Functionalized Dendrimers: Promising Nanocarriers for Theranostic Applications

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Abstract

"Nanotheranostic" is an integrative approach to achieve diagnosis and therapeutic effect simultaneously, using nanocarriers. Nanotheranostic platform can be engineered to overcome biological barriers, to target the therapeutic agent at the required locus, and to support the monitoring of drug delivery. Dendrimers are well-defined 3D globular nanoarchitectured monodisperse system, pliable to precise size control and surface modification, which could serve as a potential nanotheranostic platform to achieve image-guided therapy, distribution monitoring, and drug targeting. Dendrimers exhibit biodegradable, biocompatible, and stimuli-responsive features that could ensure the anticipated biodistribution and efficacy. In this chapter, the utility of dendrimer as a theranostic nanoplatform embodying diversified category of therapeutic, imaging, and targeting moieties has been explored. Dendrimer-based administration of imaging agents (magnetic resonance imaging, computed tomography, single-photon emission computed tomography) along with its application in chemotherapy, pharmacodynamics therapy, and gene therapy has also been discussed.

Keywords

Dendrimers · Theranostics · Chemotherapy · Computed tomography · Magnetic resonance imaging

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K. Jain, N. K. Jain (eds.), *Multifunctional And Targeted Theranostic Nanomedicines*,
https://doi.org/10.1007/978-981-99-0538-6_8

Abbreviations

AuDENPs	Dendrimer-entrapped gold nanoparticles
CNTs	Carbon nanotubes
CT	Computed tomography
DANPs	Dendrimer-assembled nanoparticles
DENPs	Dendrimer-entrapped nanoparticles
DIONPs	Dendrimer-based iron oxide nanoparticles
DOTA	1,4,7,10-Tetraazacyclododecane-N,N′,N′′,N′′′-tetra-acetic acids
DOX	Doxorubicin
DSNPs	Dendrimer-stabilized nanoparticles
DTPA	Asdi-ethylenetriamine-penta-acetic acid
EPR	Enhanced permeation and retention effect
FA	Folic Acid
FMT	Fluorescence molecular tomography
FOI	Fluorescence optical imaging
IONPs	Iron oxide nanoparticles
LHRH	Luteinizing hormone-releasing hormone
MDR	Multidrug resistance
MRI	Magnetic resonance imaging
NIR	Near-infrared radiation
NPs	Nanoparticles
NRs	Nanorods
PAMAM	Polyamidoamine dendrimer
Pc	Phthalocyanine
PDT	Photodynamic therapy
PEG	Polyethylene glycol
PET	Positron emission tomography
PLL	Poly-L-lysine
PPI	Polypropylenimine dendrimer
PTT	Photothermal therapy
RGD	Arg-Gly-Asp
SiNc	Silicon naphthalocyanine
SPECT	Single-photon emission computed tomography
SPIONs	Superparamagnetic iron nanoparticles
TOS	α-Tocopheryl succinate
TPGS	D-α-tocopherol polyethylene glycol 1000 succinate

8.1 Introduction

The word "theranostics" was introduced by Funkhouser in 2002, which unifies the modalities of treatment and diagnostic imaging, comprising the benefits of diagnosis and treatment of the disease simultaneously (Funkhouser 2002). Theranostic nanostructures enable the monitoring of biodistribution and performance of the drug along with the imaging of target tissue. Diseases can be tracked closely and cured at the same time via these "theranostic" nanosystems (McCarthy and Weissleder 2008). The theranostic system utilizes appropriate molecular probe to measure the cellular biological operation noninvasively for disease characterization. Theranostic nanoparticles (NPs) can be engineered suitably to provide a single platform to achieve passive or active targeting, molecular imaging, and stimuli-responsive controlled drug release, simultaneously (Bagre et al. 2022). Although the term was adopted recently, the concept it represents have been well explored till now in the field of molecular biology, immunology, and cancer therapy. The theranostics can also be defined based on the utilization of diagnostic tools in clinical decision-making.

Several nanosystems have been investigated till now to achieve the targeted delivery of theranostics, i.e., liposomes, micelles, nanocrystals, solid lipid NPs, graphene oxide, and dendrimers (Fig. 8.1a) (Jain et al. 2020; Juneja et al. 2022). The engineering of functionalized nanotheranostic is complicated due to the obstacles like inherent toxicity of the nanocarrier components, production cost, nanosystems' stability, and intellectual property control. Theranostics nanosystem contains two different entities, i.e., diagnostic agent and therapeutic component. The

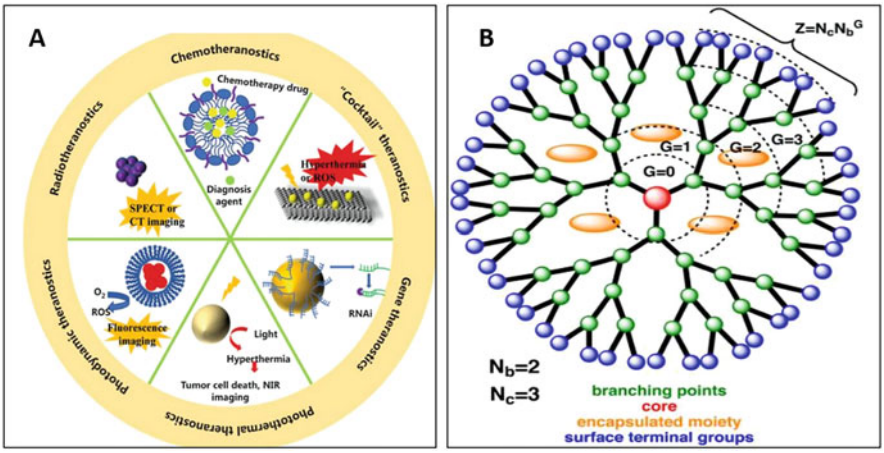

Fig. 8.1 (**a**). Schematic representation of theranostic nanosystems for cancer therapy (Xue et al. 2021). (**b**) Dendrimer with core (red), branching sites (green), surface terminal moieties (blue), and incorporated therapeutic agent. Dotted boundaries signifying generation (G) and N_c indicating the number of branches emerging from the core, while N_b represents the multiplicity of branch cell (Ray et al. 2018)

Table 8.1 Features of diagnostic modalities

Imaging modalities	Probe	Advantages	Disadvantage
FOI	Fluorescent dyes, quantum dots	High sensitivity, no exposure of radiation, provides functional information	Limited tissue penetration and low resolution
CT	Heavy elements (iodine)	High spatial resolution, ability of tissue differentiation	High cost
MRI	Para- and superparamagnetic metals (Mn, Gd)	High-resolution imaging of physiological and anatomical elements	Cannot be used in patients' metallic devices (with pacemakers)
Ultrasound	Gas-filled microbubbles	Noninvasive and easy procedure	Low resolution
Gamma scintigraphy	Radionuclides	Can image biological processes	Radiation and low resolution

diagnostic agent provides rapid, high-fidelity glimpse of precise locus by enhancing the signal-to-noise ratio with respect to adjacent tissues. Depending upon the clearance kinetics of the contrast agent, low or high molecular weight agents are used. The efficient theranostic agent have some give and take between controlled drug release, imaging sensitivity, and targeting accuracy. Various modalities that have been utilized for imaging in theranostics are fluorescence optical imaging (FOI), magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), single-photon emission computed tomography (SPECT), gamma scintigraphy, and ultrasound. Each diagnostic modality has its characteristic feature with relative advantages and disadvantages (Table 8.1) (Saluja et al. 2021).

Dendrimers have emerged as a unique class of 3D nanoarchitectured macromolecule offering surface functionality that can be structured precisely to achieve high degree of molecular uniformity (Fig. 8.1b). Dendrimers may be considered as the ideal vectors for therapeutic agents and imaging modalities as they offer many advantages as compared to other delivery system, i.e., strong surface functionalization, high structural homogeneity, higher cell membrane penetration, higher water solubility with adequate surface functionalization, and high drug loading capacity (Jain 2017; Jain 2018; Gauro et al. 2021a). Drug may interact with the dendrimers via physical encapsulation, electrostatic interactions, or covalent conjugation (Gauro et al. 2021a). However, the translational issues comprising good manufacturing practices and high cost of production are major drawback for dendrimers (Mignani et al. 2021). Yet, the advantages of dendrimers as a versatile delivery system have contributed to its enormous development in the field of nanomedicine for drugs, gene, peptides, and diagnostic agents (Jain and Ahmad 2022).

In this chapter, the utility of dendritic polymer as nanotheranostic platform has been discussed. The dendrimers are well-suited for the theranostic application due to

the (a) presence of modifiable exterior, which can be surface-modified with targeting moieties, (b) improved plasma circulation time and physiochemical properties, and (c) conjugation and encapsulation of contrast and therapeutic agents at predetermined proportions (Bhavana et al. 2021). Further, we will also discuss about dendritic nanoplatform integrating imaging and therapeutic agent and its utility in disease management.

8.2 Dendrimer-Based Molecular Imaging

Various types of dendrimers are available such as polyamidoamine (PAMAM), polypropylenimine (PPI), poly-L-lysine (PLL), glycodendrimer, or metallodendrimer (Gauro et al. 2021b). The surface groups of dendrimers such as carboxyl group, alcohol groups, or amine groups determine the chemical characteristic of dendrimers. The abundance of functional groups over the dendrimers' exterior surface provides optimal attachment sites for targeting ligand for site-specific targeting. The ability to attach both diagnostic and therapeutic agent simultaneously has propelled the utility of dendrimers for the development of nanotheranostic devices. The compliance of dendrimeric contrast agents is appropriate for molecular imaging of target-specific locus (Longmire et al. 2008).

"Molecular imaging" is a noninvasive imaging technique, where the biological processes at the molecular level can be visualized, quantified, and characterized. Molecular imaging methods assists in the estimation of therapeutic response, drug release monitoring, and drug biodistribution quantification (Dasgupta et al. 2020). Figure 8.2 shows the systematic representation of drug release from functionalized nanotheranostic dendrimer in tumor cells. The techniques used for imaging are MRI, CT, PET, SPECT, and FOI. Each technique represents diverse anatomical and molecular imaging information based on the specific attributes it confers, such as sensitivity and specificity. Among these techniques, CT and MRI are utilized to obtain morphological information, while PET and SPECT are used to obtain molecular information (Janib et al. 2010).

In the following sections, dendrimer-based single and multi-model techniques have been focused. The utility of dendrimer-based theranostic techniques to predict the therapeutic response and disease progression imaging has also been discussed.

8.2.1 Dendrimer-Based MRI

MRI is a noninvasive molecular imaging modality, which utilizes strong magnetic field and radio waves. MRI can be used to visualize the anatomical morphology, tumor diagnosis, and treatment monitoring. Pharmacokinetic and biodistribution analysis as well as drug release studies can be estimated by using this technique (Zheng et al. 2019). The uniform orientation of magnetically active nuclei and relaxation in the applied magnetic field generates the signal to create MR images. Specific endogenous contrast image is generated for specific tissues as different

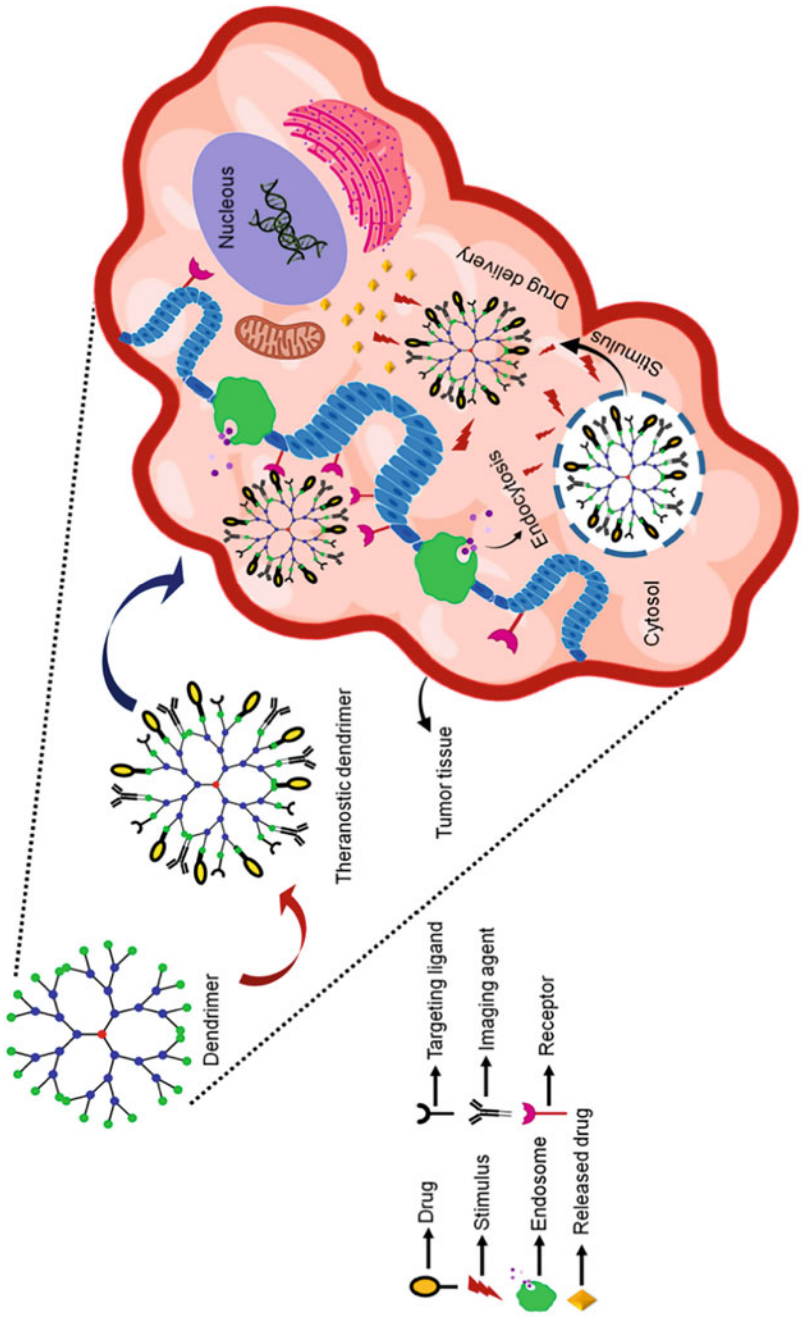

Fig. 8.2 Diagrammatical representation of functionalized nanotheranostic dendrimer (Saluja et al. 2021)

tissue relax at different rates. The time taken for the protons to relax entirely is measured in two ways, i.e., spin-lattice (T1) and spin-spin (T2) relaxation time.

The contrast modalities of MRI are classified as T1 positive, for instance, gadolinium (Gd) chelates, which accelerate the longitudinal relaxation rate and produce brighter image, and T2 negative, which includes superparamagnetic iron that provides darker signal in T2 images by facilitating transverse relaxation rate. Paramagnetic agents such as Gd or manganese can be labeled onto the nanocarrier, while iron oxide nanosystem are innately superparamagnetic that can be tagged over nanocarriers' surface (Shu et al. 2021; Ahmad et al. 2022). The ligand employed in Gd complexes are macrocyclic polyamino carboxylates such as asdi-ethylenetriamine-penta-acetic acid (DTPA) and 1,4,7,10-tetraazacyclododecane-N, N′,N′′,N′′′-tetra-acetic acids (DOTA) (Yan and Zhuo 2001). Superparamagnetic iron nanoparticles (SPIONs) have been explored extensively for imaging contrast enhancement in dendrimer-based MRI.

The longitudinal relaxation of MRI contrast agents determines their efficiency. It was reported that water proton longitudinal relaxation rates, which determines the efficiency of MRI contrast agent, escalate with an increase in dendrimeric generation. The rotational correlation time increases with the increasing molecular mass of dendrimers, which causes increased relaxivity of dendrimers with generation. The terminal functional groups of dendrimers attach covalently with the Gd^{3+} chelates, which upsurges the relaxation rates. Relaxation rates of the contrast agents increases with the increase in the dendrimeric generation and number of terminal functional groups, which leads to improved efficiency (Song et al. 2020). Various dendrimer-based MRI have been mentioned in Table 8.2**.**

To fabricate advanced biocompatible contrast agent, dendrimer-based iron oxide nanoparticles (DIONPs) are being employed for T2-weighted MRI to obtain in vivo diagnostic imaging. The DIONPs can be classified as dendrimer-assembled nanoparticles (DANPs) and dendrimer-stabilized nanoparticles (DSNPs). The DANPs are designed via assembly of dendrimers and pre-developed NPs, which are ruled by electrostatic interactions or covalent bonding. The IONPs can be fabricated and coated with multiple dendrimers simultaneously for stabilization in DSNP. The interaction between dendrimers and NPs plays an important role in stabilization (Strable et al. 2001). Researchers developed DSNP via solgel method, covalent conjugation, and physical absorption to obtain a theranostic nanocarrier for doxorubicin (DOX) delivery. Dendrimers were conjugated with targeting peptides GX1 and RGD to achieve receptor-mediated targeted delivery at vascular endothelial growth factor and αvβ3 integrins, respectively. Further, superparamagnetic IONP coated with dendrigraft of lysine was utilized as an MRI contrast agent. The conjugate showed significant antitumor activity and efficient biodistribution in HepG2 tumor-bearing Balb/c mice (Shen et al. 2017). The varied applications of dendrimeric theranostic nanostructures are attributed to the characteristics such as size flexibility, surface modification, and low toxicity.

Table 8.2 Dendrimer-based MRI contrast agents

MRI contrast agent	Dendrimeric nanoconjugate	Dendrimers	Targeting ligand	Uptake studies	Application	References
Copper (II)	G3.0-Cu	G3.0 phosphorus dendrimer	Ultrasound-targeted microbubble destruction	Mice	Pancreatic cancer	Fan et al. (2019)
DOTA-Gd	RGD-Gd-Au-G5.0-PAMAM	G5.0 PAMAM dendrimer	RGD (Arg-Gly-Asp) peptide for αvβ3 integrins expressing tumor cells	Mice	Lung cancer	Liu et al. (2019)
Manganese (II)	RGD-Au-Mn-G2.0-PAMAM	G2.0 PAMAM dendrimer	RGD peptide	Mice	Brain glioma	Xu et al. (2019)
SPIONs	G4.0-IONPs	G4.0 PAMAM dendrimer	–	MCF_7 and HDF_1 cell line	Breast cancer	Salimi et al. (2018)
SPIONs	SPION-FA-G4.0-PAMAM-curcumin	G4.0 PAMAM dendrimer	Folic acid (FA) to target folate receptors overexpressed over carcinoma cell surface	SKOV3 and HeLa cancer cells	Ovarian and cervical cancer	Luong et al. (2017)
SPIONs	FA-PEG-G3.5-PPI-PTX@IONP	G3.5 PPI dendrimer	FA	Mice	Liver cancer	Chang et al. (2013)
DTPA-Gd	Gd-DTPA-D3.0-PEG-chlorotoxin	G3.0 PLL dendrigraft	Chlorotoxin for MMP-2	Nude mice	Brain tumor	Huang et al. (2011)

8.2.2 Dendrimer-Based CT

CT is another noninvasive molecular diagnostic modality, which exploits specialized X-rays to generate cross-sectional 3D illustrations of organ or tissue with excellent spatial resolution (Hyun and Cho 2019). A contrast agent requires high-electron-density agents such as iodinated molecules and barium sulfate suspension to produce anatomical images of good resolution by increasing imaging area density. However, the drawbacks of these agents include the accumulation at nonspecific targeted site, short imaging duration due to fast clearance of contrast agents, and high dose requirement that may cause renal toxicity (Li et al. 2021). The properties of contrast agent used for CT imaging involves (i) nontoxicity, (ii) good sensitivity even at lower concentration, (iii) targeting at specific site, (iv) higher solubility at physiological medium, (v) complete systemic elimination, and (vi) adequate systemic circulation for imaging (Yeh et al. 2017). The anticipated pharmacokinetic and biodistribution profile conferred by dendrimer could be utilized to fabricate a suitable nanoplatform for CT contrast agents. Dendrimers possess stable highly ordered molecular architecture with low polydispersity index, which makes them an appropriate nanocarrier for contrast agent to achieve targeted therapy, biocompatibility, and imaging (Qiao and Shi 2015).

Dendrimer-entrapped gold nanoparticles (AuDENPs) can be exploited to achieve targeted chemotherapy along with CT imaging of cancers cells. For this purpose, G5.0 PAMAM dendrimer bearing amine as a terminal group was functionalized with polyethylene glycol (PEG)-modified α-tocopheryl succinate (α-TOS), PEGylated FA, and fluorescein isothiocyanate. The conjugated PAMAM dendrimer was further used as a template for the preparation of AuDENPs. The in vitro cell line studies demonstrated that the conjugate generated enhanced CT contrast of cancer cells, where FA receptors were overexpressed and also improved therapeutic efficiency of α-TOS was obtained. The performance of AuDENPs was evaluated for targeted cancer CT imaging in vivo in xenografted U87MG tumor model. After 24 h post-injection of FA-conjugated AuDENPs, the bright tumor CT image was obtained which suggests the FA-mediated active targeting via the theranostic carrier (Zhu et al. 2014). The study suggested that AuDENPs could serve as a versatile nanotheranostic platform to achieve targeted therapy and diagnosis in biological systems.

Scientists developed nanotheranostic system based on dendrimer to obtain CT imaging and targeted chemotherapy. For the preparation of AuDENPs, DOX was first conjugated with the partially acetylated G5.0 PAMAM dendrimer via acid-sensitive cis-aconityl linkage and functionalized with the FA, which were then entrapped within gold nanoparticles (AuNPs). The nanocarrier showed pH-responsive drug release due to the cis-aconityl linkage. The conjugate indicated efficient targeting to FA receptor, which were overexpressed over U87MG glioblastoma cancer cell lines. The CT imaging of the FA receptor-overexpressing carcinoma cells with enhanced contrast sensitivity was obtained (Zhu et al. 2018). The therapeutic delivery system integrated with a targeting ligand and imaging capability

holds a promising potential to achieve chemotherapy and CT imaging of cancer cells simultaneously.

Liu et al. synthesized AuDENPs using G5.0 PAMAM dendrimers to achieve targeted CT imaging of hepatocellular carcinoma cells using lactobionic acid as targeting ligand, which targets asialoglycoprotein receptors. The fluorescein isothiocynate and PEG-coupled lactobionic acid was utilized as a template to develop AuDENPs, where the ligand-conjugated AuDENPs demonstrated exceptional X-ray attenuation activity as compared to the iodine-based CT contrast agents. The developed theranostic nanoprobe showed specific imaging of in vitro human hepatocellular carcinoma cell lines and in vivo xenografted tumor model (Liu et al. 2014). In another study, FA and methotrexate-functionalized G5.0 PAMAM were used as template to design AuDENPs, which were utilized as a nanotheranostic platform for CT imaging and targeted chemotherapy successfully (Zheng et al. 2013). The results suggested that an effective nanotheranostic platform can be developed by decorating the AuNPs with dendrimers and targeting ligands, which obliges them with higher affinity toward overexpressed receptors over carcinoma cell surface that results in the effective CT imaging and chemotherapy simultaneously. Therefore, AuDENPs could serve as an efficient nanotheranostic tool in cancer therapy.

Nanotheranostics with CT imaging uses gold, bismuth, or iodine, which holds high electron density and is reported to overcome shortcomings related to conventional contrast agent. They exhibit prolonged vascular residence time and lower clearance rate and reduce the leakage across the capillary vessels. Dendrimers offer predictable biodistribution and pharmacokinetic profile. Liu et al. created RGD peptide-modified zwitterionic gadolinium (III)-complexed AuDENPs for targeted dual-mode CT/MRI of lung cancer metastasis model. The developed formulation was cytocompatible, displayed specific targeting to αvβ3 integrin-expressing cancer cells, and had good X-ray attenuation property (Liu et al. 2019). In another study, dendrimeric nanotheranostic platform was developed to obtain CT imaging along with the targeted curcumin delivery in chemotherapy. G5.0 PAMAM-based AuDENPs were conjugated with mucin-1 aptamer and loaded with curcumin, where targeted curcumin delivery and CT imaging in colorectal adenocarcinoma were achieved successfully (Alibolandi et al. 2018). Dendrimer-based theranostic system has several benefits over the conventional contrast agents such as prolonged blood circulation time, extended imaging time, desired biocompatibility, facile surface functionalization, and enhanced imaging parameter.

8.2.3 Dendrimer-Based SPECT/PET

Radiopharmaceuticals utilize a radioactive isotope to obtain the image of diseased site noninvasively. Radiopharmaceuticals can be explored to design nanotheranostic platform, as it may offer the advantages of both therapy and diagnosis simultaneously. Generally, metallic radionuclides are used as ionizing radiation source due to its easy availability, rich coordination chemistry, and wider range of nuclear

properties. The SPECT/PET is a radionuclide molecular imaging technique, which provides detailed and quantitative information regarding the disease's pathology and therapy response. These methods can produce high signal-to-noise ratios of the radionuclide due to the exceptional photon tissue-penetrating ability, and therefore the detailed information regarding nanomedicine pharmacokinetics and biodistribution can be obtained (Israel et al. 2019). Dendrimeric nanotheranostics based on radiopharmaceuticals are comprised of (i) a targeting probe, (ii) radiometals (for imaging and treatment), and (iii) bifunctional chelator (Xiao et al. 2020).

SPECT uses a γ-emitting radionuclide isotopes (^{99}mTc, ^{111}In, ^{123}I, and ^{201}Tl), while PET uses a positron-emitting isotopes (^{18}F, ^{11}C, ^{13}N, and ^{15}O). The PET scans offer higher resolution and sensitivity as compared to SPECT; still SPECT is mostly exploited in nanomedicine due to cost-effectiveness and accessibility of longer half-lived isotopes of SPECT. Zhao et al. explored the nanotheranostic capability of ^{131}I-labeled G5.0 PAMAM dendrimer and conjugated with chlorotoxin (targeting ligand), 3-(4′-hydroxyphenyl)propionic acid-OSu (HPAO), and PEG. The in vivo investigations showed excellent SPECT imaging signal intensity and antitumor activity due to the labeling of radioactive ^{131}I in mice glioma model (Zhao et al. 2015). The developed dendrimeric nanotheranostic platform for SPECT imaging and radiotherapy showed good cytocompatibility and organ compatibility in the studies.

Recently, to improve the drawbacks associated with PET/SPECT, i.e., low spatial resolution, multi-modular diagnostic techniques such as PET-CT/SPECT-CT/SPECT-MRI have been introduced to obtain high spatial resolution and desired anatomical distribution of probe (Nolte et al. 2020). AuDENPs using G5.0 PAMAM dendrimer were developed to achieve DOX chemotherapy and to obtain SPECT/CT dual-mode imaging of tumor apoptosis. Dendrimer was conjugated with PEG monomethyl ether, fluorescein isothiocyanate, and PEGylated duramycin for specific targeting at the tumor apoptotic site, where phosphatidylethanolamine was overexpressed. The multifunctionalized dendrimers were utilized as the templates to entrap AuNPs via DOTA chelation and radiolabeled with radionuclide technetium (^{99m}Tc) for SPECT/CT imaging of chemotherapy-induced tumor apoptosis at the targeted locus. SPECT/CT imaging studies suggested that apoptotic C6 cells exposed with the duramycin-dendrimeric AuNPs have higher CT value as compared to the cells treated with the dendrimeric AuNPs, and SPECT images showed brighter image of the targeted site than those of ^{99m}Tc-dendrimeric AuENPs (without targeting ligand). The result of studies suggested that the developed nanotheranostic system was suitable for the monitoring of therapeutic response and confirmed the targeting role of ligand-conjugated AuDENPs for early detection of apoptosis after chemotherapy (Xing et al. 2018). It may be concluded that dendrimers may serve as a viable platform to obtain the molecular imaging of specific target.

8.2.4 Dendrimer-Based FOI

FOI is a noninvasive molecular imaging technique, being explored frequently due to the admirable contrast agent sensitivity and cost-effectiveness. FOI can be utilized to monitor the biodistribution and target site accumulation of nanocarrier. Fluorescence reflectance imaging is one of the FOI techniques based on a planer epi-illumination technique, used to monitor nanotheranostic accumulation in superficial tissues. An advanced tomographic technique, i.e., fluorescence molecular tomography (FMT), has been introduced to overcome the limitations of planer imaging. FMT allocates the nanomedicine accumulation assessment at the non-superficial tissues and represents the better depth resolution. However, drawbacks of this optical imaging technique involve the incorrect signal assignment to precise anatomical locus owing to the strong light absorption by well-perfused organs and scattering of fluorescence signals. To overcome this issue, the hybrid imaging techniques have been introduced to assign accurate accumulation of nanotheranostic to a precise anatomical region, which will enable the assessment of non-superficial tissues (Saluja et al. 2021).

Li et al. designed a theranostic system to achieve chemotherapy and fluorescence imaging, using hybrid nanocarriers, i.e., G5.0 PAMAM dendrimers and blue-emitting carbon dots (CDs) along with chemotherapeutic agent (DOX). Dendrimers were conjugated with RGD peptide and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) and further complexed with CDs/DOX conjugate via electrostatic interaction. The TPGS overcomes multidrug resistance (MDR) by inhibiting the P-glycoprotein overexpressed over cancer cell surface, which results in the enhanced drug accumulation within the tumor cells. The fluorescence imaging of free CDs and hybrid nanoconjugate was compared using A549 cell line. The results suggested that hybrid nanoconjugate assisted intracellular complex tracking and enabled the excellent fluorescence imaging without quenching due to bright blue luminescence exhibited by CD (Li et al. 2019). The combination of dendrimer/CD nanohybrid could be a promising theranostic nanoplatform to achieve chemotherapy along with the fluorescence imaging of cancer cells. Therefore, dendrimer could serve as functional theranostic system for tumor diagnosis and treatment, where near-infrared (NIR) fluorescence imaging and active tumor targeting can be achieved simultaneously.

8.3 Application of Dendrimer-Based Theranostic System

Theranostic applications of dendrimers is a significant area of research, which involves improved therapeutic agent delivery, diagnostic application, and reduced side effects. Owing to the unique characterizations of dendrimer and their potential to be developed as multifunctional nanotheranostic vector, it can provide treatment and diagnostic platforms for several diseases including cancer. However, clearance and interactions of dendrimer with extra- and intracellular molecules need to be considered. Dendrimers have numerous surface groups to conjugate various molecules such as drug, linker, aptamer, and antibody (Jain et al. 2013; Jain et al.

2014; Jain and Jain 2014; Jain et al. 2010). In the following subsection, application of dendrimer in theranostic-based nanomedicine have been discussed.

8.3.1 Nanotheranostic-Assisted Chemotherapy

One of the major drawbacks of conventional chemotherapy is the resistance of the cancerous cells to the free drug. Often, the traditional chemotherapy is associated with administration at nonspecific site, which causes the systemic toxicity and adverse effect on healthy cells. Dendrimers are a unique class of therapeutic agent carrier, different from conventional polymers, have well-defined 3D nanoarchitectures, and offer the functionalization over its surface through which active targeting can be achieved. Dendrimers have emerged as an excellent noninvasive nanotheranostic functional platform, which can be used for (1) characterization and quantification of biological events involved in the diagnosis of early cancer, (2) tracking cellular events, and (3) stimulation of specific drug delivery to tackle tumor progression (Mignani et al. 2021).

The nanosize and limited dendrimeric cargo space make the dendrimer suitable for diagnostic and imaging application, where fast renal clearance is desirable. Generally, theranostic nanocarriers required three basic components: signal emitter, therapeutic payload, and targeting ligand. Researchers fabricated multifunctional nanocarriers based on 4G, 5G, and 6G PAMAM dendrimer, fixed over polydopamine-coated magnetite NPs (Fe_3O_4), and studied the theranostic application of the nanocarrier for combined chemo- and photothermal therapy (PTT) of liver cancer cells in vitro. The synthesized nanocarriers were nontoxic, exhibited strong photothermal properties, and have competitive contrast properties in MRI. The nanosystem showed synergistic effect in the combined chemotherapy and PTT of liver carcinoma cells at low NPs concentrations (Jędrzak et al. 2019). Therefore, the presence of abundant terminal functional moieties over dendrimer can be functionalized with targeting moiety and imaging modalities to constitute multipurpose theranostic dendrimers.

Zu et al. reported the multifunctional gadolinium-loaded G5.0 PAMAM dendrimer, modified with targeting ligand FA via PEG spacer and encapsulated with DOX within the dendrimeric core. The in vitro cell line studies of the developed dendrimeric nanotheranostic system showed targeted intracellular delivery of DOX in κB carcinoma cells, where FA receptors are overexpressed. Quantitative measurements of the MR signal-to-noise suggested that κB cells treated with the dendrimeric theranostic system enabled MR imaging of FA receptor-overexpressing cancerous cells through FA-mediated active targeting pathway (Zhu et al. 2015a). The multifunctional dendrimer with imaging agents and physically incorporated drug within the core holds enormous potential to be utilized as a theranostic platform, where the imaging and treatment can be achieved simultaneously.

FOI is a noninvasive imaging modality for tumor detection with accuracy, where real-time evidence of tumor margins can be specified and magnitude of cancer span can be determined. Xu and the group developed Pep-1-decorated PEGylated

PAMAM to improve the distribution across blood-brain tumor barrier and homing to glioblastoma cells. The Pep-PEG-PAMAM dendrimeric system showed excellent penetration inside the cancer cells. The in vivo real-time fluorescence imaging with Cy5.5 in U87MG tumor-bearing mice suggested that the accumulation of theranostic system at tumor site was 2.02 times greater as compared to the untargeted group (Jiang et al. 2016).

Luong et al. synthesized polyvalent theranostic nanocarriers based on the superparamagnetic Fe_3O_4 decorated with FA-G4.0 PAMAM dendrimer that encapsulates chemotherapeutic agent 3,4-diflourobenzylidene-curcumin. FA dendrimer and Fe_3O_4 were linked with 3-aminopropyl trimethoxy-silane chain. As compared to nontargeted NPs, the FA-conjugated nanocarrier exhibited rapid cellular uptake in SKOV3 and HeLa cancer cell lines. Also, enhanced MRI contrast was obtained for the targeted carcinoma cells (Luong et al. 2017). Researchers fabricated dendrimeric nanotheranostic system to achieve tumor targeting and CT imaging by using G5.0 PAMAM AuDENPs decorated with fluorescein isothiocyanate, PEGylated TOS, and RGD peptide through PEG chain. α-TOS triggers the proliferation inhibition and carcinoma cell apoptosis, while the RGD rendered the targeting specificity to these nanocarrier toward U87MG cells to enhance the therapeutic efficiency of the nanocarrier. The fabricated AuNP-TOS-RGD dendrimer NPs showed better X-ray absorption properties than Omnipaque (currently used in clinic) (Zhu et al. 2015b). The nanosize, degree of branching, and functionalization of the dendrimers can be controlled through synthetic methods. This tunable architecture linked to the application-related properties, like biocompatibility, stimuli-responsiveness, and self-assembly capability, which are the crucial feature for the chemotherapeutic theranostics.

Dendrimers possess nanometric size, which facilitates the passive and active targeting of the therapeutic agents, where the enhanced permeation and retention effect (EPR) effect promotes accumulation of the dendrimers in the tumor microenvironment through leaky vessels, while the functionalization of dendrimeric surface through the tumor-specific ligands delivers the drug to the targeted cells. The EPR effect also supports the longer circulation and increased therapeutic payload to the tumor tissue (Felder-Flesch 2021). The advanced nanotheranostic multifunctional dendrimeric systems are capable of diagnosing and delivering drug to the cancer site through sustained/controlled release of encapsulated contrast agents and chemotherapeutics (Dendrimer-Based Nanotherapeutics 2021). The multifunctional dendrimeric system facilitates endocytosis and provides a platform to deliver chemotherapeutic agent, avoid MDR, and render an all-in-one single theranostic nanoplatform anchored with targeting ligands for targeted therapy.

8.3.2 Nanotheranostic-Assisted Photothermal Therapy

To improve the cancer treatment outcome, nanocarrier with higher selectivity and good therapeutic efficiency is required along with the minimal invasiveness. PTT triggers the reaction against cancer cells in the presence of light and has brought

predominant attention to achieve specific targeting and effective ablation of the irradiated carcinoma cells in chemotherapy. However, development of multifunctional theranostic nanoplatforms with improved diagnostic sensitivity and photothermal therapeutic efficiency is still a great challenge. Dendrimer-based theranostics have immense potential in cancer phototherapy, as it confers several structural advantages as compared to linear polymers. Dendrimers can be functionalized easily with photoreactive agents and targeting ligands to achieve targeted PTT.

Nava et al. fabricated a dendrimeric system, where AuNPs were incorporated inside FA/bombesin-functionalized and ^{177}Lu-labeled G4.0 PAMAM dendrimers. Bombesin moieties are linked with the fluorescence imaging, while the targeted radiotherapy and PTT can be achieved due to ^{177}Lu-labeling and entrapped AuNPs, respectively. The viability of T47D human breast cancer cells was reduced significantly after the cells were treated with laser irradiation along with the drug-loaded nanosystem. In vivo imaging revealed that ^{177}Lu-dendrimer-AuNP-FA-bombesin retained within the cancer cells up to 96 h followed by intratumoral radiopharmaceutical administration (Mendoza-Nava et al. 2016). The ^{177}Lu-labeled G4.0 PAMAM dendrimers could have application in theranostics due to its combined optical, radioactive, and thermoablative properties. This study depicts the utility of receptor-specific radiopharmaceuticals incorporating dendrimer nanocarrier in targeted radiotherapy and chemotherapy.

AuDENPs have been fabricated and studied for their potential application toward PTT of malignant tissue. For this purpose, G5.0 PAMAM dendrimer-entrapped AuNPs were covalently linked to fluorescein isothiocyanate and surface modified with FA for targeted delivery to tumor cells. The dendrimers showed binding to human epithelial carcinoma cell line κB cells, in vitro, and internalized into lysosomes within 2 h. The dendrimeric nanocarrier represented targeted hyperthermia treatment of cancer through inductive tumor cell heating followed by particle internalization. Dendrimeric AuNP therapeutics was visualized in the targeted cells because of the high-electron-density contrast of the Au atoms (Shi et al. 2007). AuNP represents flexible localized surface plasmon resonance and suitable optical characteristics that make them suitable for imaging and effective for PTT, which could be exploited in cancer therapy along with the dendrimers for targeted delivery.

Ge et al. developed NIR-guided G5.0 PAMAM dendrimer theranostic platform to achieve improved antitumor efficacy by combined chemo-phototherapy. For this purpose, dendrimer was covalently conjugated with a fluorescent targeting agent, i.e., indocyanine green derivative cypate and iRGD (tumor-penetrating peptide). Further, docetaxel was encapsulated within the PAMAM cavity to develop a single agent-based multifunctional nanotheranostic platform, i.e., iRGD-cypate-PAMAM-Docetaxel, to obtain the synergistic effect of phototherapy and chemotherapy. Figure 8.3a represents the schematic synthesis of the nanotheranostic platform with low polydispersity index and average size of 150.67 ± 12.58 nm (Fig. 8.3c). The results suggested that the developed theranostic system could enhance the singlet oxygen species while retaining its fluorescence intensity and heat generation capability followed by NIR irradiation. Figure 8.3b represents the absorption

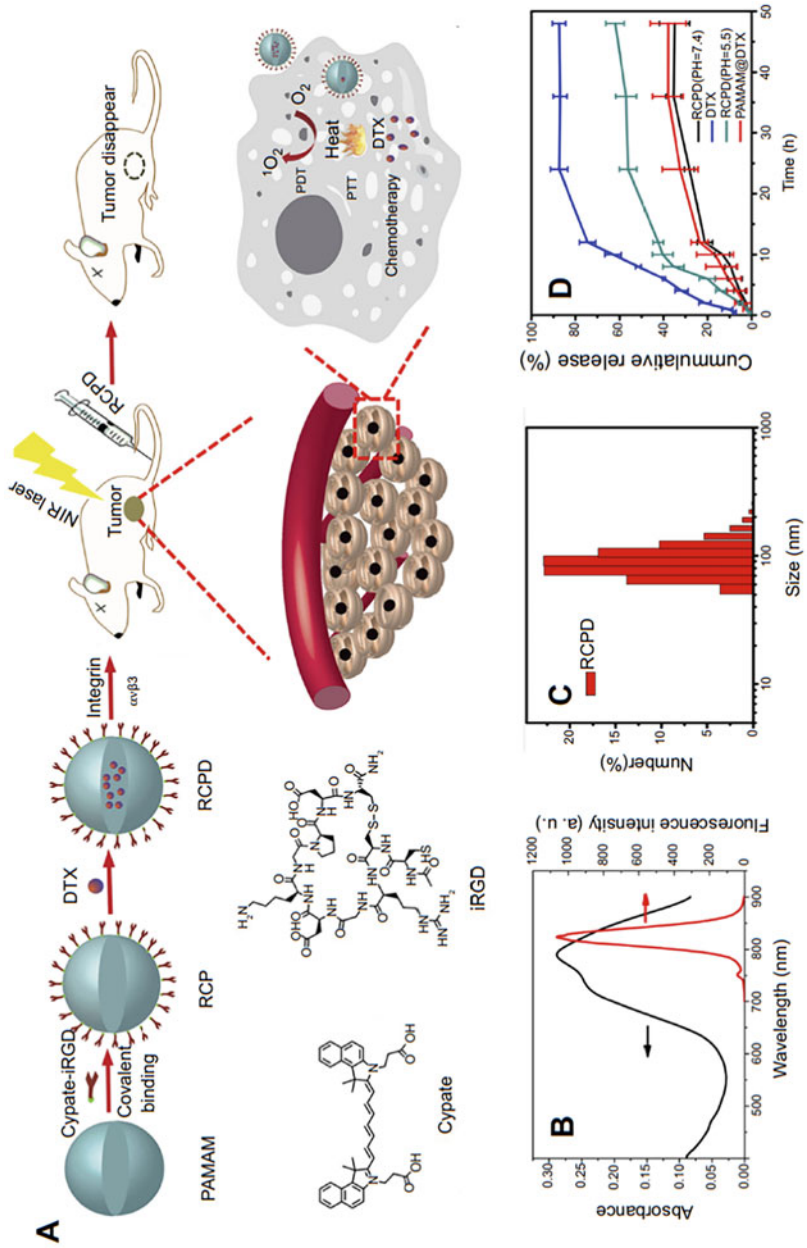

Fig. 8.3 Systematic representation of NIR-guided G5.0 PAMAM dendrimer theranostic platform. (**a**) Synthesis of dendrimeric theranostic nanoplatform. (**b**) UV-visible absorption and fluorescence spectra of iRGD-cypate-PAMAM-Docetaxel. (**c**) Size distribution of the nanotheranostic carrier. (**d**) In vitro drug release studies of drug from the dendrimeric theranostic system (Ge et al. 2019). (DTX=Docetaxel)

spectra, which showed monomer and dimer peak at 790 nm and 730 nm, respectively, while fluorescence spectra exhibited the maximum emission wavelength at 820 nm, which suggests that the dendrimeric system could be utilized for NIR imaging. The in vitro drug release studies demonstrated that the docetaxel was released from the formulation at the faster rate at pH 5.5, while slow release of drug was obtained at the pH 7.4, which suggest that the premature drug release in the systemic circulation can be circumvented, and drug will be released at tumor site (Fig. 8.3d). The in vitro and in vivo studies suggest that the multifunctional theranostic platform can significantly improve the antitumor efficiency (Ge et al. 2019).

Carbon nanotubes (CNTs) exhibit unique physical attributes such as higher absorption capacity in the NIR region than other photothermal agents. The dendrimeric nanohybrids can be developed by conjugating dendrimer with CNTs, which could be further exploited in PTT. Recently, CNT-G4.0-PAMAM-CdS photothermal agent was developed by conjugating PAMAM with CNTs and cadmium sulfide (CdS) nanocarriers. The nanosystem showed photothermal conversion efficiency of 32% under 980 nm NIR laser irradiation than earlier reported Au-based photothermal agents (Ouyang et al. 2021). Dendrimers conjugated with CNTs or quantum dots have unique properties that can be exploited for theranostic application along with thermal ablation for cancer therapy.

8.3.3 Nanotheranostic-Assisted Gene Therapy

Gene therapy is a promising therapeutic approach, which is independent of the utilization of therapeutic drug. Theranostic imaging monitors the expression of gene therapy enzymes, and the therapeutic outcome from the gene therapy can be evaluated. Nanotheranostic imaging applications save the time via assessing therapeutic efficacy while measuring the therapeutic gene expression level. Recently, personalized therapy has been explored widely as promising chemotherapy strategy. With the incorporation of diagnostic imaging agent in the gene therapy, the aftermath of the therapy can be calculated (Sekar and Paulmurugan 2016). Xiong et al. developed mRNA-based dendrimer-lipid nanoparticle nanotheranostic system containing PEGylated BODIPY dyes for mRNA delivery and NIR imaging simultaneously. The result suggested that the developed nanocarrier could mediate luciferase mRNA expression in the tumors and simultaneously illuminate the tumors through the pH-activatable NIR imaging (Xiong et al. 2020).

In RNA interference delivery, which holds great promise in chemotherapeutic application, researchers synthesized gold nanostar stabilized with RGD peptide-modified G3.0 PAMAM dendrimers (Au-RGD-G3NSs). The developed dendrimeric system was used as a gene delivery vector and complexed with siRNA to achieve CT imaging, PTT, and gene therapy simultaneously. The outcomes showed that Au-RGD-G3NSs compact the siRNA to deliver the siRNA within the $\alpha_v\beta_3$ integrin-overexpressed cancerous cells. Followed by NIR and incubation with the Au-RGD-G3NSs/siRNA polyplexes, the viability of U87MG

cancer cells was 20.2%, which is lower than the cells treated with single PTT (44.34% cell viability) or gene therapy (46.9% cell viability). The in vivo studies suggested that Au-RGD-G3NSs/siRNA polyplexes enabled tumor CT imaging and thermal imaging after intratumoral injection (Wei et al. 2016). The study describes the role of dendrimer as a multifunctional nanocarrier for tumor imaging, combinational PTT, and gene therapy.

Recently, researchers explored the utility of dendrimer-functionalized gold nanorods (NRs) to achieve gene therapy, PTT, and CT imaging of the colon cancer, simultaneously. G3.0 PAMAM dendrimer-modified gold NRs were grafted with GX1 peptide (a cyclic 7-mer peptide, CGNSNPKSC), which was utilized as a vector for gene delivery, FAM172A, which controls the apoptosis of colon cancer cells. The results suggested that the polyplex, AuNR-PAMAM-GX1/FAM172A, had tremendous transfection efficiency. The HCT-8 colon cancer cells exposed to AuNR-G3.0-PAMAM-GX1/FAM172A showed viability of 20.45%, under laser irradiation. The in vivo studies showed that the dendrimeric nanosystem can be utilized for combinational tumor thermal imaging, PTT, CT imaging, and gene therapy after tail vein injection (Ye et al. 2021). Therefore, the dendrimer offers a nanotheranostic platform, to exert anticancer activity, and improved diagnostic level of cancer cells.

8.3.4 Nanotheranostic-Assisted Photodynamic Therapy

Photodynamic therapy (PDT) involves the systemic administration of photosensitizers such as porphyrin and phthalocyanine derivatives, followed by photoactivation of photosensitizers at the disease site with the light of specific wavelength. The photosensitizers accumulate intensely in pathological locations, where it excites at the target site by specific light radiating wavelength and generates a series of biochemical reactions leading to the death of diseased cells (Xie et al. 2022). NIR optical properties of phthalocyanine confers enormous potential as theranostic agent, for fluorescence image-guided delivery of therapeutic agent by PDT. Researchers fabricated G4.0 PPI-based theranostic platform to enhance the water solubility, reduce aggregation, and achieve tumor-targeted delivery of phthalocyanine. The phthalocyanine-PPI complex was further surface modified with PEG and luteinizing hormone-releasing hormone (LHRH) peptide to improve biocompatibility and tumor-targeted delivery, respectively. The in vivo studies suggested that LHRH targeted nanocarrier had effective internalization ability within tumor cells. The nanoformulation demonstrated lower cytotoxicity ($IC_{50} = 28$ μg/mL) in dark, whereas the light irradiation on cancerous cells transfected with nanotheranostic agents showed considerable PDT activity ($IC_{50} = 0.9$ μg/mL) due to the excessive release of toxic reactive oxygen species (Taratula et al. 2013). The studies determined the potential of the dendrimeric-based nanosystem as a competent NIR theranostic system.

Dendrimers offer multifunctional theranostic platforms, where NIR fluorescence imaging and phototherapy can be obtained simultaneously for cancer diagnosis and

treatment. A dendrimer-based theranostic nanosystem was developed for NIR fluorescence imaging, with dual PTT and PDT therapeutic mechanism. Silicon naphthalocyanine (SiNc) was developed into biocompatible nanocarrier (SiNc-NC) via SiNc encapsulation within hydrophobic cavity of G5.0 PPI dendrimer followed by surface functionalization with PEG. Encapsulation of SiNc within the dendrimer preserves the NIR fluorescence and PDT and PTT properties of SiNc. Under NIR irradiation, SiNc-NC produces reactive oxygen species and demonstrated heat generation capability required for PDT and PTT, respectively. Studies demonstrated that the PTT mediated by the SiNc can kill the MDR ovarian cancer cells efficiently (Taratula et al. 2015). The PPI dendrimer has hydrophobic cavities, which offer the encapsulation for separate SiNc molecules and thus diminish their aggregation and preserve imaging, PDT, and PTT properties.

8.4 Conclusion

Dendrimers are synthetic polymeric macromolecules with tuneable surface morphology. Various functionalities, i.e., therapeutic, imaging, or targeting, could be functionalized over the dendrimeric surface or encapsulated within the void space of the dendrimers. Dendrimeric nanotheranostic system incorporates therapy (chemotherapy, PDT, PTT) and diagnosis (MRI, CT, SPECT, PET) simultaneously. The judicious dendrimer functionalization for the therapeutic agent, targeting ligand, and the diagnostic agent could deliver the cargo, with negligible toxicity to the targeted locus. The imaging functionality in conjugation allows the drug distribution monitoring, visualization of disease progression, and therapeutic response assessment.

Acknowledgments The authors acknowledge Department of Pharmaceuticals (DoP), Ministry of Chemicals and Fertilizers, government of India, for providing facilities to write this manuscript. Authors, Dr. Keerti Jain and Ms. Anchal Pathak, acknowledge Indian Council of Medical Research (ICMR), New Delhi, for the financial support in the form of ICMR Extramural Research Project (Project ID: 2020-4686; Ref. No. 5/13/34/2020/NCD-III). The NIPER-Raebareli communication number for this manuscript is NIPER-R/Communication/388.

Conflict of Interest The authors declare no conflict of interest related to this manuscript.

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