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Literature Search on Using Dendrimer Nanoparticles as Drug Delivery Vehicles

Sivateja Kasaraneni
Governors State University

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Sivateja Kasaraneni

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Dendrimer nano particles as drug delivery vehicles

Abstract

The architectural design of dendrimers, multivalency, well-defined molecular weight and higher degree of branching differentiates them as unique and excellent nanocarriers in therapeutic applications such as drug delivery, gene transfection, tumor therapy, imaging and diagnostics. Nanoparticle drug-delivery systems are well known to increase the stability and selectivity of therapeutic agents. However immunogenicity, reticuloendothelial system uptake, drug leakage, cytotoxicity, hemolytic toxicity, poor aqueous solubility restrict the use of these drug delivery systems. These defects are overcame by surface engineering of the dendrimer molecule.

Drug molecule can be efficiently conjugated or encapsulated into the interior of the dendrimer or physically adsorbed onto the surface of the dendrimer. And therefore, desired properties of the drug delivery system to specific needs of the medicine and its therapeutic functions such as in anticancer therapies and diagnostic imaging has highlighted the advantage of these systems as newest class of macromolecular nano-scale delivery devices. The focus of this review is mainly on the work done in the usage of dendrimer nanoparticles as drug delivery vehicles and its development in recent years.

Dendrimer nano particles as drug delivery vehicles

Introduction

Many of the novel drugs discovered by the pharmaceutical industry today are hydrophobic compounds and have low solubility making difficult the delivery of these new drugs, also affect the delivery of many existing drugs .Since we have limited choices of delivery technologies and higher complexity in dissolution testing the ability to deliver these low solubility profile drugs through any novel systems is gaining significance lately as most of these new drugs are based upon a larger share of revenue within the pharmaceutical market by pioneer companies.

Most of the poorly soluble drugs have instigated the growth of many drug delivery technologies through either mechanical or chemical modification of the outer part of drug molecule or by physically converting the macro molecular characteristics of drug particles. These mechanization processes include particle size reduction through spray drying and communition, drug dispersion in carriers, cyclodextrin mediated inclusion complexes and micellar solubilization [1-3]. But the employment of micelle mainly depends on their structure and stability; it is important to seek micelles with stable size and structure. Dendrimers with hydrophilic exterior and hydrophobic interior have shown to exhibit micelle like properties[4] and has been proven to be advantageous over conventional polymer micelles since their structure is maintained at all concentrations because the interior hydrophobic segments are covalently attached.

The unique properties of Dendrimer such as its multivalency, immense branching, globular shape and controlled surface functionalities make them promising candidates for drug

delivery [5-8], magnetic resonance imaging [9-11] and as gene carriers [12-15] to the development of antivirals and anti-cancer drugs [16-19]. Dendrimers also provide path to various novel polymer structures that are possibly relevant to drug delivery applications besides contributing a multivalent backbone to attachment of the drug.

Design and constitution

Dendrimers are built from a series of branches around an inner core, providing products of different generations. They can be constructed from any core molecule and the branches similarly constructed from any bi-functional molecule. Certain general principles are being established [20] for preparing these novel systems as delivery vehicles which are listed as: i) dendrimer design can effectively influence pharmacokinetics; ii) neutral and negatively charged dendrimers are normally bio-compatible; iii)targeting components bound to surface of dendrimer can be used to specifically treat cancerous cells with over-expressed receptors; iv)targeting components can also be internalized into the empty space present between core and periphery, or bonded covalently to surface functional groups.

The structure of dendrimer can be put into three parts: a) multivalent surface, with a high number of possible reactive sites; b) The ‘outer shell’ just beneath the surface having a well-defined micro environment protected from outside by the dendrimer surface; c) The core, wherein higher generation dendrimers are protected from the surroundings, creating a smaller environment surrounded by the branches of dendrimers [21]. Thus, dendrimer as a host provides the best interior for encapsulation of the guest substances. The multivalent surfaces on a higher-

generation dendrimer can contain a very large number of functional groups. This makes the surface of the dendrimer and outer shell best for host–guest interactions.

The stepwise synthesis of these novel systems with level of control yields molecules with unique molecular weight, high degree of branching, and with a number of well-defined peripheral groups which is not possible with many linear polymers and also these dendritic carriers provide the passive targeting of drugs to tumor sites. The unique properties of dendritic polymers over linear polymers make them interesting candidates for the development of anticancer drug delivery systems.

In a dendrimer the branching units are termed as generation, initiating with the central branched core as generation 0 and increasing with each consecutive addition of branching units in which number of end groups rises exponentially with these additions and attain a more globular shape due to increase in diameter[22]. Researchers have studied the effect of solubility enhancement with dendrimer generation and most of them noted that increasing generation number resulted in increased solubility of a hydrophobe. But as compared to higher generations, dendrimers unto generation 3 have proved to be more biocompatible and less immunogenic.

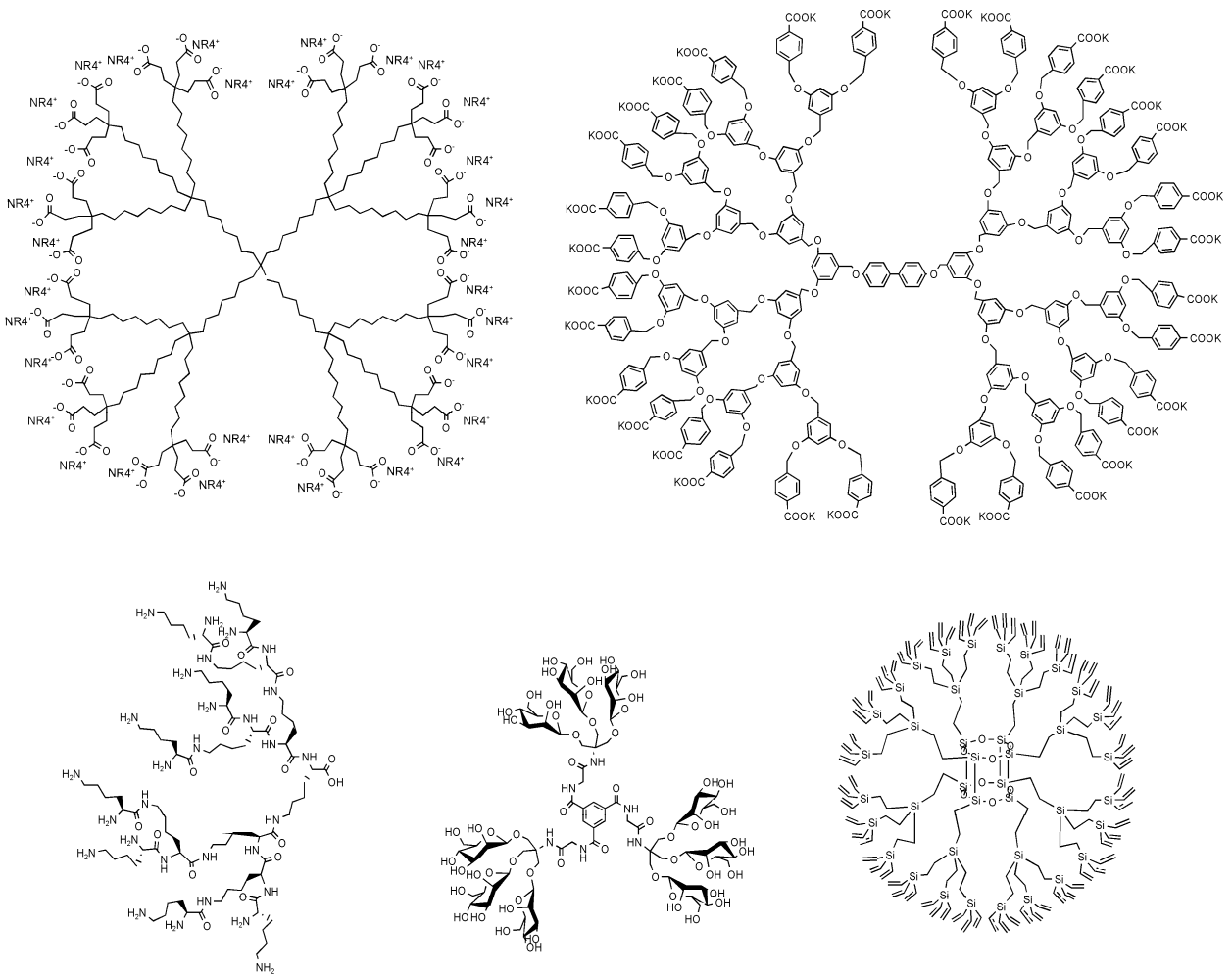


FIGURE 1.Designs of various dendrimers. Top left: unimolecular micelle [23]; top right: polyaryl ether dendrimer [24]; bottom left: polylysine [25]; bottom middle: carbohydrate dendrimer [26]; bottom right: silicon based dendrimer [27].

Synthesis

Two strategies have been into use for synthesis of dendrimers one process is known as divergent method invented by Tomalia and Newkome [28-30] which dendrimer can be grown from a central core towards outside and built out generation by generation. Nevertheless, the

high number of reactions which have to be performed on a single molecule (with many equivalent reaction 'sites'), demands very effective transformations (yield=99+ %) to avoid defects. One good example is PAMAM (polyamidoamine) dendrimers and the other one is known as Frechet's convergent method on which dendrimer can be grown from the periphery inwards, ending at the core [31], example polyaryl ether dendrimers. In this method only a small number of reactive sites are functionalized in each step, giving less number of possible side-reactions in each step. Each synthesized generation of the dendrimer hence can be purified, although purification in the higher-generation dendrons becomes more massive, because of the increasing similarity between reactants and formed product. Anyhow, with proper purification after each step, dendrimers without any defects can be obtained. It is also possible to produce an interesting asymmetric dendrimer structures by joining two different segments of dendrimer in a strict fashion.

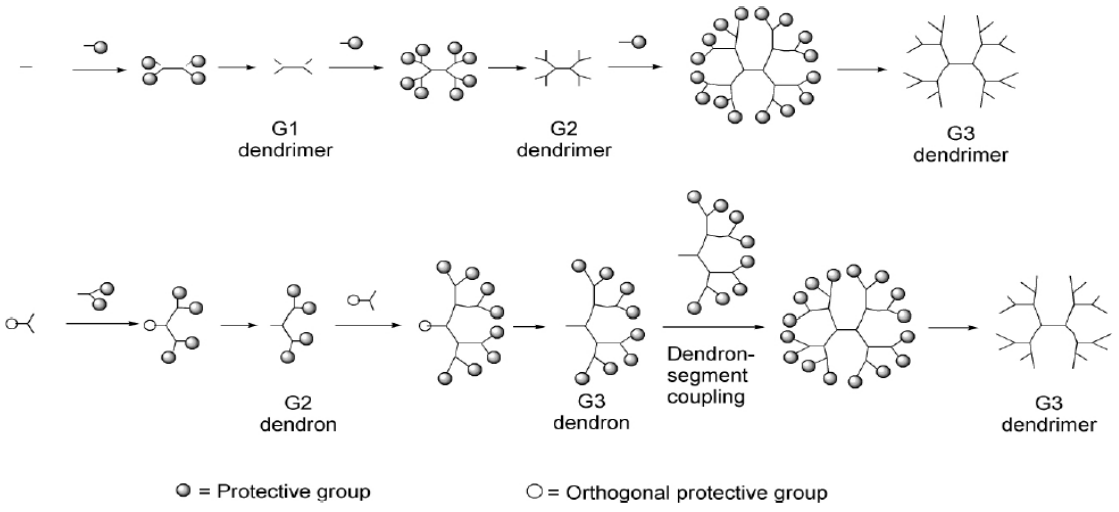


FIGURE 2 -Schematic Dendrimer synthesis Top: Divergent strategy, Bottom: Convergent strategy [32]

Development of biodegradable dendrimers

Apart from biocompatible and water soluble dendrimers, recently a few dendrimers have been designed to be biodegradable, and monomers that are products in metabolic pathways or intermediates in a chemical reaction have been included. For instance, many peptide based dendrimers like those based on polylysine (figure 3c) [33] with suitable peripheral changes [34] have been noted and have been developed as promising vaccines and antibacterial substances. Highly compatible PEO {poly (ethylene oxide)} has been lately prepared by Frechet et al [35] as a challenging and promising backbone for biological applications. They have also explored polyester dendrimers [36, 37] based on the monomer 2, 2-bis propionic acid (figure 3d) with PEO as substances for development of delivery systems for anticancer drugs. Grinstaff et al [82] also prepared polyester dendrimer based on glycerol, succinic acid (figure 3e), lactic acid and phenylalanine which have been successfully used in tissue engineering. Several other dendrimers such as triazines prepared by Simanek et al and their biological applications has been demonstrated [38].

Dendrimers as drug delivery vehicles and their pharmaceutical applications

Controlled release to the desired target, biodistribution of drug and pharmacokinetics are the key factors which help in producing an ideal dendrimer and such ideally produced dendrimer should also exhibit low toxicity, drug-loading capacity and high aqueous solubility, favorable retention, specificity, appropriate bioavailability and biodistribution, biodegradability [39]. A drug is either covalently conjugated or non-covalently encapsulated inside the dendrimer to form macromolecular prodrugs, thereby used for drug delivery.

In order to obtain particular cellular treatment, drug carriers must be designed to direct the drug into the cell and one good example for cell specific dendritic drug vehicles is a dendrimer derivatized with folic acid (pteroyl-L-glutamic acid). Folic acid is an important substrate for uptake in cells by the folate receptor pathway. Since the folate receptor is over-expressed in cancerous cells, these folic acid derivatized dendrimers are taken up by cancer cells as an alternative to normal cells, making these dendrimers well-suited for the cancer specific drug delivery of cytotoxic candidates[40,41].

Dendrimers as drug carriers into DNA

Dendrimer mediated drug delivery has mainly been focused on the delivery of DNA drugs into the cell nucleus for gene or anti-sense therapy, and many reports have been published on the possible use of unmodified amino-terminated PPI or PAMAM dendrimers as non-viral gene transfer agents, improving the transfection of DNA into the cell nucleus. It has also been found that partially fragmented dendrimers are better suited for gene delivery than the complete dendrimers since they have a more flexible structure (fewer amide bonds) and form a more tightly packed complex with DNA, and a fragmentation step consisting of hydrolytic cleavage of the amide bonds is needed to enhance the transfection efficiency. As experiments suggests a few cationic, amino-terminated dendrimers which are partially covalently modified with drugs, can be used as extracellular ‘stickers’ in ‘extracellular matrix-targeted local drug delivery,’ giving a very high local concentration of the drug near the cellular surface[42]. However, this drug (gene) delivery technique is only appropriate if a particular drug or gene has to be introduced into a broad range of cells.

Dendrimer nano particles as drug delivery vehicles

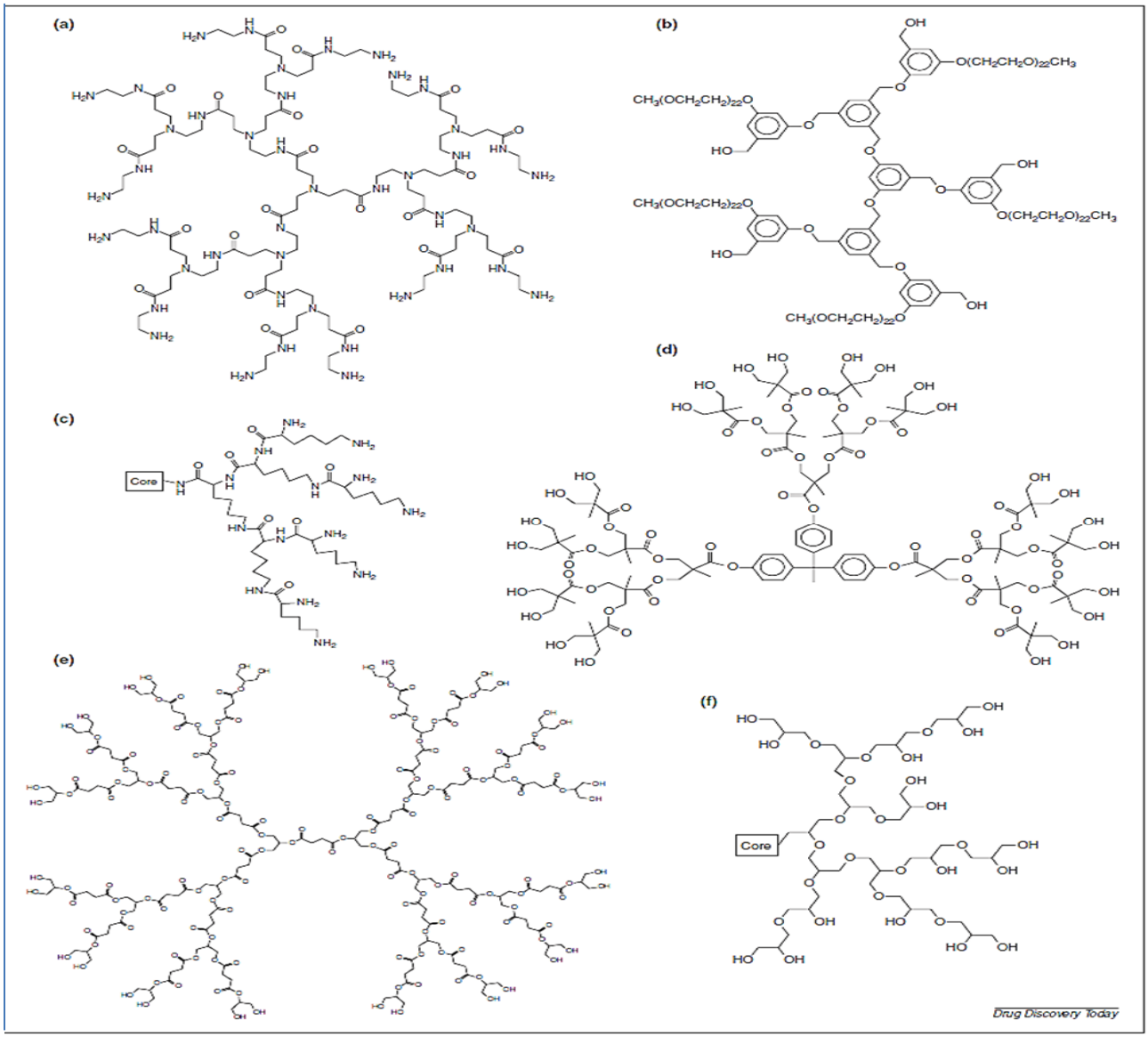


Figure 3.[31-38].Biocompatible dendrimers.(a) PAMAM dendrimer (b) Polyaryl ether dendrimer(c) Polylysine dendron (d) Polymer dendrimer based on 2,2-bis(hydroxymethyl)propionic acid(e) Dendrimers based on glycerol and succinic acid (f)Dendritic polyglycerol.

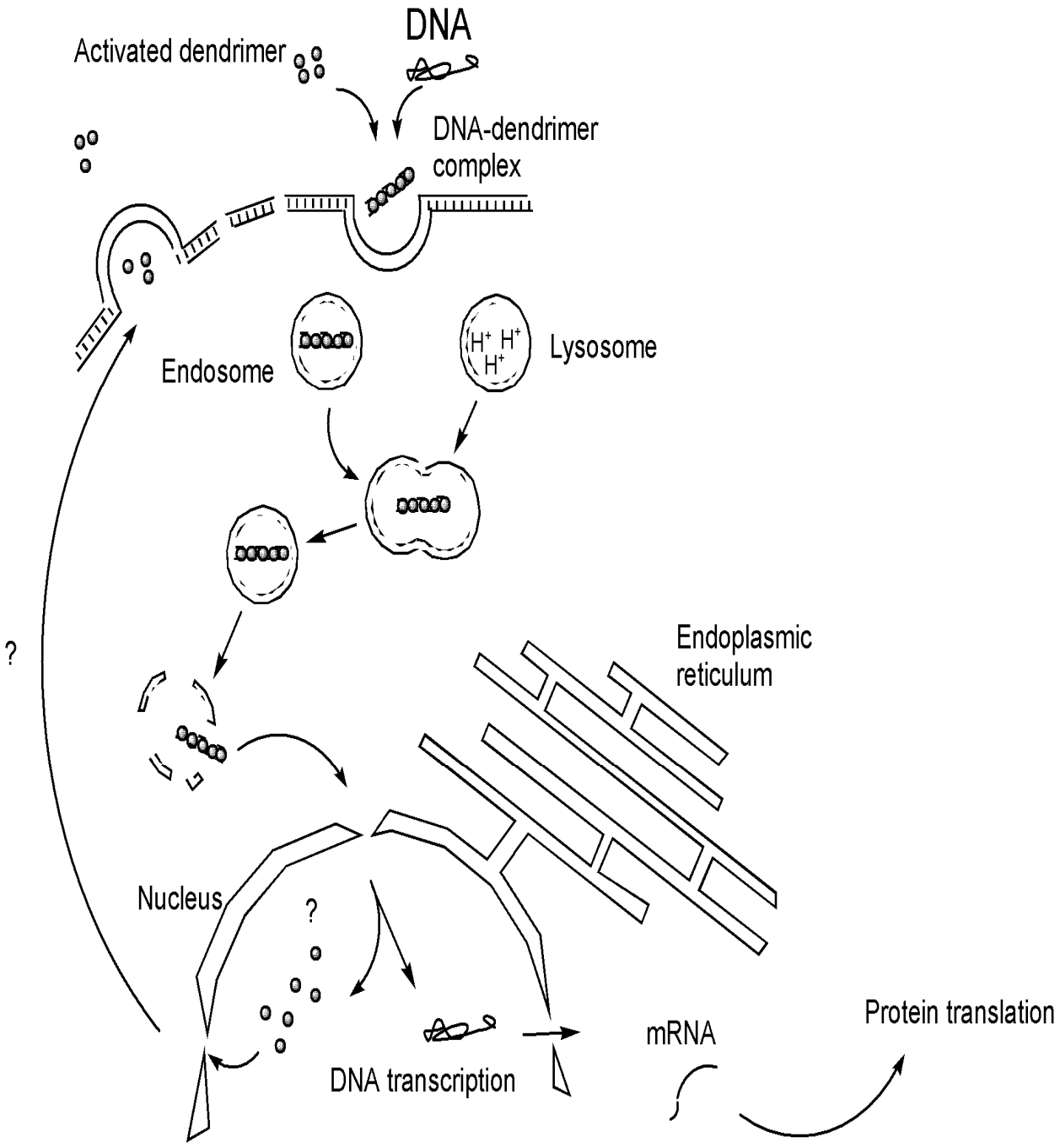


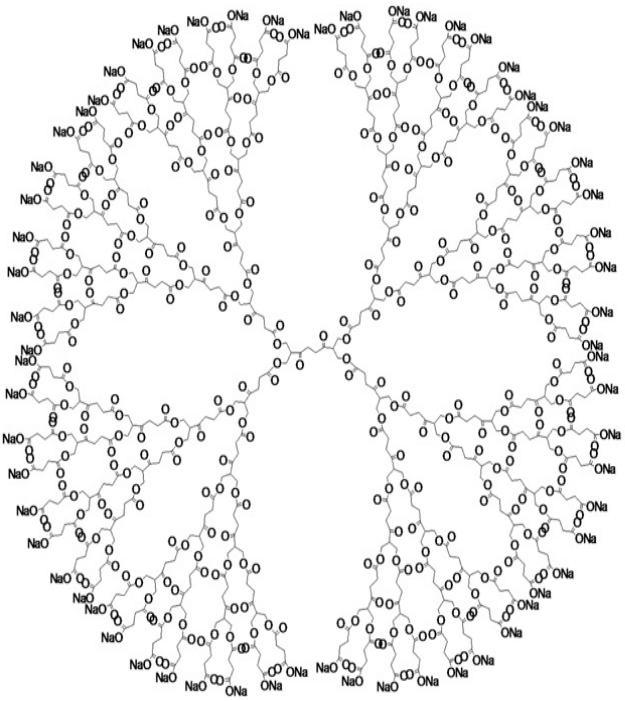
FIGURE 4.Transfection of DNA into the cell nucleus with the help of 'activated' dendrimers [32].

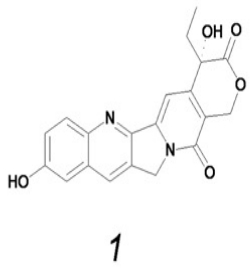
Delivery of anticancer drugs through dendrimers

Passive targeting of the drug into tumor site by these polymeric carriers has been possible because of the limited lymphatic drainage and increased permeability of tumor vasculature to macromolecules [43]. Both of these factors lead to the accumulation of macromolecules in tumor site in which the phenomenon termed as the enhanced permeation and retention (EPR) effect. Dendritic unimolecular micelles integrated with anticancer drugs such as methotrexate, 5-fluorouracil has attained greater scope by addition of stabilizing PEO chains on the periphery of the dendrimers. Release of drugs can be controlled from encapsulated compartment of micelle by using hybrids of PEO and pH-sensitive hydrophobic acetal groups on the dendrimer periphery.Poly (glycerol and succinic acid) dendrimers for the delivery of group of anticancer drugs such as camptothecins were investigated. In a basic study by Griffin et al, G4-PGLSA dendrimers attached with carboxylate or hydroxyl peripheral groups were used to encapsulate 10-hydroxycamptothecin for delivery to carcinogenic cells [44]. Because of the precipitation of G4-PGLSA-OH solution, relatively high water soluble G4- PGLSA-COONa polymeric dendrimer was used and 10-HPCT was favorably encapsulated and this has shown significant cytotoxicity with less than 5% of viable cells at 20μM when exposed to MCF-7 human breast cancer cells whereas the void dendrimer showed no cytotoxicity. A 3400 Da PEG core was inserted into the G4-PGLSA where 20 fold increase in water solubility of 10-HPCT was noted down following encapsulation and same cytotoxicity's were observed for encapsulated and free 10-HPCT when examined by HT-29 human colon cancer cells and hence, conclusions drawn from above two studies led to the selection of G4- PGLSA-COONa polymeric dendrimer as a drug carrier for 7-butyl-10-aminocamptothecin (BACPT) [45] and 10-HPCT.

Dendrimer nano particles as drug delivery vehicles

Investigations were carried out for the anticancer activity on a human cancer cell line panel including MCF-7 breast carcinoma, HT-29 colon cancer, SF-268 astrocytoma and NCI-H460 large cell lung carcinoma. Cellular uptake, cellular retention and solubility studies were also done for MCF-7 cells.10-HCPTencapsulated G4-PGLSA-COONa showed entire release of the drug within nearly 6 hours, indicating that the delivery system is more efficient when administered via intratumoral injection. Delivery of BACPT and 10-HCPT aided by dendrimer resulted in lowered IC50s for all cell lines tested (Fig. 5); When compared to free 10- HCPT dissolved in DMSO the encapsulated 10-HCPT exposed to HT-29,MCF-7, NCI-H460, and SF-268 cells, IC50s were surprisingly reduced by 3.5, 7.1, 1.9, and 2.8-fold respectively. Exposure of BACPT to the successive cell lines above led to IC50 reductions of 1.2, 3.2, 1.9, and 5.7-fold respectively. Uptake studies proved that 10-HCPT encapsulated dendrimer was localized much faster than free 10-HCPT, with 8-fold intracellular concentrations at 10 h and 16-fold intracellular concentrations at 2 h and also longer retention time in the cell was showed by drug delivered through the dendrimers, with 50% of delivered 10-HCPT available in the cell after 30 min, in comparison to 35% of free drug. Hence, an improved uptake and retention was observed because of the increased toxicity of delivered camptothecins.





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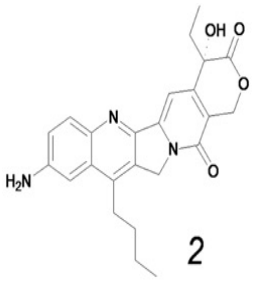

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Enhanced Anti-Cancer Activity of Dendrimer-Encapsulated Camptothecin Analogues

Cell line	IC_{50} (nM)		Enhancement over DMSO	IC_{50} (nM)		Enhancement over DMSO
	Encaps-ulated 10HCPT	DMSO dissolved 10HCPT		Encapsulated BACPT	DMSO dissolved BACPT	
HT-29	113.0	32.3	**3.5**	11.9	10.0	**1.2**
MCF-7	72.0	10.1	**7.1**	26.7	8.3	**3.2**
NCI-H460	32.4	16.7	**1.9**	1.2	0.6	**1.9**
SF-268	13.1	4.6	**2.8**	6.6	1.2	**5.7**

FIGURE 5.Dendrimer aided drug delivery based on succinic acid and glycerol. Left, chemical structure of G4-PGLSA-COONa.Right,chemical structures of (1)10-hydroxycamptothecin and (2)7-butyl-10-aminocamptothecin with IC50 values for HT-29 colorectal adenocarcinoma, MCF-breast carcinoma,NCI-H460 large cell lung carcinoma, and SF-268 astrocytoma human cancer cell lines[45].

Some of the anticancer drugs like etoposide and doxorubicin were also encapsulated within the micelles where etoposide which is more lipophilic attained a loading capacity of approximately 22% compared to doxorubicin. Etoposide encapsulated dendrimer showed equivalent toxicity to free etoposide at identical concentrations of the drug whereas the unloaded one was non-cytotoxic to epithelial cells of porcine kidney. Paclitaxel, a mitotic inhibitor used in cancer chemotherapy achieved improved water solubility (ranging from 80-128µg/mL with

increasing generations from G3-G5) with polyglycerol dendrimer proving that a hydrophobic core is not so essential for solubilization and encapsulation of non-polar drugs [46].

Improved solubility and increased toxicity (lower IC50) of hydrophobic anti-cancer drugs through non-covalent encapsulation was shown by medium-generation dendrimers (G4–G6).Therapeutic agents are localized within the inner core space or by micellar arrangement of the dendrimers. These delivery systems are more efficient when administered via intratumoral injection because they are deprived of controlled release pharmacokinetics when compared to most of the other systems releasing their payload over several hours. Reduced drug toxicity and enhanced solubility have been shown when melamine-based dendrimers were used with the anticancer drugs such as methotrexate and 6-mercaptopurine [47].Sub chronic doses of drug-encapsulated dendrimers were given to C3H mice and ALT levels were tested to determine hepatotoxicity. ALT levels were reduced by 36% for the 6-mercaptopurine dendrimers and by 27% for methotrexate-encapsulated dendrimers compared to same C3H mice treated with drug alone.

Dendrimer drug conjugates

Another way to the development of dendrimers as anti-neoplastic agents is to take advantage of their well-defined multivalency for covalent attachment to the peripheral groups of the dendrimer. It offers various advantages over encapsulated drug dendrimers. Multiple drug molecules can be attached to any of the dendrimer and drug release can be controlled by introducing degradable linkages between the dendrimer and drug. Payload of the drug can also be turned by changing the generation number of the dendrimer.

Dendrimer nano particles as drug delivery vehicles

Kannan et al reported the synthesis of PAMAM-methotrexate conjugates from amine-terminated G3 PAMAM or carboxylic acid-terminated G2.5 PAMAM in order to check the activity of dendrimer-delivered methotrexate to sensitive and resistant CCRF-CEM human acute lymphoblastoid leukemia and CHO (Chinese hamster ovary cell lines) [48]. Amine-conjugated G3PAMAM showed no increased sensitivity compared to free methotrexate while carboxylic acid-conjugated G2.5 PAMAM system showed increase in sensitivities of 8- and 24-fold for MTX-resistant cell lines CEM/MTX and RII despite both polymers were conjugated to the drug by the formation of amide bonds. Charge of the dendrimer carrier after cleavage of methotrexate from the peripheral groups was the main reason for differences in cytotoxicity. Decrease in lysosomal residence time for the cationic PAMAM is caused by the lysosomotropic effect, in which the dislocation of small basic molecules from the lysosome by positively-charged dendrimers is associated by an increase in pH and overall lysosomal disruption. As a result, the conjugates experience reduced interactions with proteases and diminished drug release indicating higher probability of dendrimer-drug conjugates for the treatment of carcinomas importantly those that have manifested immunity to chemotherapeutics.

Frechet and Szoka reported an another remarkable dendritic drug delivery where an asymmetric doxorubicin-functionalized bow-tie dendrimer was produced by PEGylation of one side of a third generation 2,2-bis(hydroxymethyl)propionic acid dendrimer and attachment of the drug through an acyl hydrazone linkage to the other side (G4)resulting in a total of 8–10 wt.% doxorubicin [49] (Fig.6). A pH sensitive linkage has been used in between the drug and dendrimer to release the drug promptly in the cell. Tumor uptake was nearly 9-fold higher compared to free doxorubicin when intravenous injection to BALB/c mice with sub cutaneous C-

26 colon carcinoma tumors was given. No cures were observed with drug alone treatments whereas a single injection of the drug dendrimer conjugate of doxorubicin caused complete tumor recession and 100% survival of mice in a period of two months.

An interesting research has been carried out by Duncan et al. who have prepared conjugates of PAMAM dendrimers with cisplatin [50,51], a potent anticancer drug which is used to treat several types of cancers including sarcomas, some carcinomas, lymphomas, and particularly testicular cancer. But the main problem is they have poor aqueous solubility and nonspecific toxicity. The dendrimer platinum complex show decreased systemic toxicity, increased solubility and selective accumulation in solid tumors and has also been found to show increased ability relative to cisplatin in the treatment of B16F10 melanoma.

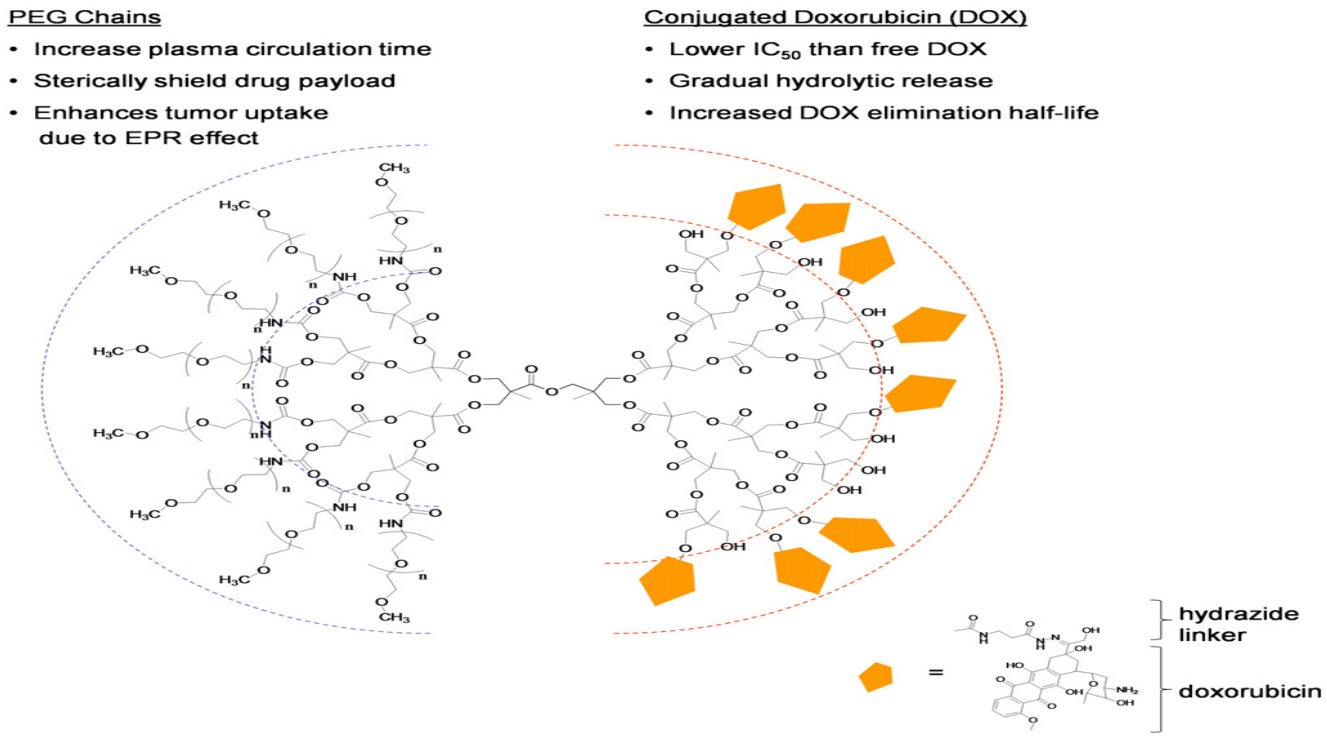

Fig.6.Doxorubicin conjugated dendrimer.PEGylated polyester dendrimer with altering molecular weight, pharmacokinetics, aqueous solubility, biodistribution and drug-loading [49].

Dendrimer nano particles as drug delivery vehicles

Aliphatic polyester dendrimers on 2, 2-bis (hydroxymethyl) propionic acid are promising dendrimer backbones for the advancement of anticancer drug conjugates. In initial studies, a water-soluble polyester dendrimer was found to be biocompatible in vitro and in vivo [52]. Biodistribution studies in mice showed that the fourth-generation dendrimer with a molecular weight of 3800 had a circulation half-life of less than 10 min and was rapidly excreted in the urine. Although the observed lack of accumulation of the dendrimer in vital organs is a desirable feature for many biological applications, a longer half-life is required to obtain passive tumor targeting via the EPR effect.

In other study, hybrids of polyester dendrimers and PEO star polymers (Fig.7a) [53] have been synthesized with an increase in molecular weight to 22,000. Hybrids with similar polydispersity are given by PEO since it is highly biocompatible [54] and available in low polydispersity (polydispersity index of 1.02). In addition to supplying a multivalent backbone for adherence of the drug, dendrimers also provide path to various new polymer architectures that are potentially relevant to drug delivery applications and one good example is 'Bow-tie' hybrids [55] of polyester dendrimers and PEO which were prepared by Gillies and Frechet group (Figure 7b) with various molecular weights and architectures by modifying the number of PEO arms and their molecular weights.

Biodistribution studies in vivo show that these new carriers with a molecular weight of more than 40,000 are generally long circulating with half-lives greater than 24 h, biodegradable and nontoxic in vitro. These highly branched carriers are excreted at a slower rate into the urine

by glomerular filtration, presumably as a consequence of their decreased flexibility and ability to axially diffuse through pores relative to linear polymers. Significant levels of the high molecular weight, long circulating bow-tie polymers is incorporated in subcutaneous B16F10 solid tumors via the EPR effect, making these new carriers, promising candidates for chemotherapeutic applications.

Lately, some advances made in polymer and dendrimer chemistry have also provided access to a new class of macromolecules termed ‘dendronized polymers’ that is, linear polymers that bear dendrons at each repeat unit. Extended rigidified conformations of dendronized polymers are attained as a result of steric interactions, at high-generation numbers. Grayson, Fréchet and Lee et al. [56] have prepared polyester dendronized polymers having polyester dendrons based on backbones ranging from nondegradable poly (4-hydroxy) styrene to biodegradable polymers such as substituted polycaprolactone (Figure 7c) .As a result of their solubilizing groups, long circulation half-lives, numerous peripheral groups for the attachment of drugs and targeting moieties these polymers also show an assurance for drug delivery applications.

Dendrimer nano particles as drug delivery vehicles

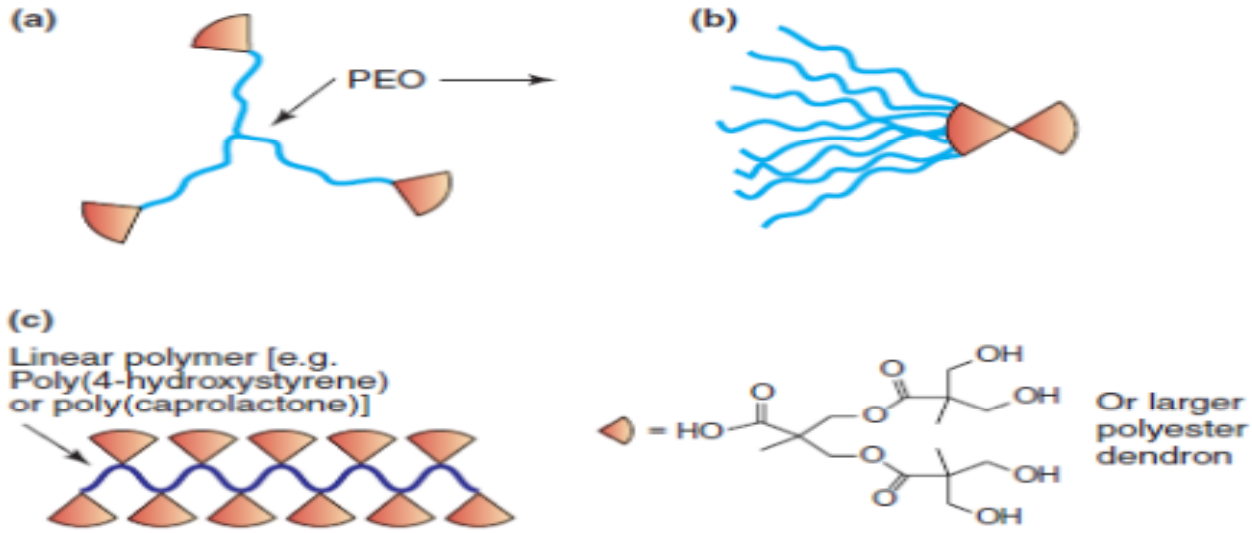

Figure 7.Linear polymer 'bow-tie' hybrids (a) Hybrid of polyester dendrons and PEO star [53] (b) 'Bow-tie' hybrid of PEO and polyester dendrimers [55] (c) Polyster dendronized linear polymer [56].

Boron neutron capture therapy

Boron neutron capture therapy (BNCT) involves a lethal 10B (n, α) ^{7}Li capture reaction that occurs when ^{10}B is irradiated with low-energy thermal neutrons to yield high energy α-particles and ^{7}Li nuclei. These particles have limited path lengths in tissue (<10 μm) and thus their toxicity is limited to cells that have internalized ^{10}B [57]. The use of BNCT as an important clinical treatment modality has been limited by either a lack of enough of tumor targeting or sub therapeutic ^{10}B accumulation in cancer tissues. So in order to achieve tumor targeting in case of BNCT, macromolecular delivery vehicles have been prepared to enhance both the quantity and targeting of ^{10}B to tumor cells by conjugating boron-containing complexes to monoclonal antibodies [58].

Human gliomas have been targeted with boronated G5-PAMAM conjugated to anti-EGF receptor monoclonal antibodies, which work against overexpressed tumor cell receptors. Boronated dendrimer was delivered through intratumorally or convection enhanced delivery (CED), a positive pressure method that facilitates transport across the blood–brain barrier, resulting in high retention of boron in the gliomas, with nearly 50% more accumulation resulting from the CED method. In following studies, boronated PAMAM dendrimers were designed to target the epidermal growth factor (EGF) receptor, a surface receptor that is most commonly overexpressed in brain tumors [59]. Accumulation of boron in cell lysosomes takes place because the dendrimers were covalently attached to EGF and the resulting conjugates were found to be actively endocytosed in vitro. PEO chain and fluorescent dansyl group can also be conjugated to the linker for water solubility and spectroscopic monitoring respectively. However, a full biological evaluation of these systems has not yet been investigated.

Photodynamic therapy

Photodynamic therapy is based on the activation of a photosensitizing agent with visible or near-infrared (NIR) light. Upon excitation, a highly energetic state is formed which on reaction with oxygen yields a highly reactive singlet oxygen, leading to cell death in tumor region [60]. PDT has been shown to reduce tumors by destruction of tumor neovasculature, direct cell killing, and initiating an acute inflammatory response that attracts leukocytes to the tumor .Various studies have inquired into the use of dendrons and dendrimers composed in part of multiple 5-aminolaevulinic acid (ALA) for enhanced intracellular accumulation of porphyrins and improved delivery . Conversion of protoporphyrin IX (PpIX) a photosensitizer, which specifically gets localized in tumors [61], is caused by ALA which is formed during the first step

of the heme biosynthetic pathway. Di Venosa et al. reported the synthesis of a G0-ALA dendron with a free amine at the core and three ALA groups at the periphery [62]. Equimolar equivalents of dendron to free ALA showed similar efficacy inducing porphyrin generation upon exposure to LM3 murine mammary adenocarcinoma cells. It was noted that only one of three ALA molecules was cleaved from the dendron within the cells. In comparison to largely researched lipophilic hexyl ester derivative of ALA (He-ALA), G0-ALA dendrons resulted in high accumulations of porphyrin in vivo both through topical and systemic deliveries.

Dendritic molecules with up to 18 ALA moieties conjugated to the periphery by ester linkages that can be hydrolyzed in cellular conditions were reported by Edwards et al [63]. This delivery vehicle has been shown to result in higher toxicity after irradiation and increased production of PIX relative to free ALA. Lately, Fréchet and group [64] have used the multivalent aspect of the dendrimer surface to conjugate many two-photon absorbing chromophores to a porphyrin core. This system has been shown to generate singlet oxygen very effectively on irradiation at 780 nm. Recent studies are focused on the attachment of several solubilizing groups to the dendrimer periphery by preparing a water-soluble system.

Photo thermal therapy

This kind of therapy which involves minimally invasive tumor techniques[65-68].Nanoparticles consisting of gold atoms have been developed that strongly absorb light in the near-infrared region, assisting in deep optical penetration into tissues, generating a limited and toxic dose of heat at the site of a tumor [69]. Methods for preparing metal-encapsulated dendrimers for use in biomedical applications were reported within the last ten years with the aim of adding a finer degree of control for tuning the biological interactions shown by the metal

particles, including use as biomarkers and contrast agents with the ease of surface modification, improved biocompatibility, retention, and for photothermal therapy.

As reported by the Baker group fluorescein and folic acid were covalently conjugated to already synthesized NH2-terminated G5-PAMAMdendrimer-entrapped gold nano-particles for targeted delivery to tumor cells overexpressing folic acid receptors [70].The capacity of dendrimers to specifically bind to KB cells is shown in vitro and were internalized into lysosomes within 2 h. The applicability of these particles for targeted hyperthermia treatment and as electron-dense contrast agents was identified and further studies on in vivo performance are currently being conducted. Some of the work is pending in the study to extend the absorption spectra to the IR region.

Imaging

The important purpose served by imaging in oncology is to diagnose, locate, stage, plan treatment, and potentially find recurrence. Magnetic resonance imaging (MRI) and Computed tomography (CT) are two methods of imaging associated with cancer diagnoses. For visualizing both tumor vasculature and lymphatic involvement Gd-labeled PAMAM systems have been used. G8-Gd-PAMAM contrast agents play an important role in aiding to notice changes in tumor permeability after a single large dose of radiation treatment through MRI [71]. An advantage of using fluorescent probes for tumor detection is improved biocompatibility compared to other types of contrast agents, but is affected from the poor penetration of light through tissue. Thomas et al. prepared G5-PAMAM dendrimers conjugated to folic acid and a fluorescent probe (6-TAMRA, 6T) to provide a minimally invasive solution to this obstacle,

which were consequently targeted to tumors in vivo and observed by a two-photon optical probe[72].

Nonpharmaceutical Applications of dendrimers

Dendrimers have also been used as solubilizing agents in nonpharmaceutical areas apart from employment in the pharmaceutical field. Neofotistou et al. [73] used dendrimer as a solubilizing agent in a desalination system. In this study, they found that the scaling was totally inhibited scale deposition with the use of starburst NH_2-PAMAM dendrimers (generation0.5, 1, 1.5, 2, and 2.5).Ogava et al. studied the potential of water-soluble dendrimers as a potential fluorescent detergent to form micelles at very low CMC. The self-assembly of pyrene-cored poly (aryl ether) dendrimers have been studied, and it was shown that poly (aryl ether) dendrimers act as surfactant, which aggregate at quite low concentration in aqueous solution (1.8 - 10^{-5} M) to form micelles which was different from CMC of common detergents [74]. Cooper et al. synthesized DABdendr-$(NH_2)_{32}$, functionalized with a CO_2-philic shell derived from a heptamer acid fluoride of hexafluoro propylene oxide, (CF_3 CF_2 CF_2 (OCF (CF_3) $CF_2)_5$ which was a fourth generation hydrophilic dendrimer. These dendritic surfactants were able to distillate methyl orange (a CO2 insoluble dye and a hydrophilic compound) from a solution of liquid carbon dioxide [75].

Conclusion

Today many of the pharmaceutical companies and large number of patents focused on development of dendrimers for several therapeutic applications. Practical solutions to drug solubility issues, biodistribution and targeting were possible through these novel systems. Many studies have demonstrated that architecturally designed dendrimer can be modified for

bioavailability, biocompatibility, pharmacokinetics and targeted drug delivery to treat malignancies. Recent researches lead to the successes in simplifying and optimizing the preparation of dendrimers such as the ‘click’ and ‘lego’ approaches [76, 77], provide immense variety of structures and at the same time reducing the cost of their production. Areas that require continued research is the biodistribution behavior of dendrimers and the effect of peripheral dendritic groups on tissue localization.

Some of the ongoing developments include the release of drug from dendrimer because of the huge globular architecture thus making difficult the engineering techniques involved in enzymatic cleavable linkages [78-80] and the other one is development of drug dendrimer conjugates as anti-cancer agents in order to ease administration and improve safety for patients by Starpharma [81]. Finally, from many of the research studies done on dendrimers it can be concluded that these multifunctional nanoparticulate systems are promising scaffolds for drug delivery with their various applications in targeting, imaging, diagnostics and therapy.

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