lines (A2780, A2780cisR, MCF-7, and CACO-2 cells) as well as a non-cancer cell line (BJ cells). The degree of cytotoxicity exhibited by metallodendrimers was found to be contingent upon both the specific cell line being studied and the particular coordination mechanism employed, whether it be mono- or bidentate. The A2780 and A2780cisR cell lines exhibited more selectivity in comparison to non-cancerous BJ cells, and, in general, metallodendrimers showed stronger potency than cisplatin (50).

Cisplatin toxicity is reduced, and its accumulation in breast cancer tumors is increased by using PAMAM dendrimers to encapsulate the drug (51). Scaffolds made of PAMAM dendritic polymers are commonly used in breast cancer treatment (48). MCF-7R Breast Cancer cells, which were

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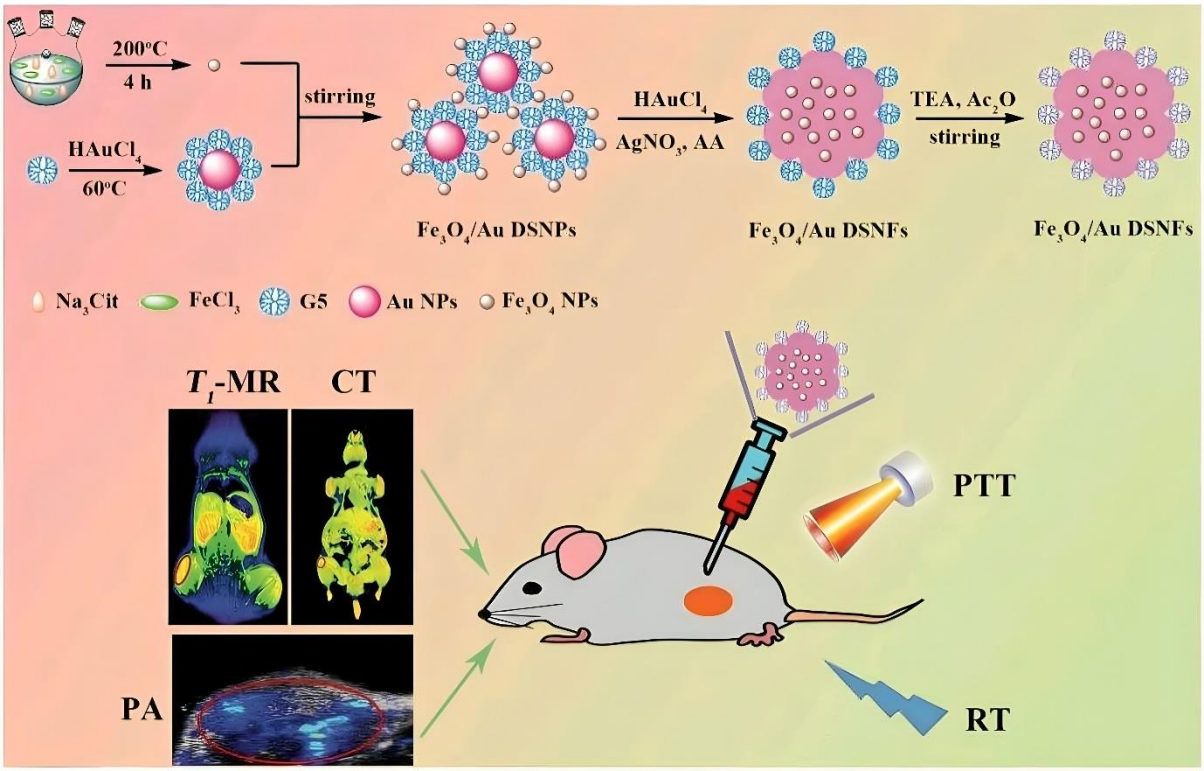

Figure 4. Schematic illustration of the preparation of the Fe3O4/Au DSNFs for multimode imaging–guided combination therapy of tumors (adapted from Lu, et al., 2018)(59).

resistant to cisplatin, were used to assess the cytotoxicity of G5 PAMAM-glutaric acid dendrimers (G5-GA) coupled with cisplatin to that of free drug cisplatin. The study demonstrates that MCF-7R cells are more sensitive to G5-GA cisplatin than they are to free cisplatin (52). In addition, G4 PAMAM dendrimers have been employed to minimize side effects, enhance anticancer efficacy, and reduce nonspecific effects of CPB on organs other than the colon (53). Table 1 provides a summary of the nanoplatforms discussed in this section.

4.2. Radiosensitization

Since radiotherapy (teletherapy) employs high amounts of radiation, it also affects normal tissues in the vicinity of the tumor, which might have negative health consequences. However, fewer dosages may cause less harm to normal tissues without eliminating the tumor. As a result, the development of radiation sensitizers is a priority so that therapeutic goals can be met with little radiation exposure. Silver (Ag), gold (Au), and platinum (Pt) are just a few examples of the many nanomaterials currently in use; other examples include those based on rare earth metals (gadolinium (Gd), hafnium (Hf), semiconducting metals (bismuth (Bi), and other metals (titanium (Ti)). Chemotherapeutic agents known for their radio-sensitizing effects, such as adriamycin, catechin, docetaxel, paclitaxel, cisplatin, cyclopamine, and other platinum-based drugs, selenocysteine, mitomycin C, camptothecin, topotecan, curcumin, tirapazamine, histone deacetylase inhibitors, arsenic trioxide, etanidazole, and selenium derivatives, are combined with liposomes, proteins, polymers, dendrimers, exosomes, and other materials to create nanomedicines aimed at enhancing radiosensitization (55).

The usage of radiopharmaceuticals, such as iodine-131 (131I), yttrium-90 (90Y), and rhenium-188 (188Re), in radiotherapy methods that employ alpha (α) or beta (β) radiation, has demonstrated notable therapeutic efficacy and has found widespread application in healthcare facilities (12). The emitted particles possess non-penetrating characteristics, allowing for precise delivery to the tumor tissue while reducing harm to adjacent normal tissues (56).

In the context of tumor-targeted irradiation and single-photon emission computed tomography (SPECT) imaging, G5 PAMAM dendrimers were utilized. These dendrimers were coupled with 3-(4'-hydroxyphenyl) propionic acid-

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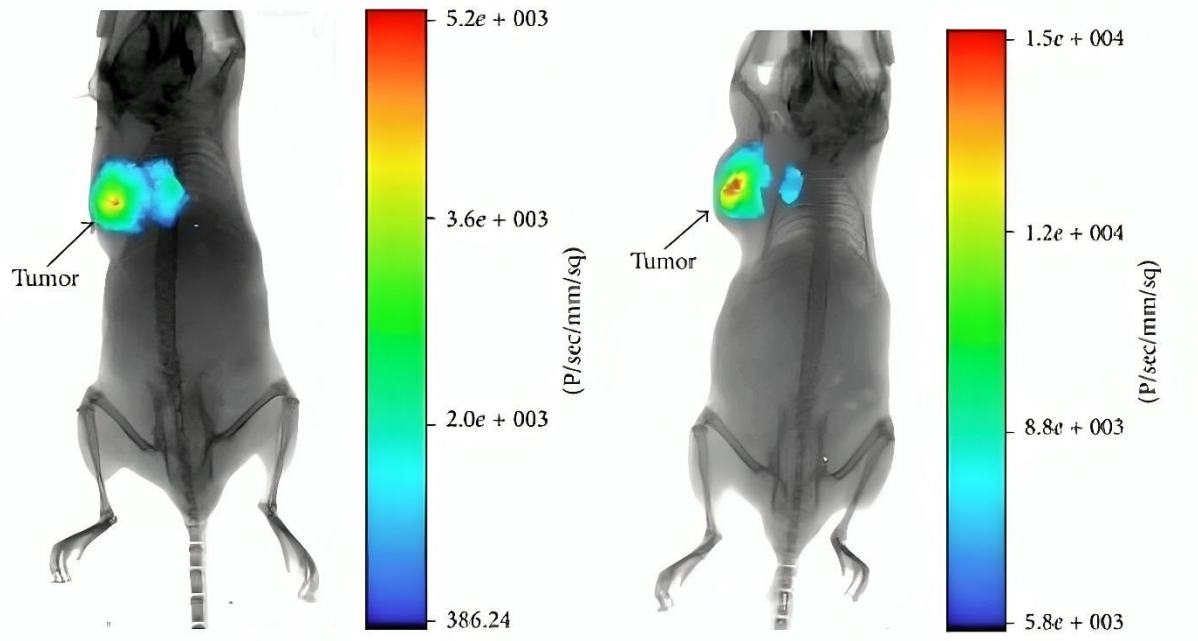

Figure 5. Use 177Lu-DenAuNP-folate-bombesin in optical imaging at 1 h and 96 h after intratumoral administration (adapted from Mendoza-Nava et al., 2016)(61).

OSu (HPAO) for 131I labeling. Additionally, they were conjugated with PEG-linked folic acid (FA) to facilitate targeting. The resulting conjugate exhibited targeted biodistribution inside the tumor and showed remarkable effectiveness in suppressing tumor growth (57).

In the study, the use of G5 PAMAM dendrimers that were coupled with pol Chlorotoxin (CTX) and tagged with radioactive 131I was employed to augment the signal intensity in SPECT imaging and the therapy of a glioma model in mice (58).

In a separate study, researchers employed G5 dendrimer stabilized Fe3O4/Au nanoflowers (Fe3O4/Au DSNFs) to achieve enhanced therapeutic efficacy in a murine breast tumor model. These nanoflowers exhibited favorable colloidal stability, cell compatibility, and efficient cellular uptake. The researchers utilized these nanoflowers for multimode T1-weighted MR/CT/PA imaging and combined radiotherapy and photothermal therapy (59).

To label the murine monoclonal IgG1 OST7 with either 111In or Gd (III), Kobayashi et al. coupled the 64-amine PAMAM of generation 4 (G4) with 43 molecules of 2-(p-isothiocyanate benzyl)-6-methyl-diethylene triamine penta-acetic acid (1B4M). PAMAM G4 generates high accumulation in human osteosarcoma xenograft tumors (KT005), rapid clearance of radioactivity in the bloodstream, and negligible loss of immunoreactivity (60).

Nava et al. developed a nanosystem that combines targeted radiotherapy, fluorescence imaging, and photothermal treatment. This was achieved by entrapping gold nanoparticles (with a diameter of 2.1 nm) within FA- and bombesin-grafted and 177Lu-labeled G4 PAMAM dendrimers. The combination of this nanosystem, laser irradiation, and radiation of 177Lu resulted in a substantial reduction in the viability of T47D cancer cells derived from a human breast cancer cell line (61). Table 2 lists some of the nanoparticles addressed in this section.

Table 2. An overview of the literature concerning the application of PAMAM dendrimer nanoparticles in tumor radiosensitization.

4.3. Imaging

The versatility of PAMAM dendrimer in diagnostic and therapeutic applications may be attributed to its distinctive characteristics, including a well-defined three-dimensional structure, remarkable molecular uniformity, limited molecular weight distribution, mono-dispersity, and multifunctional terminal surfaces (62). This chapter presents the prevailing approaches in molecular imaging commonly employed for diagnostic purposes. These techniques include Optical imaging, computed tomography (CT), magnetic resonance imaging (MRI), and

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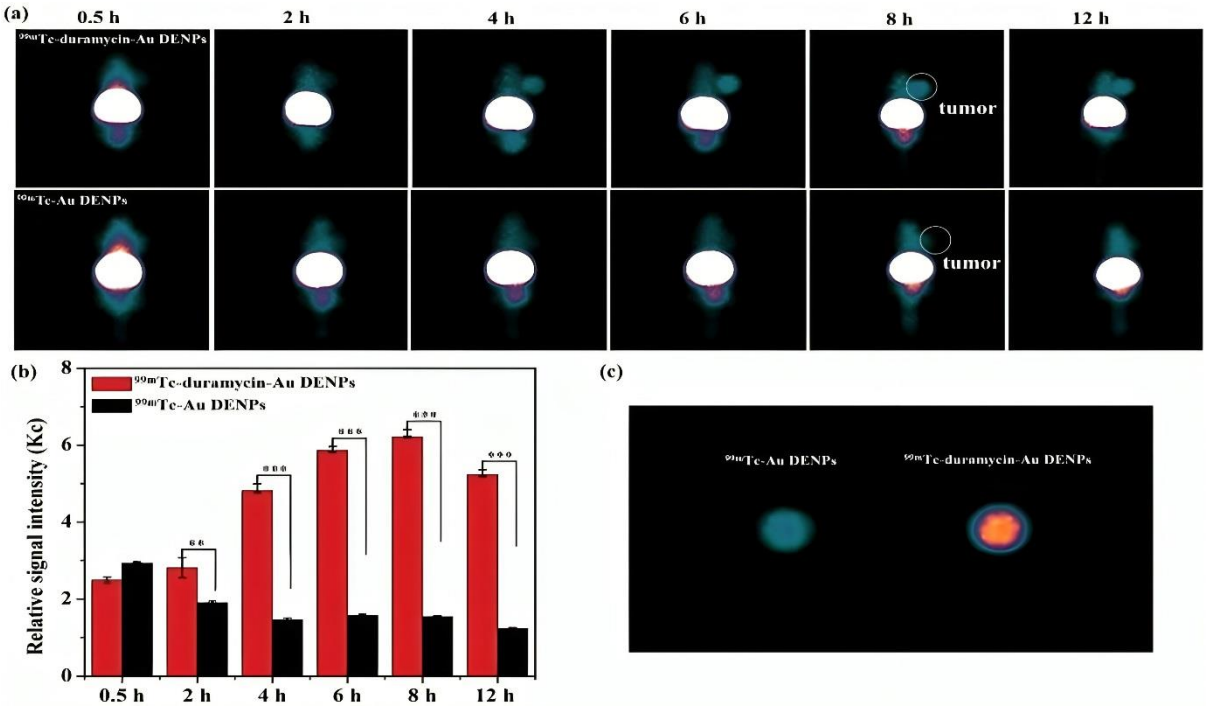

Figure 6. SPECT imaging of the nude mice with C6 xenografted tumors by 99mTc-duramycin-Au G4-PAMAM dendrimer (adapted from Xing et al., 2018) (79).

nuclear medical imaging (PET, SPECT), which utilize contrast agents (CAs).

4.3.1. Optical imaging

Optical imaging may be achieved by conjugating fluorescent dyes to the PAMAM nano-dendrimer platform. Compared to other imaging methods, fluorescence imaging is distinguished by its various detection capabilities, low cost, and high sensitivity, all of which have recently attracted more attention (56). The near-infrared spectrum has been well recognized as a very efficient optical modality for spectroscopic and imaging purposes. It has demonstrated notable efficacy in targeting the accumulation of PAMAM-dendrimer-attached dye within malignant tumors (63). The fifth generation of PAMAM showed higher efficiency in fluorescence imaging compared to other generations. The use of theranostic methods, namely PAMAM-based MR/CT/PA nanoprobes, has the potential to elucidate the course of tumors in cancer. These nanoprobes can act as multifunctional diagnostic agents (59). Fluorescence Nanoprobe used for imaging that was coupled to G5 PAMAM might bind to KB cell lines and treat resistant cervical cancer (64). PAMAM dendrimers coupled with a specific dye for photoacoustic (PA) imaging in medication delivery and therapy have exhibited noteworthy efficacy in absorption and penetration over the BBB. Consequently, investigations have demonstrated the capacity to create photoacoustic images that provide valuable insights into glioblastoma tumors' depth, size, and vascular angiogenesis (65). Fluorescence spectroscopy is an optical modality that employs high luminescence intensity to study cell uptake, among other applications. Various conjugated compositions of gold nanoparticles have been used in numerous applications, such as anticancer medication delivery and fluorescence imaging. The theranostic technique known as PEG-DOX-G4 PAMAM–AuNR has been utilized in colon cancer in a mouse model, demonstrating notable efficacy in inhibiting tumor development and facilitating the administration of drugs (34). A novel theranostic radiopharmaceutical combining dendrimer (PAMAM-G4), folate, and bombazine with gold nanoparticles (AuNPs) has shown hopeful outcomes in nuclear and optical imaging of breast cancer (61). The anticancer drug DOX was conjugated with G3 PAMAM NP has demonstrated high performance in cancer cell induction and could be used as a theranostic agent in photothermal therapy and fluorescence imaging in hepatocellular carcinoma HepG2 cells (44).

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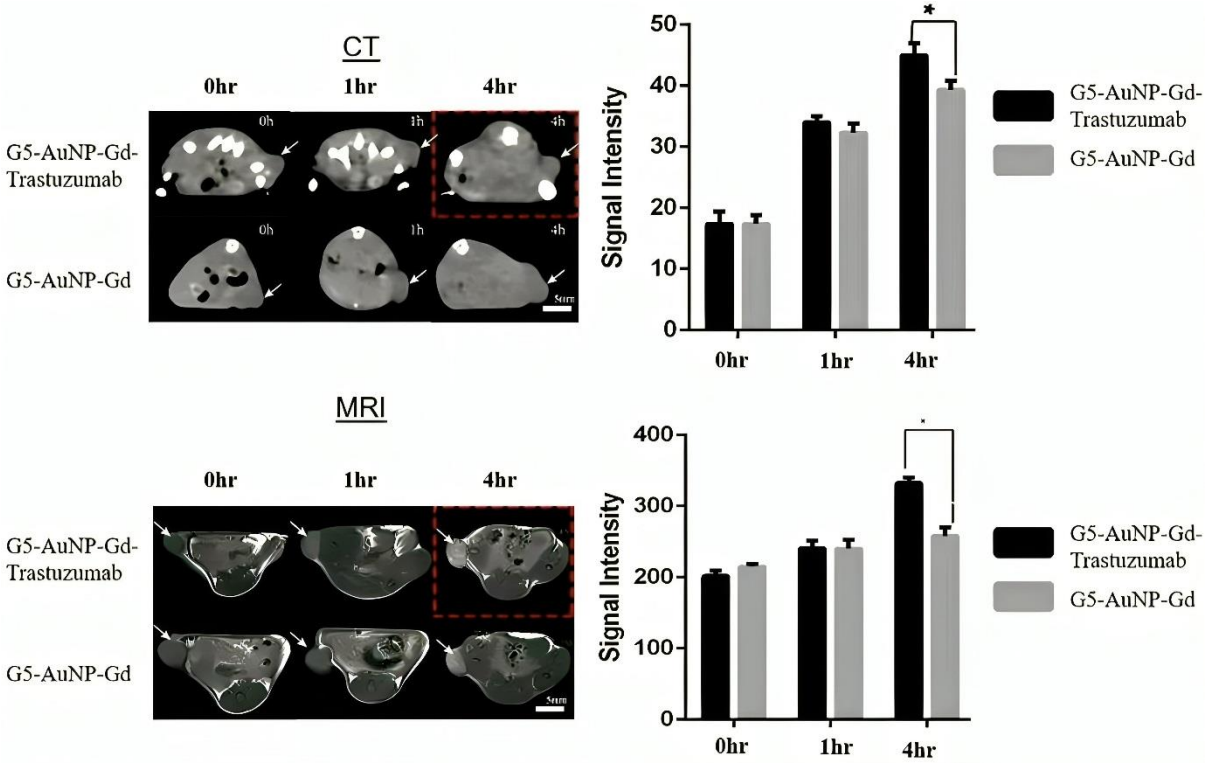

Figure 7. CT & MRI images from BALB/c nude mouse model of tumor-bearing mice inoculated with A549 cells with G5-AuNP-Gd-Trastuzumab (adapted from Chen et al., 2020) (94).

4.3.2. Nuclear imaging

Early cancer identification may be possible with the use of radiological imaging due to its ability to monitor and characterize the biological makeup of cancer cells. PAMAM-dendrimer nanoparticles with radionuclides coupled to them have been exploited as medication delivery and bio-imaging agents because of their strong biocompatibility (66).

4.3.3. SPECT/PET imaging

Nanocomposite can be used in conjunction with a variety of radionuclides in single photon emission computed tomography to demonstrate accumulation and aberrant physiologic processes in malignant tumors (67, 68). Technetium-99 (^{99m}Tc) is the primary radioisotope employed for the purpose of labeling dendrimers in order to facilitate imaging objectives. Using very pure radiochemicals ^{99m}Tc in cancer research involves binding to G5 or G4 PAMAM through direct or indirect strategies. This approach has been employed in many mouse models of cancer, including melanoma and KB-cell lines of adenocarcinomas (69, 70).

A novel approach has been implemented to highlight the effectiveness of powerful PAMAM dendrimers. This involves the incorporation of a labeled $^{111}In/^{68}Ga$ supermolecule, which exhibits noncovalent weak interactions. These interactions have demonstrated excellent efficacy and outstanding performance, making them promising candidates for bio-imaging agents aimed at passive tumor localization (71). Folic acid receptor-modified G2-PAMAM gold nanoparticles, tagged with ^{99m}Tc , have demonstrated potential as a cost-effective nanoprobe for dual SPECT/CT imaging. Notably, these nanoparticles have exhibited intriguing outcomes in both HeLa carcinoma cell lines and mice models (72)

Positron emission tomography (PET) is a nuclear medicine imaging technique that applies radionuclides with short half-lives. While effective in some applications, these radionuclides are associated with limited resolution and are less commonly employed in practice. Incorporating dendrimer-based NPs has the potential to impact the sensitivity of PET imaging and demonstrate promising outcomes in identifying malignant cells. The F-18 radionuclide is widely used in PET imaging because of its high usability. Consequently, researchers have explored many novel approaches to enhance its effectiveness.

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Table 3. An overview of the literature concerning the application of PAMAM dendrimer nanoparticles to cancer imaging

Polymers	Contrast agent/radionuclide	Linkage molecule	Drugs	Cell lines	Imaging modality	Results	Ref
PAMAM G5	FITC	FA-NHAc	Multiwalled carbon nanotubes (MWCNTs)	KB cell/cervical cancer	Optical imaging	Specifically, target cancer cells	(61)
PAMAM G5	Fe3O4 USPIO	Au DSNFs	-	4T1 tumor	MR/CT/PA	Exhibit a near-infrared absorption feature	(56)
PAMAM G5	Cy5.5	RGD- A2AAR agonist (CGS).	-	Glioblastoma	PA imaging	Good result OF PA in orthotopic GB	(62)
PAMAM G4	AuNR	PEG	DOX	Colon carcinoma	CT/Optical imaging	Higher therapeutic and imaging efficacy	(34)
PAMAM G4	Lu77	Folate-bombesin-Au	-	Breast cancer	Nuclear/ Optical imaging	Helpful as an optical and nuclear imaging agent	(58)
PAMAM G3	FITC	PEG-FA	DOX	Liver cancer	Fluorescence microscopy imaging	High performance of NP in FM imaging	(42)
PAMAM G4	Tc-99m	FITC	-	Melanoma	SPECT/Optical imaging	High tumor uptake that allowed tumor imaging	(66)
PAMAM G5	Tc-99m	Ac-PEGFA-DTPA	-	Adenocarcinoma	SPECT	Improves the tumor targeting	(67)
PAMAM	In-111	NOTA	-	Pancreatic cancer	Micro-SPECT	Significantly improved tumor imaging	(68)
PAMAM G2	Tc-99m	FA-AuNP	-	HeLa cells	SPECT/CT	High imaging efficacy	(69)
PAMAM G5	Cu-64	FITC-FA-DOTA	-	Ovarian cancer	PET/Optical imaging	Significant results targeted PET imaging	(72)
PAMAM	Ga-68	AGuIX@NODAGA	-	Glioblastoma	PET/MR	There is great efficacy in PET/MR image-guided radiation therapy.	(73)
PAMAM G5	Cu-64	DOTA-FA-FI		Lung adenocarcinoma	PET	High performance in targeted PET imaging of different types of FR-expressing cancer	(72)
PAMAM	Cu-64	F3	DOX	Breast cancer	PET	High performance in therapeutic and imaging	(72)
PAMAM G4	Zr-89	(DFO)3(Bdiol)110	-	Glioma cells	PET/CT	High cell uptake of radionuclide	(74)
PAMAM G5	PEG-Au	MUC-1 DNA aptamer	Curcumin	Colon adenocarcinoma	CT	Desirable tool for imaging and therapy	(76)
PAMAM G3	AuNs	Arg-Gly-Asp, RGD	-	Glioblastoma	CT/Thermal imaging	High X-ray attenuation	(77)
PAMAM G5	Au DENPs	NHAc-(PEG)14-(Fluo-4)2	-	Activated T cells	CT/FI	A promising role in T-cell activation imaging	(36)
PAMAM G5	DENPs-Au	PEG-Gd-DOTA-FA	-	Breast cancer	CT/MR	High level of attenuated intensity of X-ray and significant r1 relaxivity	(78)
PAMAM G4	Gd2O3	PEG-DTPA	-	Animal cancer cells	MRI	Good contrast agent in T1- and T2 weighted MRI	(79)
PAMAM G6	Gd	DO3A	Cystamine	Breast cancer	MRI	Improve MR contrast between similar textures	(81)

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PAMAM G5	Gd	DOTA-florescent dye		Glioma tumor	MRI/NIR	High accumulation of agents in the glioma tumor	(82)
PAMAM G5	Gd(III)	Au-DENPs	-	Lung cancer	CT/MR	Beneficial nanoprobe for dual-modal CT/MR imaging	(83)
PAMAM G4,5,6	Fe3O4	PDA	DOX	Hepatoma HepG2 cell	MRI	High T2-weighted intensity	(84)
PAMAM	Fe2O3/Au	FA	-	Breast cancer	MRI/CT	Develop both modalities sensitivities to the detection of cancer cells.	(85)
PAMAM G3	Gd-DTPA	PEG-Au-DNGs	RGD	Pancreatic adenocarcinoma	MRI/CT	Novel nanoprobe for specific tumor CT/MR imaging	(86)
PAMAM	SPION	FA	CDF	Cervical cancer	MRI	High T2-intensity contrast agent	(87)
PAMAM G3.5	IONs	FA-PEG	DOX	Breast cancer	MRI	Enhance the effect of T2-weighted MRI contrast	(88)
PAMAM G5	Gd	PEG-Au NP-entrapped CSTDs	RGD	Breast cancer	MRI/CT	Effective for CT/MR dual mode imaging and accurate diagnosis	(89)

Comprehensive studies has been carried out for several years on the process of labeling dendrimers with non-metal radionuclides ^{18}F as well as metal radionuclides ^{64}Cu and ^{68}Ga (73, 74). PET imaging of ovarian cancer cells and epithelial cells with the extension of a recnet labeled PAMAM dendrimer with both ^{64}Cu / ^{68}Ga isotopes as a result of advances in controlling the half-life of metal radionuclides and their application in labeled dendrimer-NPs and imaging is reported (75, 76). The G5-PAMAM dendrimer has been seen to exhibit a high affinity for metal radionuclides, particularly Cu-64, which makes it a commonly utilized agent for tumor cell imaging. The introduction of FA and the application of DOTA chelation in the radiolabeling process of PAMAM with Cu-64 have been shown to exhibit notable biostability in mouse serum. Additionally, this modified PAMAM formulation has demonstrated a high degree of cellular uptake, which can be attributed to the overexpression of folate receptor alpha (FAR) in lung adenocarcinoma tumor cells (75). Unimolecular micelles derived from PAMAM-dendrimers have the potential to employ as dual-purpose agents for medication administration and imaging in the breast cancer. Micelles made from PAMAM could transport both ^{64}Cu (used in PET scans) and DOX (used to treat cancer). The distribution of manufactured radiolabeled nanoprobes in breast carcinoma cells has been observed to be notably high despite their short circulation period (77). A combination of radionuclides and a CT contrast agent might produce a strong result in undetectable tumor cells since PET/CT is a high-resolution combined structural and metabolic imaging application in whole-body imaging. The BBB of a mouse model has been pierced by Zr-89 coupled with G4-PAMAM, which might be used in brain tumor cells (78).

4.3.4. CT

Although Gold nanoparticles have been investigated as contrast agents for years in various CT imaging application, dendrimers have recently garnered more interest due to the potential for modifying new Au-dendrimer nanoparticles for CT contrast agents (12). PAMAM has hopeful promise as a suitable contrast agent for visualizing tumor angiogenesis, owing to its notable attributes of great biostability and strong x-ray attenuation. The PAMAM dendrimer serves as a framework for the improvement of new modified gold dendrimer nanoparticles, which has the potential to employ as a tool for the visualization of imperceptible malignancies such as colorectal cancer (80). In xenograft models of glioblastoma and breast cancer, Au-dendrimers encapsulated with different generations of PAMAM have been characterized as exceptional contrast agents (59, 81). PAMAM dendrimers have been employed as versatile contrast agents for dual-modality imaging in the context of cancer detection. Specifically, PAMAM dendrimers have been utilized for their ability to enhance imaging in both computed tomography/magnetic resonance (CT/MR) and computed tomography/fluorescence (CT/fluorescence) modalities. The results of the study demonstrate that a combination of encapsulation of CT/FI G5-PAMAM dendrimer in gold nanoparticles, which have been modified with PEG and covalently conjugated with fluo-4, can serve as a very effective nanoprobe for detecting activated T cells and

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assessing the likelihood of tumor development (36). A multifunctional nanoprobe, consisting of contrast agent in a dual CT/MR, has been created using G5-PAMAM modified with gadolinium chelate (DOTA). This nanoprobe has been applied in studies on human breast cancer cells in both in vitro and in vivo. The results demonstrate a high level of cellular uptake and favorable biocompatibility (82).

4.3.5. MRI

Dendrimers, a novel category of intelligent nanoprobes, can contain magnetic resonance (MR) contrast agents. These nanoprobes could be uptake in specific population of cells, such as tumor cells, hence enabling their use in tumor distinction, diagnosis, and therapy screening. The initial development of a dendrimer-based nanoparticle involved the use of G4-PAMAM, which was connected to Magnevist, a gadolinium chelates. This nanoparticle exhibited favorable characteristics such as protracted blood circulation duration and reasonable relaxation times in T1 and T2-weighted images. Consequently, it was applied as a dual contrast agent for magnetic resonance imaging in an animal cancer model (83). Nanoparticles based on PAMAM dendrimers have the potential to serve as MRI contrast agents for both T1 and T2 imaging modalities. Gadolinium-based T1-weighted contrast agents are widely used, and their PAMAM-linking has resulted in new theranostic agents (84). Increased blood CA concentration and enhanced MR contrast between breast tissue of different textures have been linked to the use of G6-PAMAM conjugated to cysteamine and encapsulated by Gd-DO3A in breast cancer (85). According to another study, PAMAM-dendrimer conjugated to Gd is an effective agent for glioma tumor MRI assessment, passing BBTB and producing a high-intensity signal (86). PAMAM has been reported to have dual-modality applications in both CT and MRI, as well as MRI and fluorescence. G5 PAMAM and Gd-Au-DENPs have been combined to create a dual (CT/MRI)agent for imaging lung cancer (87). To reduce the toxicity of Gd, ferrite (Fe_3O_4) is often associated with it. As a result, ferrite-coated G4-PAMAM magnetic nanoparticles have been improved as a multi-functional nanoprobe for cancer cell imaging and used as a drug carrier in chemical and photothermal therapies (88). Due to FAR overexpression in the tumor microenvironment, folic acid-conjugated Au/Fe2O3 connected to PAMAM has been launched as a created dual CT/MR contrast agent in the assessment of breast cancer cells (89). In another study, a T1-weighted contrast agent nanogel was improved by conjugating G3 PAMAM with Gd-DTPA. This nanogel was used to identify pancreatic cancer cell lines in a mouse model (90).

Superparamagnetic iron oxide nanoparticles (SPIONs) have emerged as metal-based MR contrast agents, exhibiting enhanced signal intensity in T2-weighted images. Due to their low toxicity profile, SPIONs have gained significant attention and have become increasingly used in both *in vitro* and *in vivo* experimental settings. The covalent attachment of folic acid to PAMAM, together with the incorporation of SPION, holds promise for the detection of elevated expression of FAR and the characterization of enhanced functionality in cervical cancer cells (91). Experimental breast cancer models have shown that a G3.5 PAMAM nanoprobe conjugated to Doxorubicin and SPIONs is an beneficial theranostic agent for both imaging and medication administration (92). Core-shell to dendrimer (CSTD) is the most recent approach to synthesizing multifunctional nanoprobes, and it is the basis for a newly developed nanoprobe consisting of G5-PAMAM encapsulated with Au NP as the core and G3-PAMAM as the shell (93). Breast cancer CT/MR imaging with these newly designed NPs has shown considerable improvement in both modalities (94). Table 3 demonstrate an overview of studies which used in this field.

5. CONCLUSION

PAMAM dendrimers possess several notable characteristics, including a narrow molecular weight distribution, monodispersity, internal cavities, multifunctional terminal surfaces, biocompatibility, resilience, and solubility in aqueous environments. These traits have established PAMAM dendrimers as highly efficient nanocarriers and vectors in the field of nanomedicine. Several studies have demonstrated that the encapsulation of anticancer medications using PAMAM dendrimers has the potential to enhance the solubility of hydrophobic pharmaceuticals, leading to increased accumulation at tumor sites. Also, this encapsulation technique has been found to effectively lower the toxicity associated with these treatments. The capacity to modulate the dimensions of molecules and the potential to attach specific ligands enables the conjugation of these nanoparticles with various medications and ligands, therefore enabling site-specific targeting and delivery of therapeutic agents. Moreover, it is worth noting that these nanoparticles can be linked with fluorescent dyes, enabling their utilization in optical imaging applications. Additionally, the use of these additives enhances the

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sensitivity of PET images in the context of tumor identification.

Furthermore, several investigations have shown evidence that PAMAM dendrimers could form complexes with gold nanoparticles as well as gadolinium and iron-based magnetic contrast agents. This interaction has significantly increased contrast in both CT and MR imaging. Although the studies discussed here have demonstrated favorable outcomes regarding the utilization of PAMAM dendrimers in the preclinical phase for cancer detection and therapy, more investigation is imperative to ascertain their suitability for clinical application.

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Conflict of interests

The authors have no relevant financial or non-financial interests to disclose

References

1. Piñeros M, Mery L, Soerjomataram I, Bray F, Steliarova-Foucher E. Scaling up the surveillance of childhood cancer: a global roadmap. JNCI: Journal of the National Cancer Institute. 2021;113(1):9-15.

2. Schiffman JD, Fisher PG, Gibbs P. Early detection of cancer: past, present, and future. American Society of Clinical Oncology Educational Book. 2015;35(1):57-65.

3. Ott JJ, Ullrich A, Miller AB. The importance of early symptom recognition in the context of early detection and cancer survival. European Journal of Cancer. 2009;45(16):2743-8.

4. Lopez-Campos F, Candini D, Carrasco E, Francés MAB. Nanoparticles applied to cancer immunoregulation. Reports of Practical Oncology & Radiotherapy. 2019;24(1):47-55.

5. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2019. CA: a cancer journal for clinicians. 2019;69(5):363-85.

6. Baker Jr JR. Dendrimer-based nanoparticles for cancer therapy. ASH Education Program Book. 2009;2009(1):708-19.

7. Shreyash N, Sonker M, Bajpai S, Tiwary SK. Review of the mechanism of nanocarriers and technological developments in the field of nanoparticles for applications in cancer theragnostics. ACS Applied Bio Materials. 2021;4(3):2307-34.

8. Karthikeyan L, Sobhana S, Yasothamani V, Gowsalya K, Vivek R. Multifunctional Theranostic Nanomedicines for Cancer Treatment: A Recent Progress and Challenges. Biomedical Engineering Advances. 2023:100082.

9. Ambekar RS, Choudhary M, Kandasubramanian B. Recent advances in dendrimer-based nanoplatform for cancer treatment: A review. European polymer journal. 2020;126:109546.

10. Sampathkumar SG, Yarema KJ. Dendrimers in cancer treatment and diagnosis. Nanotechnologies for the Life Sciences: Online. 2007.

11. Palmerston Mendes L, Pan J, Torchilin VP. Dendrimers as nanocarriers for nucleic acid and drug delivery in cancer therapy. Molecules. 2017;22(9):1401.

12. Fan Y, Sun W, Shi X. Design and Biomedical Applications of Poly (amidoamine)-Dendrimer-Based Hybrid Nanoarchitectures. Small Methods. 2017;1(12):1700224.

13. Bober Z, Bartusik-Aebisher D, Aebisher D. Application of dendrimers in anticancer diagnostics and therapy. Molecules. 2022;27(10):3237.

14. Wang J, Li B, Qiu L, Qiao X, Yang H. Dendrimer-based drug delivery systems: History, challenges, and latest developments. Journal of Biological Engineering. 2022;16(1):1-12.

15. Najafi F, Salami-Kalajahi M, Roghani-Mamaqani H. A review on synthesis and applications of dendrimers. Journal of the Iranian Chemical Society. 2021;18:503-17.

16. Vögtle F, Richardt G, Werner N. Types of Dendrimers and their Syntheses. Dendrimer Chemistry: Concepts, Syntheses, Properties, Applications. 2009:81-167.

17. Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. Progress in Polymer Science. 2014;39(2):268-307.

18. Kaurav M, Ruhi S, Al-Goshae HA, Jeppu AK, Ramachandran D, Sahu RK, et al. Dendrimer: An update on recent developments and future opportunities for the brain tumors diagnosis and treatment. Frontiers in pharmacology. 2023;14:1159131.

19. Kaur D, Jain K, Mehra NK, Kesharwani P, Jain NK. A review on comparative study of PPI and PAMAM dendrimers. Journal of Nanoparticle Research. 2016;18:1-14.

20. Tripathy S, Das MK. Dendrimers and their applications as novel drug delivery carriers. Journal of Applied Pharmaceutical Science. 2013;3(9):142-9.

21. Kaurav M, Ruhi S, Al-Goshae HA, Jeppu AK, Ramachandran D, Sahu RK, et al. Dendrimer: An update on recent developments and future opportunities for the brain tumors diagnosis and treatment. (1663-9812 (Print)).

22. Patri AK, Majoros IJ, Baker Jr JR. Dendritic polymer macromolecular carriers for drug delivery. Current opinion in chemical biology. 2002;6(4):466-71.

23. Lyu Z, Ding L, Huang A-T, Kao C-L, Peng L. Poly (amidoamine) dendrimers: Covalent and supramolecular synthesis. Materials Today Chemistry. 2019;13:34-48.

24. Kharwade R, More S, Warokar A, Agrawal P, Mahajan N. Starburst pamam dendrimers: Synthetic approaches, surface modifications, and biomedical applications. Arabian Journal of Chemistry. 2020;13(7):6009-39.

25. Sebestik J, Reinis M, Jezek J, Šebestik J, Reiniš M, Ježek J. Synthesis of dendrimers: Convergent and divergent approaches. Biomedical Applications of Peptide-, Glyco-and Glycopeptide Dendrimers, and Analogous Dendrimeric Structures. 2012:55-81.

[DOI: 10.61186/ijbc.16.4.86]

26. Santos AA-O, Veiga F, Figueiras AA-O. Dendrimers as Pharmaceutical Excipients: Synthesis, Properties, Toxicity and Biomedical Applications. LID - 10.3390/ma13010065 [doi] LID - 65. (1996-1944 (Print)).

27. Mittal P, Saharan A, Verma R, Altalbawy F, Alfaidi MA, Batiha GE-S, et al. Dendrimers: a new race of pharmaceutical nanocarriers. BioMed Research International. 2021;2021.

28. Li D, Lin L, Fan Y, Liu L, Shen M, Wu R, et al. Ultrasound-enhanced fluorescence imaging and chemotherapy of multidrug-resistant tumors using multifunctional dendrimer/carbon dot nanohybrids. Bioactive materials. 2021;6(3):729-39.

29. Abedi-Gaballu F, Dehghan G, Ghaffari M, Yekta R, Abbaspour-Ravasjani S, Baradaran B, et al. PAMAM dendrimers as efficient drug and gene delivery nanosystems for cancer therapy. Applied materials today. 2018;12:177-90.

30. Liu Y, K Tee J, NC Chiu G. Dendrimers in oral drug delivery application: current explorations, toxicity issues and strategies for improvement. Current pharmaceutical design. 2015;21(19):2629-42.

31. Braun CS, Vetro JA, Tomalia DA, Koe GS, Koe JG, Middaugh CR. Structure/function relationships of polyamidoamine/DNA dendrimers as gene delivery vehicles. Journal of pharmaceutical sciences. 2005;94(2):423-36.

32. Malik N, Duncan R, Tomalia DA, Esfand R. Dendritic-antineoplastic drug delivery system. Google Patents; 2006.

33. Cruz A, Barbosa J, Antunes P, Bonifácio VD, Pinto SN. A Glimpse into Dendrimers Integration in Cancer Imaging and Theranostics. International Journal of Molecular Sciences. 2023;24(6):5430.

34. Li X, Takashima M, Yuba E, Harada A, Kono K. PEGylated PAMAM dendrimer–doxorubicin conjugate-hybridized gold nanorod for combined photothermal-chemotherapy. Biomaterials. 2014;35(24):6576-84.

35. Carvalho MR, Carvalho CR, Maia FR, Caballero D, Kundu SC, Reis RL, et al. Peptide-Modified Dendrimer Nanoparticles for Targeted Therapy of Colorectal Cancer. Advanced Therapeutics. 2019;2(11):1900132.

36. Chen M, Betzer O, Fan Y, Gao Y, Shen M, Sadan T, et al. Multifunctional dendrimer-entrapped gold nanoparticles for labeling and tracking T cells via dual-modal computed tomography and fluorescence imaging. Biomacromolecules. 2020;21(4):1587-95.

37. Marcinkowska M, Sobierajska E, Stanczyk M, Janaszewska A, Chworos A, Klajnert-Maculewicz B. Conjugate of PAMAM dendrimer, doxorubicin and monoclonal antibody—trastuzumab: the new approach of a well-known strategy. Polymers. 2018;10(2):187.

38. Ma J, Yao H. Dendrimer-paclitaxel complexes for efficient treatment in ovarian cancer: study on OVCAR-3 and HEK293T cells. Acta Biochimica Polonica. 2018;65(2):219-25.

39. Zeqiri B, Hodnett M, Carroll AJ. Studies of a novel sensor for assessing the spatial distribution of cavitation activity within ultrasonic cleaning vessels. Ultrasonics. 2006;44(1):73-82.

40. Lin L, Fan Y, Gao F, Jin L, Li D, Sun W, et al. UTMD-promoted co-delivery of gemcitabine and miR-21 inhibitor by dendrimer-entrapped gold nanoparticles for pancreatic cancer therapy. Theranostics. 2018;8(7):1923.

41. Laheru D, Jaffee EM. Immunotherapy for pancreatic cancer—science driving clinical progress. Nature Reviews Cancer. 2005;5(6):459-67.

42. Xu L, Kittrell S, Yeudall WA, Yang H. Folic acid-decorated polyamidoamine dendrimer mediates selective uptake and high expression of genes in head and neck cancer cells. Nanomedicine. 2016;11(22):2959-73.

43. Xu X, Li J, Han S, Tao C, Fang L, Sun Y, et al. A novel doxorubicin loaded folic acid conjugated PAMAM modified with borneol, a nature dual-functional product of reducing PAMAM toxicity and boosting BBB penetration. European Journal of Pharmaceutical Sciences. 2016;88:178-90.

44. Grześkowiak BF, Maziukiewicz D, Kozłowska A, Kertmen A, Coy E, Mrówczyński R. Polyamidoamine dendrimers decorated multifunctional polydopamine nanoparticles for targeted chemo-and photothermal therapy of liver cancer model. International Journal of Molecular Sciences. 2021;22(2):738.

45. Han S, Zheng H, Lu Y, Sun Y, Huang A, Fei W, et al. A novel synergetic targeting strategy for glioma therapy employing borneol combination with angiopep-2-modified, DOX-loaded PAMAM dendrimer. Journal of drug targeting. 2018;26(1):86-94.

46. Lu Y, Han S, Zheng H, Ma R, Ping Y, Zou J, et al. A novel RGDyC/PEG co-modified PAMAM dendrimer-loaded arsenic trioxide of glioma targeting delivery system. International journal of nanomedicine. 2018:5937-52.

47. Gaitsch H, Hersh AM, Alomari S, Tyler BM. Dendrimer Technology in Glioma: Functional Design and Potential Applications. Cancers. 2023;15(4):1075.

48. Dubey SK, Kali M, Hejmady S, Saha RN, Alexander A, Kesharwani P. Recent advances of dendrimers as multifunctional nano-carriers to combat breast cancer. European Journal of Pharmaceutical Sciences. 2021;164:105890.

49. Sunoqrot S, Bugno J, Lantvit D, Burdette JE, Hong S. Prolonged blood circulation and enhanced tumor accumulation of folate-targeted dendrimer-polymer hybrid nanoparticles. Journal of controlled release. 2014;191:115-22.

50. Camacho C, Maciel D, Tomás H, Rodrigues J. Biological Effects in Cancer Cells of Mono-and Bidentate Conjugation of Cisplatin on PAMAM Dendrimers: A Comparative Study. Pharmaceutics. 2023;15(2):689.

51. Torres-Pérez SA, Ramos-Godínez MdP, Ramón-Gallegos E, editors. Effect of methotrexate conjugated PAMAM dendrimers on the viability of breast cancer cells. AIP Conference Proceedings; 2019: AIP Publishing.

52. Xu X, Li Y, Lu X, Sun Y, Luo J, Zhang Y. Glutaryl polyamidoamine dendrimer for overcoming cisplatin-resistance of breast cancer cells. Journal of Nanoscience and Nanotechnology. 2018;18(10):6732-9.

53. Nabavizadeh F, Fanaei H, Imani A, Vahedian J, Amoli FA, Ghorbi J, et al. Evaluation of nanocarrier targeted drug delivery of Capecitabine-PAMAM dendrimer complex in a mice colorectal cancer model. Acta Medica Iranica. 2016:485-93.

[DOI: 10.61186/ijbc.16.4.86]

54. Hao Y, Gao Y, Fan Y, Zhang C, Zhan M, Cao X, et al. A tumor microenvironment-responsive poly (amidoamine) dendrimer nanoplatform for hypoxia-responsive chemo/chemodynamic therapy. Journal of Nanobiotechnology. 2022;20(1):1-15.

55. Song X, Sun Z, Li L, Zhou L, Yuan S. Application of nanomedicine in radiotherapy sensitization. Frontiers in Oncology. 2023;13:1088878.

56. Saluja V, Mishra Y, Mishra V, Giri N, Nayak P. Dendrimers based cancer nanotheranostics: An overview. International Journal of Pharmaceutics. 2021;600:120485.

57. Zhu J, Zhao L, Cheng Y, Xiong Z, Tang Y, Shen M, et al. Radionuclide 131 I-labeled multifunctional dendrimers for targeted SPECT imaging and radiotherapy of tumors. Nanoscale. 2015;7(43):18169-78.

58. Zhao L, Zhu J, Cheng Y, Xiong Z, Tang Y, Guo L, et al. Chlorotoxin-conjugated multifunctional dendrimers labeled with radionuclide 131I for single photon emission computed tomography imaging and radiotherapy of gliomas. ACS Applied Materials & Interfaces. 2015;7(35):19798-808.

59. Lu S, Li X, Zhang J, Peng C, Shen M, Shi X. Dendrimer-stabilized gold nanoflowers embedded with ultrasmall iron oxide nanoparticles for multimode imaging–guided combination therapy of tumors. Advanced Science. 2018;5(12):1801612.

60. Kobayashi H, Sato N, Saga T, Nakamoto Y, Ishimori T, Toyama S, et al. Monoclonal antibody-dendrimer conjugates enable radiolabeling of antibody with markedly high specific activity with minimal loss of immunoreactivity. European journal of nuclear medicine. 2000;27:1334-9.

61. Mendoza-Nava H, Ferro-Flores G, Ramírez FdM, Ocampo-García B, Santos-Cuevas C, Aranda-Lara L, et al. 177 Lu-dendrimer conjugated to folate and bombesin with gold nanoparticles in the dendritic cavity: a potential theranostic radiopharmaceutical. Journal of Nanomaterials. 2016;2016.

62. Hosseini SM, Mohammadnejad J, Salamat S, Zadeh ZB, Tanhaei M, Ramakrishna S. Theranostic polymeric nanoparticles as a new approach in cancer therapy and diagnosis: a review. Materials Today Chemistry. 2023;29:101400.

63. Hu Z, Chen W-H, Tian J, Cheng Z. NIRF nanoprobes for cancer molecular imaging: approaching clinic. Trends in Molecular medicine. 2020;26(5):469-82.

64. Shi X, Wang SH, Shen M, Antwerp ME, Chen X, Li C, et al. Multifunctional dendrimer-modified multiwalled carbon nanotubes: synthesis, characterization, and in vitro cancer cell targeting and imaging. Biomacromolecules. 2009;10(7):1744-50.

65. Liu L, Chen Q, Wen L, Li C, Qin H, Xing D. Photoacoustic therapy for precise eradication of glioblastoma with a tumor site blood–brain barrier permeability upregulating nanoparticle. Advanced Functional Materials. 2019;29(11):1808601.

66. Zhao L, Zhu M, Li Y, Xing Y, Zhao J. Radiolabeled dendrimers for nuclear medicine applications. Molecules. 2017;22(9):1350.

67. Uehara T, Yokoyama M, Suzuki H, Hanaoka H, Arano Y. A gallium-67/68–labeled antibody fragment for immuno-SPECT/PET shows low renal radioactivity without loss of tumor uptake. Clinical Cancer Research. 2018;24(14):3309-16.

68. Xiao T, Li D, Shi X, Shen M. PAMAM Dendrimer-Based Nanodevices for Nuclear Medicine Applications. Macromolecular Bioscience. 2020;20(2):1900282.

69. Tassano MR, Audicio PF, Gambini JP, Fernandez M, Damian JP, Moreno M, et al. Development of 99mTc (CO) 3-dendrimer-FITC for cancer imaging. Bioorganic & medicinal chemistry letters. 2011;21(18):5598-601.

70. Zhang Y, Sun Y, Xu X, Zhang X, Zhu H, Huang L, et al. Synthesis, biodistribution, and microsingle photon emission computed tomography (SPECT) imaging study of technetium-99m labeled PEGylated dendrimer poly (amidoamine)(PAMAM)− folic acid conjugates. Journal of medicinal chemistry. 2010;53(8):3262-72.

71. Ding L, Lyu Z, Tintaru A, Laurini E, Marson D, Louis B, et al. A self-assembling amphiphilic dendrimer nanotracer for SPECT imaging. Chemical Communications. 2020;56(2):301-4.

72. Li X, Xiong Z, Xu X, Luo Y, Peng C, Shen M, et al. 99mTc-labeled multifunctional low-generation dendrimer-entrapped gold nanoparticles for targeted SPECT/CT dual-mode imaging of tumors. ACS applied materials & interfaces. 2016;8(31):19883-91.

73. Trembleau L, Simpson M, Cheyne RW, Escofet I, Appleyard MVCAL, Murray K, et al. Development of 18 F-fluorinatable dendrons and their application to cancer cell targeting. New Journal of Chemistry. 2011;35(11):2496-502.

74. Werner RA, Chen X, Lapa C, Koshino K, Rowe SP, Pomper MG, et al. The next era of renal radionuclide imaging: novel PET radiotracers. European journal of nuclear medicine and molecular imaging. 2019;46:1773-86.

75. Ma W, Fu F, Zhu J, Huang R, Zhu Y, Liu Z, et al. 64 Cu-Labeled multifunctional dendrimers for targeted tumor PET imaging. Nanoscale. 2018;10(13):6113-24.

76. Bouziotis P, Stellas D, Thomas E, Truillet C, Tsoukalas C, Lux F, et al. 68Ga-radiolabeled AGuIX nanoparticles as dual-modality imaging agents for PET/MRI-guided radiation therapy. Nanomedicine. 2017;12(13):1561-74.

77. Yang J, Lu W, Xiao J, Zong Q, Xu H, Yin Y, et al. A positron emission tomography image-guidable unimolecular micelle nanoplatform for cancer theranostic applications. Acta Biomaterialia. 2018;79:306-16.

78. Lee JH, Kim GG, Kim SW, Park J-H. Zr-89 Labeled PAMAM Dendrimers 5G without a Chelator for a Cancer Diagnostic Agent. Journal of the Korean Physical Society. 2020;77:409-13.

79. Xing Y, Zhu J, Zhao L, Xiong Z, Li Y, Wu S, et al. SPECT/CT imaging of chemotherapy-induced tumor apoptosis using (99m)Tc-labeled dendrimer-entrapped gold nanoparticles. (1521-0464 (Electronic)).

80. Alibolandi M, Hoseini F, Mohammadi M, Ramezani P, Einafshar E, Taghdisi SM, et al. Curcumin-entrapped MUC-1 aptamer targeted dendrimer-gold hybrid nanostructure as a theranostic system for colon adenocarcinoma. International journal of pharmaceutics. 2018;549(1-2):67-75.

81. Wei P, Chen J, Hu Y, Li X, Wang H, Shen M, et al. Dendrimer-Stabilized gold nanostars as a multifunctional theranostic nanoplatform for CT imaging, photothermal therapy, and gene silencing of tumors. Advanced healthcare materials. 2016;5(24):3203-13.

[DOI: 10.61186/ijbc.16.4.86]

82. Chen Q, Li K, Wen S, Liu H, Peng C, Cai H, et al. Targeted CT/MR dual mode imaging of tumors using multifunctional dendrimer-entrapped gold nanoparticles. Biomaterials. 2013;34(21):5200-9.

83. Mekuria SL, Debele TA, Tsai H-C. Encapsulation of gadolinium oxide nanoparticle (Gd2O3) contrasting agents in PAMAM dendrimer templates for enhanced magnetic resonance imaging in vivo. ACS applied materials & interfaces. 2017;9(8):6782-95.

84. Markowicz-Piasecka M, Sikora J, Szymański P, Kozak O, Studniarek M, Mikiciuk-Olasik E. PAMAM Dendrimers as Potential Carriers of Gadolinium Complexes of Iminodiacetic Acid Derivatives for Magnetic Resonance Imaging. Journal of Nanomaterials. 2015;2015:394827.

85. Xu R, Wang Y, Wang X, Jeong E-K, Parker DL, Lu Z-R. In vivo evaluation of a PAMAM-cystamine-(Gd-DO3A) conjugate as a biodegradable macromolecular MRI contrast agent. Experimental Biology and Medicine. 2007;232(8):1081-9.

86. Karki K, Ewing JR, Ali MM. Targeting glioma with a dual mode optical and paramagnetic nanoprobe across the blood-brain tumor barrier. Journal of nanomedicine & nanotechnology. 2016;7(4).

87. Liu J, Xiong Z, Zhang J, Peng C, Klajnert-Maculewicz B, Shen M, et al. Zwitterionic Gadolinium(III)-Complexed Dendrimer-Entrapped Gold Nanoparticles for Enhanced Computed Tomography/Magnetic Resonance Imaging of Lung Cancer Metastasis. ACS Applied Materials & Interfaces. 2019;11(17):15212-21.

88. Jędrzak A, Grześkowiak BF, Coy E, Wojnarowicz J, Szutkowski K, Jurga S, et al. Dendrimer based theranostic nanostructures for combined chemo-and photothermal therapy of liver cancer cells in vitro. Colloids and Surfaces B: Biointerfaces. 2019;173:698-708.

89. Jamshidi N, Tarighatnia A, Ghaziyani MF, Sajadian F, Nader ND. Folic acid-conjugated Fe-Au-based nanoparticles for dual detection of breast cancer cells by magnetic resonance imaging and computed tomography. Frontiers in Biomedical Technologies. 2023.

90. Xu X, Xiao T, Zhang C, Wang Z, Li G, Chen J, et al. Multifunctional Low-Generation Dendrimer Nanogels as an Emerging Probe for Tumor-Specific CT/MR Dual-Modal Imaging. Biomacromolecules. 2023;24(2):967-76.

91. Luong D, Sau S, Kesharwani P, Iyer AK. Polyvalent folate-dendrimer-coated iron oxide theranostic nanoparticles for simultaneous magnetic resonance imaging and precise cancer cell targeting. Biomacromolecules. 2017;18(4):1197-209.

92. Chang Y, Liu N, Chen L, Meng X, Liu Y, Li Y, et al. Synthesis and characterization of DOX-conjugated dendrimer-modified magnetic iron oxide conjugates for magnetic resonance imaging, targeting, and drug delivery. Journal of Materials Chemistry. 2012;22(19):9594-601.

93. Liu R, Guo H, Ouyang Z, Fan Y, Cao X, Xia J, et al. Multifunctional core–shell tecto dendrimers incorporated with gold nanoparticles for targeted dual mode CT/MR imaging of tumors. ACS Applied Bio Materials. 2021;4(2):1803-12.

94. Chen JS, Chen J, Bhattacharjee S, Cao Z, Wang H, Swanson SD, et al. Functionalized nanoparticles with targeted antibody to enhance imaging of breast cancer in vivo. (1477-3155 (Electronic)).

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