

RECENT PROGRESS OF DENDRIMERS IN DRUG DELIVERY FOR CANCER THERAPY

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ABSTRACT

With the recent advances of nanotechnology, dendrimers are emerging as a highly attractive class of drug delivery vectors for cancer therapy. Dendrimers are multifunctional smart Nanocarriers to deliver one or more therapeutic agent safely and selectively to cancer cells. The high level of control over the synthesis of dendritic architecture makes dendrimers a nearly perfect (spherical) nanocarrier for site-specific drug delivery. The presence of functional groups in the dendrimers exterior also permits the addition of other moieties that can actively target certain diseases which are now widely used as tumor targeting strategies. Drug encapsulation, solubilization and passive targeting also equally contribute to the therapeutic use of dendrimers. Dendrimers are ideal carrier vehicles on cytotoxicity, blood plasma retention time, biodistribution and tumor uptake. In this review we highlight the advantages of dendrimers over conventional chemotherapy, toxicity and its management, following anti-cancer drugs delivered by using dendrimers and recent advances in drug delivery by various types of dendrimers as well as its diagnostic applications.

Keywords: Dendrimer, Cancer therapy, Nanocarriers, Drug delivery, Diagnostic applications

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INTRODUCTION

Cancer is one of the world's most distressing diseases with no significant cure for several types of tumors [1, 2]. Cancer is principally a disease of cells identified by the loss of normal cellular growth, maturation and multiplication leading to disturbance of homeostasis. A brief consideration of the challenges facing an anti-cancer drug are—at first the drug must be able to seek out differences between a transformed cells from other healthy cells in the body. Secondly, they should provide sufficiently a high dose of toxic agent to kill the cell. Furthermore, it successfully cures a patient by eradicating each and every cancer cell [3]. However, conventional chemotherapeutic agents have several challenges such as low aqueous solubility, poor bio-distribution, unfavorable pharmacokinetics, narrow therapeutic index, poor membrane permeability, instability, rapid clearance, severe toxicity, and the emergence of multidrug resistance phenotypes.

Although, it has been observed that cancer chemotherapy is one of the best approaches to eradicate cancer and the success of chemotherapy mainly depends on the selection of optimum carrier system. These carriers include nanoparticles, nano tubes, nano rods, dendrimers, liposomes, solid lipid nanoparticles, microspheres etc.

Among all these, dendrimeric system appears to be promising in cancer chemotherapy, especially via ligand or Receptor-mediated

endocytosis as it possess numerous properties [especially surface property] to target cancer and also to overcome all these limitations of conventional chemotherapeutic agents, there is an immediate need for developing safe and effective carrier vectors such as dendrimers that can protect the drug from degradation during transit and enhance targeting efficiency and also reduce adverse toxic effects caused by cytotoxic drugs [2].

Dendrimers are highly branched, nanosized, symmetric molecules with well defined, homogenous and monodisperse structure having diameter in 2-10 nm range. The word Dendrimer is based on the Greek words—"Dendron meaning tree or branch" and "merosmeaningpart" [3]. The structure of the denrimers is shown in fig. 1. The three component of dendrimer are central core, repetitive branching units and terminal groups. The "Generation number" of dendrimer is determined by the increase in a number of branching units which results in globar structure formation [4-7]. Palmerston Mendes L, Pan J, Torchilin VP 2017, has inferred in their review article that the presence of functional groups in the dendrimer's exterior also permits the addition of other moieties that can actively target certain diseases and improve delivery which is now widely used as tumor targeting [4]. The presence of unique properties makes them ideal carriers for the targeted delivery of therapeutic and diagnostic agents [8].

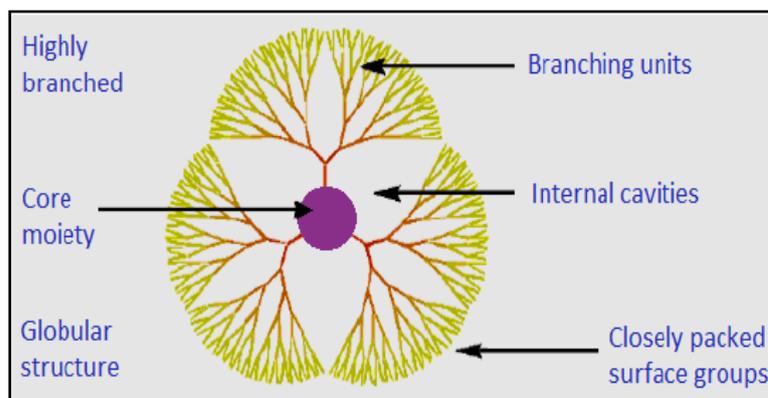


Fig. 1: Structure of dendrimer
Source-bitspace.com

Advantages of dendrimers over conventional anti-cancer agents

- High drug loading capacity
- Dendrimers having appropriate nanosize ranging 1-100 nm for pre detectable release profile, favorable pharmacokinetics and targeting potentials [2, 9].
- Dendrimer improve the solubility of poorly soluble anti-neoplastic drugs.
- Clearance is reduced through Reticuloendothelial system due to small size [10-12].
- Multiple functional groups are present on outer surface of dendrimers, which can be used to attach vector devices for targeting to particular site in the body.
- Presence of numerous peripheral functional groups on dendrimers is responsible for tumor cell-specific delivery.

Toxicity and its management

- It is known that all classes of dendrimers present cytotoxic and hemolytic properties which raise concern according to their safety.
- The toxicity is dependent on the dendrimer characteristics and can be related to the chemistry of the core but mainly to surface end groups [4, 13].

➤ Interaction of the cationic dendrimers surfaces with negative biological load membranes damaging cellular membranes causing hemolytic toxicity and cytotoxicity [14].

➤ This strong interaction with the negatively charged cell membranes can cause cell destabilization with leakage of cytoplasmic proteins and subsequently lysis [4, 15-16].

E. g.: Interaction with lipid bilayers of cells occurs with the cationic Dendrimer G7-PAMAM which comes to form holes 15-40 nm in diameter, which disturbs the flow of electrolyte causing cell death. [14, 17-19]

➤ **Surface modification** of dendrimers can be useful to improve their safety and can be easily achieved through conjugation molecules with the reactive terminal groups of nanocarriers.

➤ PEG is frequently used to increase plasma circulation time and tumor accumulation through enhanced permeability and retention effect [EPR] [4, 20-22].

➤ Linking or conjugation of dendrimers with PEG chains has been shown as an important step in reducing the cytotoxicity of dendrimers

➤ PEGylation increase the physical dendrimers size which reduces renal clearance since the glomerular filtration limits reached [4, 23-26].

Table 1: Anti-cancer drugs delivered by using dendrimers

S. No.	Anti-cancer drugs	Dendrimer type
1	5-FU(5-Flurouracil)	PAMAM-mPEG-PDEA PAMAM Polyglycerol
2	CDDP(Cisplatin)	PAMAM PAMAM-COOH
3	MTX(Methotrexate)	Polyether-co-polyester PAMAM
4	PTX(Paclitaxel)	Poly Glycerol PAMAM Triazine PPI
5	DOX(Doxorubicin)	PEGylated-PAMAM Poly ester
6	Camptothecin	PAMAM
7	Adriamycin Tamoxifen	PAMAM

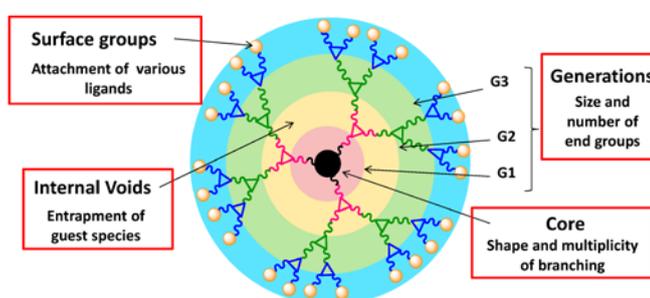


Fig. 2: General representation of the model structure of a dendrimer
Source: pubmed

Drug delivery as carriers

Dendrimers act as a carrier for the delivery of anti-cancer drugs by either encapsulation of the drug in the interior of the dendrimer or conjugating covalently to form macromolecular prodrug [27].

Drug encapsulated dendrimers

- Poly (glycerol-succinic acid) dendrimers were investigated as delivery vehicles for camptothecin. In a preliminary study reported by the Grinstaff group, G4-PGLSA dendrimers with hydroxyl and

carboxyl peripheral groups were used to encapsulate 10-hydroxy camptothecin for delivery to cancer cells [28].

- Melamine-based dendrimers were used to solubilize the anti-cancer drugs Methotrexate and 6-mercaptopurine, as well as to reduce toxicity [29].

- A major drawback to these delivery systems is a lack of controlled drug release kinetics, with most systems releasing their payload over the course of several hours. For this reason, drug encapsulated dendrimer systems may best be utilized via direct intratumoral injection.

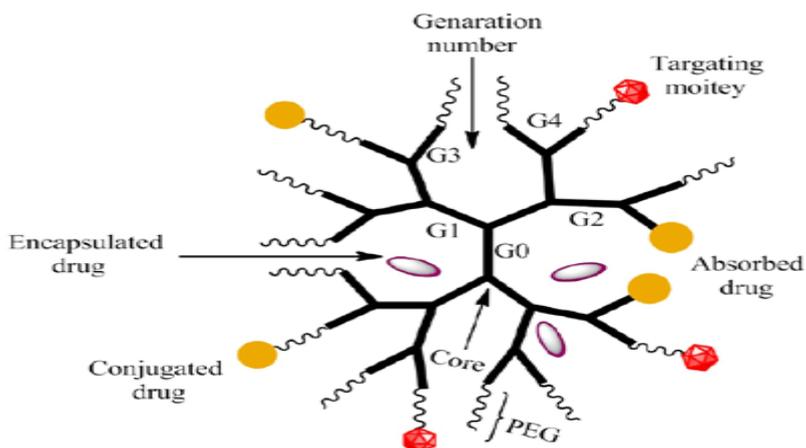


Fig. 3: Encapsulation of various types of drug into dendrimers
Source: Pubmed

Dendrimer drug conjugates: [27]

- Dendrimer drug conjugate consists of anti-neoplastic agent covalently attached to the peripheral groups of the dendrimer.
- This method has distinct advantages over drug encapsulated systems such as
 1. Multiple drug molecules can be attached to each dendrimer molecule.

2. Nature of linkages controls the release of therapeutic molecules.

- Paclitaxel was conjugated to PEG or G4PAMAM to compare the anti-cancer activity of the drug delivered by a linear or dendritic carrier [30]. Both PEG and PAMAM increased the aqueous solubility of paclitaxel (0.3mcg/ml) dramatically to 2.44mcg/ml and 3.2 mcg/ml respectively upon exposure to human ovarian carcinoma A2780 cells.

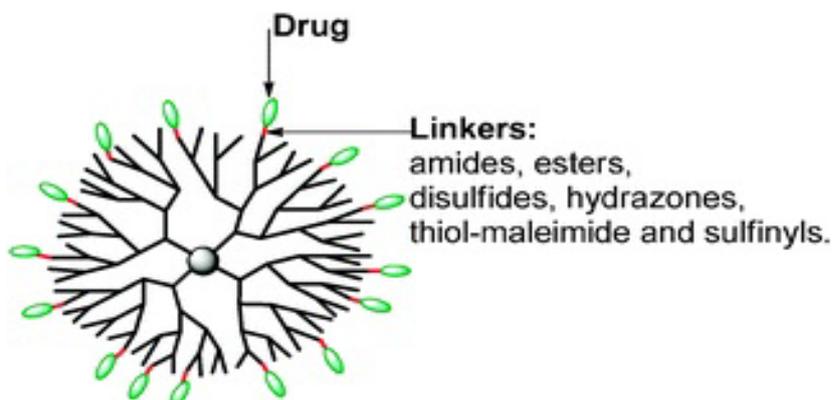


Fig. 4: A representation of drug-dendrimer conjugate
Source: Pubmed

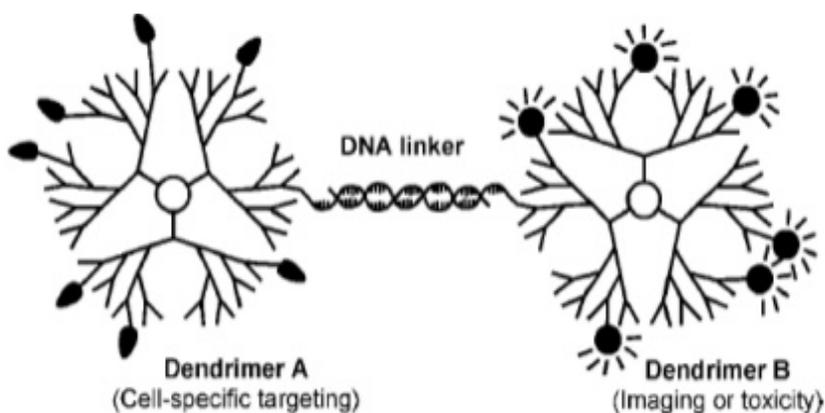


Fig. 5: A typical DNA-dendrimer conjugate for cancer targeting
Source: Pubmed

Drug delivery by various types of dendrimers

The utility of dendrimers can be well known by their ability to traverse several delivery barriers using two principles, namely active and passive tumor targeting.

❖ **Passive targeting**-utilizes EPR effect which involves dendrimers to extravasate and accumulates selectively in the tumor tissue.

❖ **Active targeting**- It involves conjugation of specific targeting ligands on nanocarrier surfaces can facilitate their selective binding to overexpressed receptors on specific tumor cells.

Moreover, a Passive targeting approach (or) the EPR effect is only applicable to highly permeable solid tumors. However, the permeability of several tumor types is very low or non-uniform throughout heterogeneous tumors. These shortcomings can be resolved by Active targeting approach only which enables conjugation of a variety of cancer targeting ligands.

1. PAMAM dendrimers (Poly amidoamine) dendrimers

It is principally used as carriers for anti-cancer therapy.

e. g.:

a) Phosphoryl choline-conjugated fifth generation PAMAM dendrimers have been developed for the delivery of an anti-cancer drug "Adriamycin" [2].

b) To improve the drug accumulation in lungs tumor, prepared DOX-dendrimer conjugates and investigated their ability to decrease metastatic lung burden through the administration of these Nanosystems [4].

4.0 G PAMAM dendrimers have been conjugated with two targeting ligands, namely Transferrin (T_F) and wheat germ agglutinin (WGA) and utilize d for the purpose of traversing the blood-brain barrier and Ingestion of drugs by brain tumor cells. Thus, provide a potential application for brain cancer therapy [2, 31].

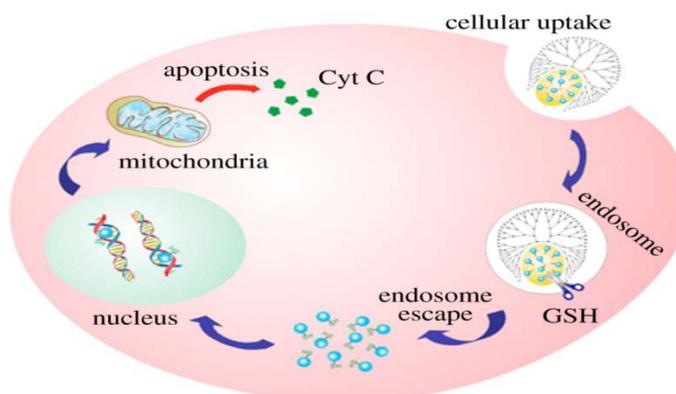


Fig. 7: Cellular uptake of drug from dendrimer by passive targeting
Source: Science direct article Reference No. 2

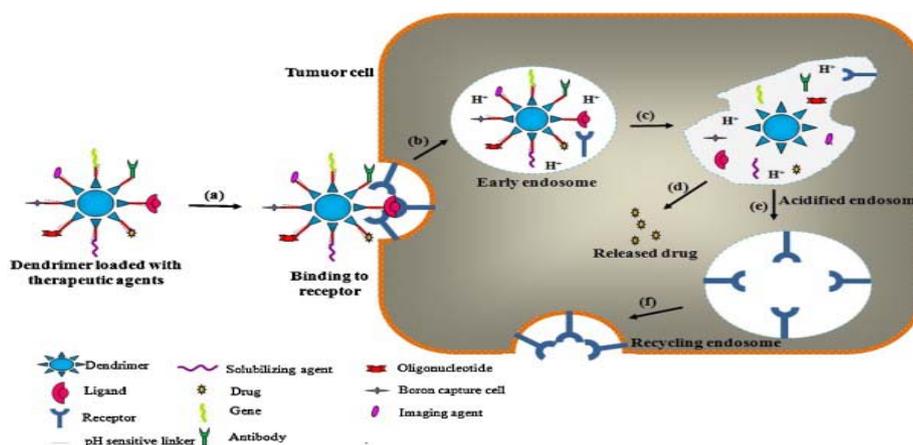


Fig. 8: Cellular uptake of drug from Dendrimer by Active targeting
Source: Science direct article Reference No. 2

2. PPI Dendrimers (Poly-propylene Imine) dendrimers

• These are amine terminated hyperbranched macromolecules that are mainly synthesized by a divergent method [2, 32].

• Amine groups on periphery enable various cancer-targeting ligands such as Folates, amino acids, carbohydrates, antibodies, peptides that are explored for active targeting.

E. g.:

a) G4.5PPI dendrimers that were carboxylic acid terminated to conjugate the monoclonal antibody mAbk1 to encapsulate paclitaxel

(PTX). It targets Mesothelin protein, overexpressed in some cancers but not in normal cells [4, 33]

b) Nanoconjugates of DOX were prepared by coupling with fifth generation PPI dendrimers using unique aromatic azo linkers (L1-L4) that could be selectively recognized and cleaved using azoreductase enzymes present in the cytoplasm of hepatic cancer cells. Hence, this approach could be successfully explored for controlled delivery of drugs to hepatic cancer cells [2, 34].

c) Polysorbate-80 conjugated PPI dendrimers were explored for targeted delivery of DTX to the brain tumor.

3. PLL Dendrimers: (Poly-L-lysine) dendrimer

PLL dendrimers less well studied than PAMAM or PPI. Also, they found to be greatly associated with DOX and improve the drugs anti-cancer activity while showing fewer adverse events than the free drug [44, 21, 35, 36].

E. g.:

a) The hydrophobic cavity of 6.0G PLL dendrimers anchored with PEG-linked hydrophobic pentaphenyl alanine are used to deliver

DOX by I. V. which resulted in tumor accumulation by the EPR effect and led to the suppression of tumor growth without loss of body weight [2, 37].

b) PLL Dendrimers of generation 6 had well anti-angiogenic activity in an *in vivo* B16F10 Xenograft model (brain, lung, liver cancer) even in absence of therapeutic molecule. By associating the PLL dendrimers with DOX they attempted to combine the anti-cancer effect of the drug and anti-angiogenic effect of carrier [4, 36].

Table 2: Commonly used dendrimers as drug carriers [4]

S. No.	Polymer	Generation	Pay load	Application
1	PAMAM	G4	Doxorubicin	Lung metastasis
		G4	Paclitaxel	Breast cancer
		G4	Docetaxel	Breast cancer
2	PPI	G3-G5	Melphalan	Breast cancer
		G4.5	Paclitaxel	Ovarian cancer
3	PLL	G6	Doxorubicin	Melanoma
		G6	Doxorubicin	Rectum cancer

A glimpse of researches of dendrimers in cancer therapy

Sylwia Michlewska *et al.*, 2018, stanch to study interactions between new carbosilane-based metallo dendrimers containing ruthenium and anti-cancer small interfering RNA (siRNA). Formation of complexes between anti-cancer siRNAs and Ru-based carbosilane dendrimers was evaluated by transmission electron microscopy, circular dichroism, and fluorescence. The zeta-potential and the size of dendriplexes were determined by dynamic light scattering. The internalization of dendriplexes was estimated using HL-60 cells. Results show that ruthenium dendrimers associated with anticancer siRNA have the ability to deliver siRNA as non-viral vectors into the cancer cells. Moreover, dendrimers can protect siRNA against nuclease degradation [38].

Kelly E. Burnsa, James B. Delehanty 2018, had developed a peptide-dendrimer-drug conjugate system for the pH-triggered direct cytosolic delivery of the cancer chemotherapeutic doxorubicin (DOX) using the pH Low Insertion Peptide (pHLIP). In their research, they synthesized a pHLIP-dendrimer-DOX conjugate in which a single copy of pHLIP displayed a generation three dendrimer bearing multiple copies of DOX via disulfide linkages. Biophysical analysis showed that both the dendrimer and a single DOX conjugate inserted into membrane bilayers in a pH-dependent manner. Time-resolved confocal microscopy indicate the single DOX conjugate may undergo a faster rate of membrane translocation, due to the greater nuclear localization of DOX at 24 h and 48 h post-delivery. At 72 h, however, the levels of DOX nuclear accumulation for both constructs were identical. Cytotoxicity assays revealed that both constructs mediated ~80% inhibition of cellular proliferation at 10 μ M, the dendrimer complex exhibited a 17% greater cytotoxic effect at lower concentrations and greater than three-fold improvement in IC50 over free DOX. Their findings show proof of concept that the dendrimeric display of DOX on the pHLIP carrier (1) facilitates the pH-dependent and temporally-controlled release of DOX to the cytosol, (2) eliminates the endosomal sequestration of the drug cargo, and (3) augments DOX cytotoxicity relative to the free drug [39].

Jun Cao *et al.*, 2018, has used small nanoparticles as a potentiator of conventional chemotherapy by co-administration with free chemotherapeutic agents. Their strategy avoided the problems associated with drug loading and controlled release encountered in NDDS, and was also much simpler than NDDS. Negatively charged poly (amidoamine)-2,3-dimethylmaleic monoamide (PAMAM-DMA) dendrimers were prepared, which possessed low toxicity and can be converted to positively charged PAMAM dendrimers responsive to tumor acidic pH. The *in situ* formed PAMAM in tumor tissue promoted cellular uptake of co-administered doxorubicin by increasing the cell membrane permeability and subsequently

enhanced the cytotoxicity of doxorubicin. The small size of the dendrimers was found to be favorable for deep penetration in tumor. Co-injection of PAMAM-DMA with doxorubicin into nude mice bearing human tumors almost completely inhibited tumor growth, with a mean tumor weight reducing by 55.9% after the treatment compared with the treatment with doxorubicin [40].

Kuruville SP *et al.*, 2018, were interested to see if tri-valent NAcGal ligands (i.e. NAcGal3) displayed on G5 dendrimers (i.e. G5-cPEG-NAcGal3; tri Gal) could improve their ability to target hepatic cancer cells compared to their mono Gal counterparts. They, therefore, synthesized a library of tri Gal particles, with either 2, 4, 6, 8, 11, or 14 targeting branches (i.e. cPEG-NAcGal3) attached. Conventional flow cytometry studies showed that all particle formulations can label hepatic cancer cells in a concentration-dependent manner, reaching 90-100% of cells labeled at either 285 or 570 nM G5, but interestingly, monoGal labeled more cells at lower concentrations. To elucidate the difference in internalization of monoGal versus triGal conjugates, we turned to multi-spectral imaging flow cytometry and quantified the amount of internalized (I) versus surface-bound (IO) conjugates to determine the ratio of internalization (I/IO) in all treatment groups. Results show that regardless of NAcGalvalency, or the density of targeting branches, all particles achieve full internalization and diffuse localization throughout the cell (I/IO ~ 3.0 for all particle compositions). This indicates that while tri-valent NAcGal is a promising technique for targeting nanoparticles to hepatic cancer cells, mono-valent NAcGal is more efficient, contrary to what is observed with small molecules [41].

Narsireddy Amreddy *et al.*, 2018, Co-administered functionally distinct anti-cancer agents as an efficient strategy in lung cancer treatment. The study reported that they required a specially designed drug delivery system to co-encapsulate functionally different agents, such as a combination of siRNA and chemotherapy, for targeted delivery. Hence they developed a folic acid (FA)-conjugated polyamidoamine dendrimer (Den)-based nanoparticle (NP) system for co-delivery of siRNA against HuR mRNA (HuRsiRNA) and cis-diamine platinum (CDDP) to folate receptor- α (FRA)-overexpressing H1299 lung cancer cells. The co-delivery of HuRsiRNA and CDDP using the FRA-targeted NP had a significantly greater therapeutic effect than did individual therapeutics. Further, the FRA-targeted NP exhibited improved cytotoxicity compared to non-targeted NP against lung cancer cells. Finally, the NP showed negligible toxicity towards normal MRC9 lung fibroblast cells [42].

Chuda Chittasupho *et al.*, 2017, hypothesized that targeted inhibition of CXCR4 in breast cancer cells should suppress CXCR4-positive tumor cells toward secondary metastatic sites. They emphasized their research to identify the efficacy of CXCR4 targeted dendrimers

carrying DOX (LFC131-DOX-D4) on cellular binding, cytotoxicity and migration of BT-549-Luc and T47D breast cancer cells was investigated. PAMAM dendrimers encapsulating DOX was surface functionalized with LFC131 peptide which recognized CXCR4 expressed on the surface of breast cancer cells. The LFC131-DOX-D4 bound to breast cancer cells resulting in significantly enhanced *in vitro* cellular toxicity as compared with non-targeted dendrimers. The LFC131-D4 exhibited remarkable reduced migration of BT-549-Luc breast cancer cells toward chemoattractant. Finally, the work demonstrated the potential utility of LFC131-dendrimer conjugates for breast cancer therapy and metastasis [43].

Nigam S, Bahadur *Det al.*, 2017, demonstrates the fabrication and characterization of a new class of cationic, biocompatible, peptide dendrimers, which were then used for stabilizing and functionalizing magnetite nanoparticles for combinatorial therapy of cancer. The synthesized peptide dendrimers have the edge over the widely used PAMAM dendrimers due to better biocompatibility and negligible cytotoxicity of their degradation products. The surface engineering efficacy of the peptide dendrimers and their potential use as drug carriers were compared with their PAMAM counterparts. The peptide dendrimer was found to be as efficient as PAMAM dendrimers in its drug-carrying capacity, while its drug release profiles substantially exceeded those of PAMAM's. A dose-dependent study was carried out to assess their half maximal inhibitory concentration (IC₅₀) *in vitro* with various cancer cell lines. A cervical cancer cell line that was incubated with these dendritic nanoparticles was exposed to the alternating current magnetic field (ACMF) to investigate the effect of elevated temperatures on the live cell population. The DOX-loaded formulations, in combination with the ACMF, were also assessed for their synergistic effects on the cancer cells for combinatorial therapy. The results established the peptide dendrimer as an efficient alternative to PAMAM, which can be used successfully in biomedical applications [44].

Ozturk *Ket al.*, 2017, developed a dendrimer-based drug delivery system targeting Flt-1 (a receptor for vascular endothelial growth factors (VEGF)) receptor to improve the therapeutic efficacy of gemcitabine in pancreatic cancer. Synthesized polyethylene glycol (PEG)-cored PAMAM dendrimers, which bear anionic carboxylic acid groups on the surface were modified with PEG chains, which were then conjugated with Flt-1 antibody. Following structural and chemical characterization studies, gemcitabine HCl-dendrimer inclusion complexes were successfully prepared. These complexes were efficiently engulfed by Flt-1 expressing pancreatic cancer cells, which enhanced the cytotoxicity of gemcitabine. Moreover, pancreatic tumors established in mice were highly targeted by PEG-cored Flt-1 antibody-conjugated dendrimers and increased accumulation of these gemcitabine-loaded complexes exhibited satisfactory *in vivo* anti-cancer efficacy [45].

Bodewein L *et al.*, 2016, has tested polyamidoamine (PAMAM) dendrimers of generations G3.0, 3.5, 4.0, 4.5 and 5.0 and polypropyleneimine (PPI) dendrimers G3.0, 4.0 and 5.0 in zebrafish embryos for 96h and human cancer cell lines for 24h, to assess and

compare developmental *in vivo* toxicity with cytotoxicity. The zebrafish embryo toxicity of cationic PAMAM and PPI dendrimers increased over time, with EC₅₀ values ranging from 0.16 to just below 1.7 μ M at 24 and 48hpf. The predominant effects were mortality, plus reduced heartbeat and blood circulation for PPI dendrimers. Apoptosis in the embryos increased in line with the general toxicity concentration-dependently. Hatch and dechorionation of the embryos increased the toxicity, suggesting a protective role of the chorion. Lower generation dendrimers were more toxic in the embryos whereas the toxicity in the HepG2 and DU145 cell lines increased with increasing generation of cationic PAMAMs and PPI dendrimers. HepG2 were less sensitive than DU145 cells, with IC₅₀ values $\leq 2\mu$ M (PAMAMs) and $\leq 240\mu$ M (PPIs) for HepG2 and $\leq 13.24\mu$ M (PAMAMs) and $\leq 12.84\mu$ M (PPIs) for DU145. Neither in fish embryos nor cells toxicity thresholds was determinable for anionic PAMAM G3.5 and G4.5. Their study demonstrated that the cytotoxicity underestimated the *in vivo* toxicity of the dendrimers in the fish embryos [46].

Prashant Kesharwani *et al.*, 2014, describes comparative data pertaining to generation dependent cancer targeting propensity of Poly (-propyleneimine) (PPI) dendrimers. PPI dendrimers of different generations (3.0G, 4.0G and 5.0G) were synthesized and loaded with Melphalan. Results from loading, hemolysis, hematologic, cytotoxicity and flow cytometry assay depicted that as the generation of dendrimer increased from fourth to fifth, the only parameter i.e. toxicity is increased exponentially. However, others parameters, i.e. loading, sustained release behavior, and targeting efficacy increased negligibly. Kaplan-Meier survival curves clearly depicted comparable therapeutic potential of PPI4M with PPI5M. *In vivo* investigations in Balb/c mice again favored 4.0G PPI dendrimer to be preferable nanocarrier for anticancer drug delivery owing to analogous anticancer potential. The outcomes of the investigation evidently projects 4.0G PPI dendrimer over 3.0G and 5.0G dendrimer in respect of its drug delivery benefit as well as superior biocompatibility [47].

Wenjun Yang *et al.*, 2009, executed their research by conjugating partially acetylated generation 5 (G5) polyamidoamine (PAMAM) dendrimer with the targeting moiety (biotin) and the imaging moiety (fluorescein isothiocyanate, FITC), and the resulting dendrimer-biotin conjugate was characterized by ¹H NMR, UV-vis spectrum. As revealed by flow cytometry and confocal microscopy, the bifunctional conjugate (dendrimer-biotin-FITC) exhibited much higher cellular uptake into HeLa cells than the conjugate without biotin. The uptake was energy-dependent, dose-dependent, and could be effectively blocked by dendrimer-conjugated biotin. Their results indicated that the biocompatible biotinedendrimer conjugate might be a promising nano-platform for cancer therapy and cancer diagnosis [48].

Diagnostic applications of dendrimers

Advances in nanotechnology have enabled development of dendrimers that can be used as diagnostic aids in diverse molecular imaging application, particularly diagnostic applications such as-

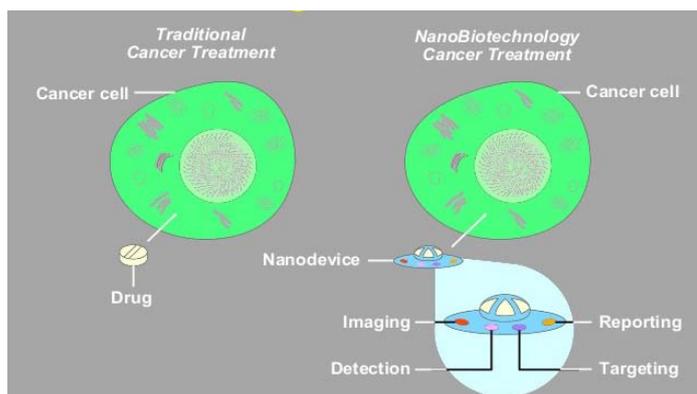


Fig. 9: Nanodevices as a link between detection, diagnosis and treatment

- a. Cancer Imaging
- b. Photodynamic therapy
- c. Boron neutron capture therapy
- d. Tecto-dendrimer Nanodevice
- e. Photothermal therapy

a. Cancer imaging

➤ Imaging techniques are used in cancer therapy to diagnose and identify the location of the disease sites, stage, plan treatment and potentially find recurrence.

➤ MRI is a non-invasive technique for the diagnosing tumors in soft tissues [8].

➤ MRI agents were linked with dendrimer molecules for contrast enhancement, improved clearance characteristics and potential targeting.

E. g.: Gadolinium contrast agents have been conjugated to PPI and evaluated for use as macromolecular MR contrast agents [27, 49].

➤ Computer tomography is a standard method of imaging associated with cancer diagnosis.

➤ Similar to Gd-Dendrimer for MRI, Iodinated contrast agents used for CT.

E. g.: Synthesis of iodinated contrast agents based on Iobitridolconjugated G3-G5 poly (lysine) dendrimers with PEG cores of varying lengths for possible tumor microvasculature CT-Imaging [27, 50].

b. Photodynamic therapy: (PDT)

➤ Photodynamic therapy relies on the activation of a photosensitizing agent with visible or near IR light [27].

➤ When photosensitizer exposed to specific wavelength of light, they produce form of oxygen which kills cancer cells [51, 52].

➤ PDT has been shown to reduce tumors by direct cell killing, destruction of tumor neovasculature and triggering of an acute inflammatory response that attracts leukocytes to the tumor [27].

➤ Dendrimers in PDT are designed to-[51,52]

- Deliver the agent only to affected tissues by recognizing the specific molecule on cancer cell.
- Fasten the rate of treatment.
- No need to wait for elimination of photosensitizer from normal cells.

c. Boron neutron capture therapy-(BNCT)

➤ BNCT is based on a lethal $[^{10}\text{B}(n,\alpha)^7\text{Li}]$ capture reaction that occurs $[^{10}\text{B}]$ is irradiated with low energy thermal neutrons to produce high energy α -particles and 7 Li nuclei

➤ The emergence of BNCT as a significant clinical treatment has been limited by either lack of sufficient tumor targeting or sub-therapeutic $[^{10}\text{B}]$ accumulation in malignant tissues.

➤ To this end macromolecular delivery vehicles have been prepared to enhance both the quantity of and targeting of $[^{10}\text{B}]$ to tumor cells by conjugating Boron containing complexes to monoclonal antibodies or receptor targeting agents [27, 52].

➤ Boron present adjacent to the tumor cells disintegrates after capturing neutrons produce high energy heavy charged particles that destroy only cells in close proximity to it leaving adjacent normal cells [51,52]

E. g.: Dendrimers like PAMAM-transfer 5000 Boron derivatives.

d. Tectodendrimer as nanodevice [51]

Tecto dendrimers are multifunctional devices built from a core dendrimer, surrounded by shell dendrimers. Each shell dendrimer performs one function

e. Photothermal therapy [27]

➤ Gold-based nanoparticles have been developed that strongly absorb light in the near IR region, facilitating deep optical penetration into tissues, generating a localized lethal dose of heat at the site of the tumor.

➤ Dendrimer-encapsulated gold nanoparticles have been prepared and identified for their potential use towards the photothermal treatment of malignant tissue.

E. g. Amine-terminated G5-PAMAM dendrimer-entrapped gold nanoparticles were prepared and covalently conjugated to fluorescein and folic acid for targeted delivery to tumor cell overexpressing folic acid receptors.

CONCLUSION

Nowadays understanding the disease, development of newer targeted therapies and treatment of several forms of cancer remains a major challenge. Among all the latest developed Nanotechnologies, Dendrimer mediated drug delivery has emerged as a superior opinion to overcome the shortcomings of conventional chemotherapy. Dendrimer act as a carrier for the delivery of drug to tumor by encapsulation (or) conjugation. This delivery to tumor site mostly occurs through PAMAM, PPI, and PLL dendrimers by either passive or active targeting. Many advances have been made to obtain safe and efficacious dendrimer-based formulation for increasing the specificity and efficacy towards diagnosis and treatment of cancer. The future scope of dendrimers in research depends on its applicability in areas such as synthesis, drug delivery, biotechnology, nanotechnology, detection, catalyst and cosmetics.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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