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REVIEW ON: DENDRIMERS NEW HOPE IN PHARMACEUTICAL FIELD

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ABSTRACT

Pharmaceutical research and development heavily depend on synthetic polymers like dendrimers. The development of multifunctional "smart" nanocarriers that can carry one or more therapeutic drugs to cancer cells safely and selectively, including intracellular gene-specific targeting, is a result of advances in the application of nanotechnology in medicine. Dendrimers are a very desirable family of medication and gene delivery vectors due to their 3D nanopolymeric structures. Scientists now have the ability to modify a person's DNA to treat or prevent disease because to advances in our understanding of and ability to manipulate genes. Gene therapy has been used in clinical studies for the past ten years. The primary rationale for the development of gene therapy for the treatment of cancer is the silencing of tumour suppressor genes. Viral vectors, liposomes, cationic polymers and dendrimers, cell-penetrating peptides, gold and magnetic nanoparticles, and other delivery approaches have all been studied. The best way to improve the safety of gene therapy, which is still in its infancy in the field of cancer research, is to use a well-designed vector. In order to maximise the therapeutic efficacy of gene therapy for its potential in the treatment of a wide range of malignancies, more experimental and clinical experiments are concentrating on the development of well-designed and efficient dosages of vectors.

Keywords

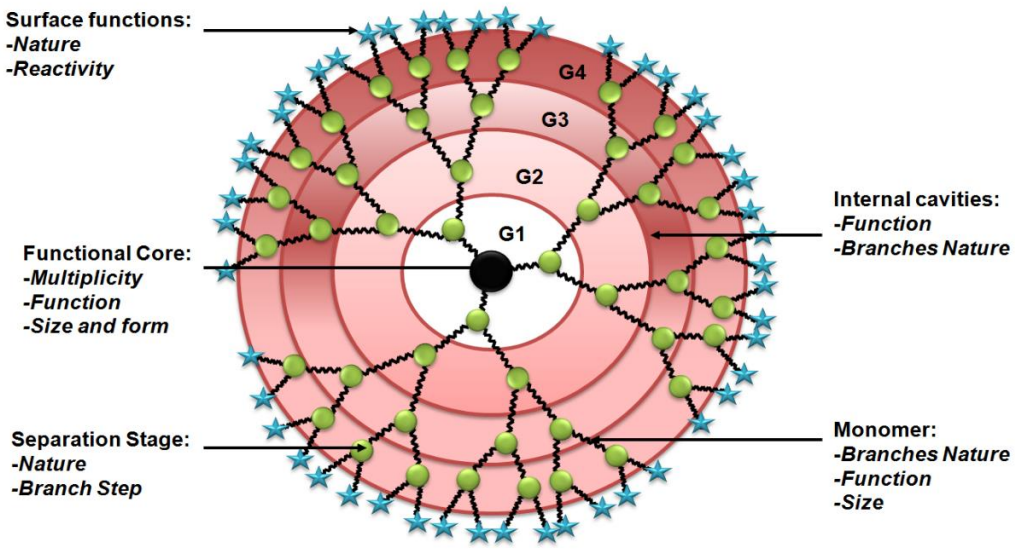
Nanocarriers, targeted therapy, gene therapy cancer, drug delivery system, RNA therapeutics

INTRODUCTION

Molecules with many branches make up dendrimers. The enormous amount of literature on dendritic structures, including dendrimers, dendronized, hyperbranched, and brush polymers, has produced a wide range of erroneous words and meanings, making it extremely challenging to present this subject in a clear and succinct manner. Generally speaking, a dendrimer is referred to as a macromolecule with a highly branching three-dimensional structure that offers a high level of surface functionality and adaptability. The "Polymers of the 21st century" have frequently been referred to as dendrimers. Fritz Vogtle and colleagues originally presented dendrimer chemistry in 1978 [1]. The first "cascade molecules" were created by him. Donald A. Tomalia created the first family of dendrimers in 1985. [2] The Greek words dendron, which means tree, and meros, which means portion, are where the name "dendrimer" comes from. Similarly, Newkome et al. [3] independently reported the synthesis of related macromolecules at

the same time. They referred to them as "arborols" after the Latin word "arbor," which also means "tree." Although the name "cascade molecule" is also used, "dendrimer" is the most well-known. Dendrimers have sparked a great deal of interest in the fields of chemistry and biology because of their multivalent and monodisperse nature, particularly in applications like chemotherapy, gene therapy, and drug administration. Due of dendrimers' distinctive molecular design, scientific interest in them then skyrocketed.

Dendrimers have three distinct architectural elements, including an initiator core, inner layers (generations) made up of repeating units that are radially linked to the interior core, and an outside (terminal functionality) that is attached to the outermost interior generations (Figure 1) [4, 5].



DENDRIMERS

A central core, a hyperbranched mantle, and a corona with peripheral reactive functional groups make up the three separate domains of the architecture of dendrimers, which are globular macromolecules with a size range of 1-100 nm. Dendrimers are virtually perfect (spherical) nanocarriers with predictable characteristics because of the high degree of control over the synthesis of dendritic architecture. Polyamidoamine (PAMAM), poly(propylene imine) (PPI), poly(glycerol-co-succinic acid), poly-l-lysine (PLL), melamine, triazine, poly(glycerol), poly[2,2-bis(hydroxymethyl)propionic acid], poly(ethylene glycol) (PEG), and dendrimers based on carbohydrates and citric acid have all been developed successfully for drug delivery [-].The two dendrimers PAMAM and PPI have received the greatest attention as potential medicinal application vectors. These two amine-terminated dendrimers exhibit drug release behaviour that is stimuli-responsive and pH-dependent. Back folding, also known as tertiary amine deprotonation, is the collapse of the dendrimer inward when it is exposed to high pH (alkaline) conditions. By utilising two main concepts, active and passive tumour targeting, dendrimers may get through a variety of delivery hurdles, demonstrating their usefulness.

Properties of dendrimers

Many of the properties of dendrimers include

1. Nanoscale sizes that are comparable in size to significant bio-building components like proteins and DNA.

2. The quantity of terminal surface groups (Z) appropriate for bio-conjugation of medication, signaling, targeting, or biocompatibility groups.

3. Surfaces having potential functional group designs to promote or inhibit transcellular, epithelial, or vascular biopermeability.

4. Imaging moieties, metals, or small molecule medicines may be enclosed in an inner empty area. Reduced medication toxicity and more regulated release are benefits of encapsulating in the empty region.

5.An association between lower generation neutral polar or anionic terminal surface groups and favourable biocompatibility patterns as opposed to higher generation neutral apolar and cationic surface groups.

6. The majority of dendrimer surfaces treated with minor functional groups or polyethylene glycol (PEG) exhibit non- or mild immunogenicity.

7.Modifiable surface groups, such as those for receptor-mediated targeting, therapeutic dose, or controlled drug release from the internal space, that can be used to improve biodistribution

METHOD OF SYNTHESIS

The classical polymerization process which results in linear polymers is usually random in nature and produces molecules of different size, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis.

1. Divergent Method
2. Convergent Method
3. Double Exponential and Mixed Method
4. Hypercores and Branched Monomers Growth

1.Divergent Method

Characteristic: Dendrimer formation start from core.

Merit: Lagre quantity of dendrimer produced by this method.

Demerit -To prevent problem during synthesis large quantity of reagent required.

Product purification is very tedious tas

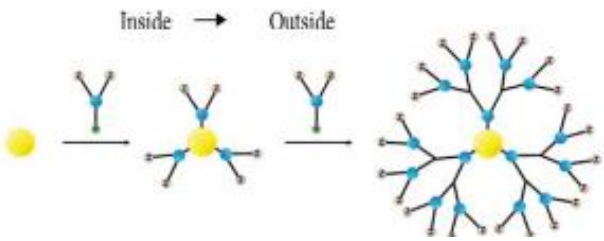


Diagram:

2.Convergent Method

Charactristics: Dendrimer formation from Surface.

Merit: -Defects in the final structure are less. Product easily purified.

Demerit: -Due to steric hindrance higher generation dendrimer cannot be formed.

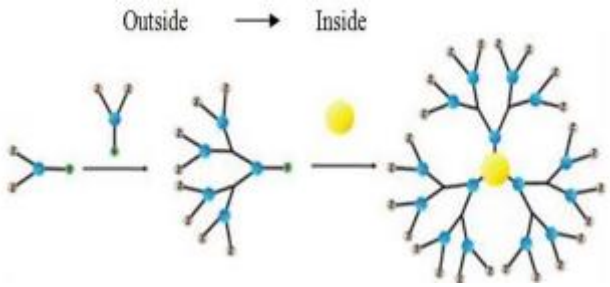


Diagram:

3.Double exponential and mixed method

Charactristics:-This method both Divergent and Convergent method used.

Merit: -Rapid growth technique for linear polymers, Fast method

4.Hypercores and branched monomers growth

Characteristics

This method involved the pre-assembly of oligomeric species which can be linked together to give dendrimers.

Merit

Fewer steps, Higher yields

Application of Dendrimer

- **Dendrimers as drug delivery systems**

Dendrimers have been created as nanodevices, either as pharmaceuticals themselves or as nanocarrier drug delivery systems. Terminal moieties are what give dendrimers their biological impact, which is what gives them their overall efficiency. Dendrimers are effective in overcoming the physicochemical restrictions of conventional medications (such as solubility, specificity, stability, biodistribution, and therapeutic efficiency) because of their appropriate, repeatable, and optimised design characteristics. They can also avoid biological issues including the first-pass effect, immunological clearance, cell penetration, and off-target interactions in order to hit the proper targets. Dendrimers are one of the more often utilised polymers as a non-viral delivery technology. Polymers are frequently used materials for nanoparticles-based distribution. The optimal drug carrier should fulfil a number of criteria, including drug retention, release, immune system invulnerability, lengthening duration in blood circulation, and precise targeting to cells or organs. When a drug carrier is injected into a patient, it enters the bloodstream and begins a complex journey before it can reach the target region. They proceed through the endocytosis process once they have attached to the target cell membrane. Dendrimers have a number of characteristics that might make the procedure easier. The importance of the body's structure, including its size, form, extra chemistry on its surface, and mechanical flexibility, must also be emphasised. The nanoparticles are safe for the tiniest capillaries and cannot block them since, when administered intravenously (IV), they have a significant influence on circulation time due to their small size. Particle size affects cellular uptake by phagocytosis and endocytosis as well. Dendrimers have a special uniformity that allows them to pass through the cancer cell membrane. The anticancer medication may be covalently conjugated to the dendrimer's surface or non-covalently contained in the dendrimer's core, allowing for the customization of the drug release patterns through controlled depolarization processes. It is beneficial to use amphiphilic dendrimers, which have hydrophilic branches and a hydrophobic core, to encapsulate anticancer medications in local therapies such intratumoral injections. Drugs that are hydrophobic can be made to dissolve in such a solution without being changed. In addition to these benefits, covalent chemical bonds used to link anticancer medications to the dendrimer's surface groups have a few more advantages over non-covalent encapsulation. In addition to improving drug solubilization, it is also feasible to attach a variety of hydrophobic anticancer medications while maintaining regulated release.

Dendrimers have already been used as passive anticancer nanocarriers . There are preclinical promising results in vitro as well as in vivo with active targeting dendrimers . For example, antibody-dendrimer conjugates showed better efficacy than free antibodies . It has been also reported that dendrimers modified with folic acid on the surface generated better

tumor accumulations that untargeted controls or free drug, producing a stronger reduction of the tumor mass . Moreover, sugar-modified PPI dendrimers tested by our research team at University of Lodz, Poland, are very attractive and specific for leukemia and lymphoma cells derived from lymphocytes B. Depending on the sugar on the surface and the number of molecules, we can observe the different extend of triggering apoptosis in those cells due to the diversity in affecting particular gene pathways . Lysine dendrimers, PAMAM, PPI, and phosphorus have been reported to be able to modulate amyloid peptide aggregation in solution . The deposition of amyloid fibrils is characteristic in neurological disorders as well as prion and Alzheimer's diseases. Some of the positively charged dendrimers could even inhibit the growth of amyloid fibrils or even disrupt existing mature of these fibrils. Others could decrease the number of toxic amyloid oligomers . The slow translation of preclinical studies to clinical trials may be due to the toxicity of dendrimers , with the aim of the current research in the development of new biocompatible and less toxic alternatives . Once these molecular machines arrive at the target site inside the living organism, several barriers must be overcome. Nanocarriers are usually internalized by endocytic processes , the processes called vesicular internalization. The most widely studied endocytic pathways are clathrin-mediated endocytosis, caveolae-mediated endocytosis, and macropinocytosis, but other cellular pathways have been recently identified, including clathrin- and caveolae-independent endocytosis and phagocytosis . Molecules, which are internalized by the cell membrane, are endocytosed by the early endosomes pathway. They may progress later to late endosomes and lysosomes. If the loading of dendrimer targets the nucleus, thus the nuclear membrane is another barrier that the dendrimer should come across . We should be very careful designing the drug delivery system because unexpectedly our desired nanovector might have its own power. This is what our genetic research has shown—4th generation PPI glycodendrimers with maltotriose molecules directly trigger mechanism of apoptosis in mitochondria of lymphocytes B, particularly those transformed to the leukemic cells. That discovery was successfully patented (US 9,877,85) and applied as a potential drug for lymphoproliferative disorders coming from B cells, such as chronic lymphocytic leukemia (CLL) or B-lymphoma. The power of these glycodendrimers relied on the ability to affect several genetic pathways simultaneously, and as opposed to the commonly used drugs or the new ones already proved by FDA, they affect the cell genome very quickly and efficiently according to the natural death process initiation .

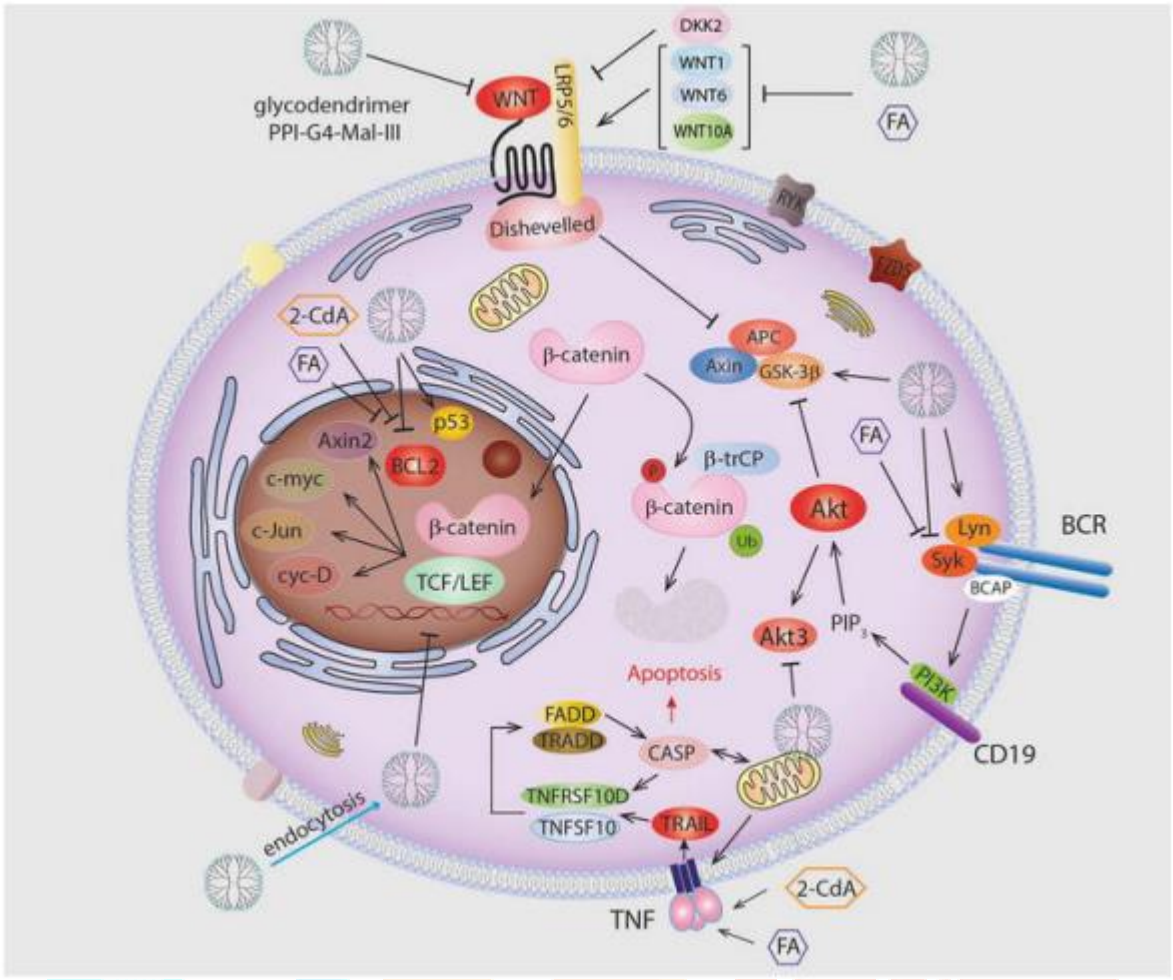


Figure : Mechanism of action—PPI-G4-OS-Mal3 dendrimers in B-lymphocyte (the illustration prepared by B. Ziemba).

Delivery of RNA therapeutics

RNA-based medications have been popular in recent years as promising options to treat disorders at the gene and RNA levels. It has been understood since 1990 that nucleic acids may be employed to alter protein synthesis in living organisms. The delivery of therapeutic RNA has, however, long been constrained by a variety of issues. It is well known that nucleases may quickly break down naked, single-stranded RNA. It is too big to passively traverse the cell membrane and can also stimulate the immune system. Furthermore, the issue enters the cell as a result of RNA's negative charge. In order to ease cellular entrance and escape from endosomes, a second solution should be offered. Typically, cationic polymers (e.g. dendrimers) are used to electrostatically condense the negatively charged RNA into nanoparticles. Very important for effective nucleic acid delivery are modifications made to RNA itself , to make it more resistant to degradation and render them unrecognizable by the immune system . RNAs can be modified by means of chemical alterations to the ribose sugar , the phosphate linkage, and the individual bases . One of such modified RNA is locked nucleic acid (LNA) modification. LNA's ribose moiety is modified with an extra bridge between the 2′ oxygen and 4′ carbon. The bridge "locks" the ribose in the 3′-endo(North) conformation. LNA nucleotides can be mixed with DNA or RNA residues in the oligonucleotide whenever preferred and hybridize with DNA or RNA according to Watson-Crick base-pairing rules. Due to the high stability of LNA-RNA it started to be used in a biotechnology field in a pharmaceutical business . The multi-valent folate (FA)-conjugated 3WJ RNP constructed to harbor anti-miR-21 LNA sequences (FA-3WJ-LNA-miR21). Specifically targeted anti-miR-21 LNA was delivered to glioblastoma cells. It caused the knock down of miR-21 expression in in vitro and in vivo models with favorable biodistribution. The results are indicative of the clinical benefit of FA3WJ RNP-based gene therapy for the successful targeted therapy of developing and even recurring glioblastoma . In the other study, (LNA)-anti-miR was reported as a blockage factor of miR-182-5p in human breast cancer cell line

(MCF-7). MTT (3-[4,5 dimethylthiazol-2- yl]-2,5-diphenyl tetrazolium bromide) assay and annexin/propidium iodide staining at different time points after LNA-anti-miR-182-5p transfection were accomplished. The results showed that miR-182-5p inhibition induces apoptosis and thus reduces the viability of MCF-7 cells. These results can be used in translational medicine for future investigation in breast cancer and approach treatment based on antisense therapy. siRNA is not the only RNA drug to be examined for protein knockdown at the clinical stage (NCT01676259) . Antisense oligonucleotides (ASO) were the first RNA drugs successfully reported in clinical trials. They are able to block protein translation through Watson-Crick base pairing with the target mRNA, similar way to siRNA mechanism, and they can also be modified to improve their stability . Despite that the ASOs inhibit protein production through the sterically blocking ribosome attachment or eliciting RNase-H activation, they are also able to promote the exon skipping, which may lead to a deletion of faulty sequences within proteins and thus it can make a protein upregulation, that can be used in diseases where certain genes are repressed . An emerging, but less clinically improved, is microRNA (miRNA) platform for protein knockdown. Endogenous miRNAs are non-coding RNAs that are regulatory factors for a variety of cellular pathways and are often downregulated in diseases . Exogenous mRNAs, or miRNA mimics, delivered therapeutically could make a knockdown of several proteins simultaneously, which might be very useful in cancer, where having a single disease-relevant target is rare . The first miRNA mimic therapy to enter clinical trials was MRX-34—a liposomal-encapsulated miRNA mimic from Mirna Therapeutics meant to treat variety of cancers . Despite the big number of carriers, mRNA molecules are significantly larger than (600–10,000 kDa) than the previously discussed siRNAs (~14 kDa) and ASOs (4–10 kDa), which poses an additional challenge for delivery of mRNA therapeutics . Therapeutic applications based on mRNA are currently being explored as vaccinations against cancer, infectious diseases, and gene editing. Cancer mRNA vaccines have experienced accelerated development in cancer immunotherapy. The majority of approaches tested in clinical trials employ adoptive transfer of DCs transfected with mRNA coding for tumor-specific antigens (TSAs) and immunomodulation of T cells with mRNAs expressing chimeric antigen receptors (CARs) or TSAs.

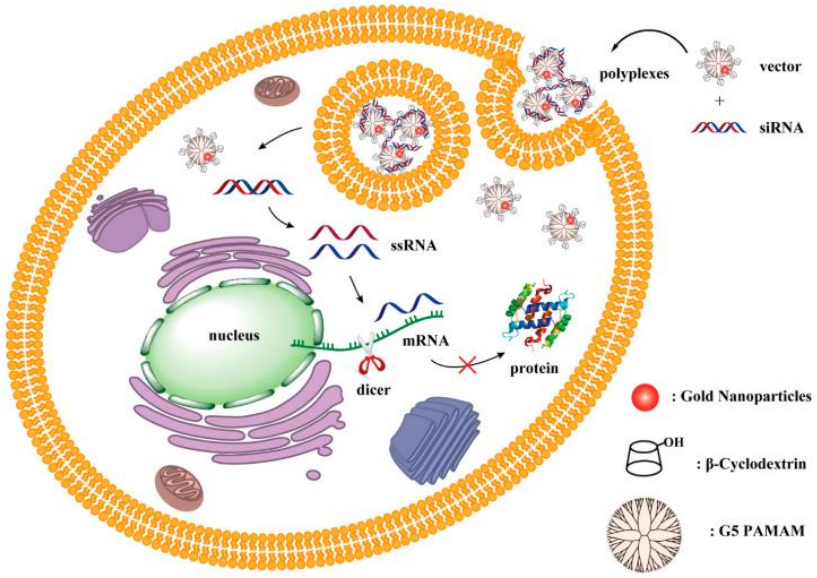
The newest and most advanced method of delivering genes is the CRISPR-Cas system, which also depends on Watson-Crick base-pairing between a single guide RNA (sgRNA) and a corresponding DNA target site, followed by a unique protospacer-adjacent motif (PAM), a 3-5 nucleotide DNA sequence necessary for binding Cas9 and cleaving the target sequence. It causes a DNA molecule to have a double-stranded break (DSB). Cells can use homology-directed repair (HDR) and non-homologous end joining (NHEJ) to repair DSBs. Permanent gene knockout is brought about through insertions and deletions caused by NHEJ. Due of mRNA expression's transient nature, CRISPR-Cas components based on nanoparticle mRNA delivery are appealing from a therapeutic standpoint. . There is also no risk of genomic integration and mRNA cytoplasmic activity, mitigating the need to overcome the nuclear barrier in comparison with pDNA . The major challenges for RNA-based drugs and CRISPR-Cas therapies will be shaping the scope of upcoming clinical trials.

Clinical studies of dendrimers for targeted cancer therapy

An efficient vector protecting siRNA that is non-toxic and can be targeted at specific cells is required to build the most effective and diverse treatments for various types of cancer. Many different kinds of dendrimers appear to be excellent oligonucleotide carriers. SiRNAs can form complexes with cationic carbosilane dendrimers (CBD), which are SiO or SiC-bonded and ended with amine or ammonium groups. Numerous studies on the idea of delivering nucleic acids via 'dendriplexes' have shown promising results. PAMAM dendrimers are the most researched dendrimer type out of the several options that have been put out, followed by poly(l-lysine) (PLL), poly(propylene imine), and other types. PAMAM dendrimers are the most explored dendrimers type, followed by poly(propylene imine) (PPI) dendrimers, poly(l-lysine) (PLL) dendrimers, and some others. PAMAM dendrimers, hydrophilic, biocompatible, and non-immunogenic particles, are build of ethylenediamine core (most commonly) and methyl acrylate and ethylenediamine branches . They have been successfully used as nucleic acid delivery systems in many in vitro and in vivo researches of which we present selected examples . The transfection efficiency of PAMAM dendrimers largely depends on their generation, which determines the structure of the PAMAM

molecule: higher generations are more compact and spherical than the low ones and provide a surface with a high density of primary amines therefore form more stable dendriplexes with higher efficiency . However, dendrimers with high generations results in higher toxicity due to a large number of terminal cationic groups which can interact with negatively charged cell components, e.g. cell membranes causing their disruption . This disadvantage can be diminishing by surface modification with different targeting or shielding moieties providing with not only low toxicity but also enhance the cell uptake and specific accumulation of nucleic acid molecules inside cells . For example, novel targeted nanoparticle system consisting of FLT3 ligand-conjugated PAMAM G7 encapsulating a pivotal tumor suppressor and negative regulator of FLT3 miRNA—miR-150, was developed by Jiang et al. to treat FLT3-overexpressing acute myeloid leukemia (AML), a leukemia associated with unfavorable prognosis. The system demonstrated high efficacy significantly inhibiting progression of FLT3-overexpressing AML in vivo with no obvious side effects on normal hematopoiesis. In other research, Liu et al. demonstrated that triethanolamine (TEA)-core PAMAM dendrimer is able to deliver Hsp27 siRNA effectively to a castrate-resistant prostate cancer model in vitro and in vivo and produce potent gene silencing of the heat-shock protein 27 (HSP27), leading to a notable anticancer effect. To further improve the delivery system, the arginine-terminated PAMAM-G4 dendrimers were developed with the aim of combining and harnessing the unique siRNA delivery properties of the TEAcore PAMAM dendrimer and the cell-penetrating advantages of the arginine-rich motif. The modification led to improved cell uptake of siRNA by comparison with non-modified bearing PAMAM-G4 and to yield potent gene silencing in human hematopoietic CD34+ stem cells and anticancer effects with no discernible toxicity in both in vitro and in vivo models . Another example of a delivery system where the modification aiming at increasing the efficiency yield is FA-decorated PAMAM G4 (G4-FA) used as a vector for local delivery of siRNA against vascular endothelial growth factor A (siVEGFA) in a xenograft HN12 tumor mouse model of head and neck squamous cell carcinomas. The G4-FA/siVEGFA complex exhibited high tumor uptake, sustained retention properties and pronounced tumor suppression in even single- or two-dose regimen studies . Thioaptamer (TA)-modified PAMAM dendrimers, on the other hand, are proposed as effective miRNA deliver system to breast cancer cells constituting a prototype that it could be safely used in pre-clinical and clinical research.

Dendriplexes are frequently used in combination with recognised anticancer medications as part of anticancer treatment. Hepatocellular carcinoma (HCC), a deadly malignancy with no effective treatment, was combated by researchers from Virginia Commonwealth University using nanoplexes of PAMAM dendrimer with polyethylene glycol and lactobionic acid complexed with AEG-1 siRNA. Combining the compound with all-trans retinoic acid (ATRA) resulted in a significant and synergistic suppression of tumour development in the human HCC xenograft model, indicating that a combinatorial approach may be a useful strategy to treat cancers that are resistant to standard treatments. In order to overcome multidrug resistance (MDR) in human breast cancer MCF-7/ADR cells, Liu et al. employed PAPMAM dendrimers as a nanoparticle delivery platform for an MDR1 gene targeting siRNA. This PAMAM-siMDR1 complex decorated additionally with phospholipid demonstrated high gene silencing efficiency and enhanced cellular uptake of siMDR1 resulting in rising of cellular accumulation of doxorubicin (DOX), inhibition of the tumor cell migration, and due to synergistic work with paclitaxel (PTX), increase of cell apoptosis, and cell phase regulation [ ]. More complex system designed in order to achieve effective treatment to MDR breast cancer is PAMAM functionalized graphene oxide (GOPAMAM) which can load DOX and MMP-9 shRNA plasmid at the same time. Delivering anticancer medications to brain tumours while navigating the blood-brain barrier (BBB) is still a difficult issue. He and his colleagues just put up an intriguing strategy. Transferrin and wheat germ agglutinin have both been conjugated with G4.0 PAMAM dendrimers as two specific ligands. These conjugates were employed to incorporate medicines into brain tumour cells and cross the BBB. The DOX was successfully delivered into the brain tumour thanks to that dual-targeting drug carrier technology, offering a possible treatment for brain cancer.



A 1,4-diaminobutane core and branches made of propylene imine make up poly(propylene imine) (PPI) dendrimers. The PPI dendrimers' positively charged surface interacts with nucleic acids, making it possible to employ the dendritic scaffold as a vector for gene transfection.

The 3rd generation of PPI-Mal-DS dendrimers did not exert the same effect. There was observed no increase in pro-inflammatory cytokine secretion which is a very promising result . PPI-5G dendrimers, similar to PAMAM, also possessed the ability to deliver anticancer drugs to brain tumors. Gajbhije and Jain reported polysorbate-80-conjugated PPI dendrimers for targeted delivery of docetaxel (DTX) to the brain tumor . This complex reduced the tumor volume more than 50% after 1 week of treatment. It is because this formulation owing the higher BBB permeability of polysorbate-80-anchored dendrimers . The other report showed that PPI-5G dendrimers conjugated with thiamine exhibited improved delivery of PTX across the BBB and the preferential brain uptake of PTX by the nanoconjugates might be attributed to the association with the thiamine transporters or increased passive diffusion secondary to an improved concentration gradient of the dendrimers located at the BBB interface

- **Blood Substitution**

Dendrimers are used as blood substitutes. Their steric bulk surrounding a heme mimetic centre significantly slows degradation compared to free heme, and prevents the cytotoxicity exhibited by free heme.

- **Oral Drug Delivery**

Oral route most widely used route Strong acid and enzyme present in stomach causes degradation of drug. Dendrimer interior is hollow so it provides good site for drug entrapment. This entrapment increases solubility as well as stability of drug. Eg. PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging. Dendrimer provide protective layer reduces the effect of acid and enzyme.

Ocular drug delivery

For the delivery of ophthalmic drugs, dendrimers provide special answers to challenging delivery issues. Utilizing PAMAM dendrimers with carboxylic or hydroxyl surface groups, recent study has improved the residence duration of pilocarpine in the eye. It was anticipated that these surface-modified dendrimers would increase the bioavailability of pilocarpine. [15] The most often prescribed mode of administration for treating a variety of ocular illnesses is topical application of active medications to the eye. It is commonly acknowledged that topical medications have very low intraocular bioavailability. These

effects are mostly attributable to the nasolacrimal duct's drainage of the extra fluid and tear turnover's removal of the solution. By utilising specialised delivery methods like polymers and liposomes, several scientific advancements in ocular medication delivery systems have been produced. Ideal ocular drug delivery systems should be non-irritating, sterile, isotonic, biocompatible, does not run out from the eye and biodegradable [16] . Transdermal drug delivery Dendrimers designed to be highly watersoluble and biocompatible have been shown to be able to improve drug properties such as solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently [17]. The viscosity imparting property of a dendrimer solution allows for ease of handling of highly concentrated dendrimer formulations for these applications. Dendrimers have been shown to be useful as transdermal drug delivery systems for nonsteroidal anti-inflammatory drugs (NSAIDs), antiviral, antimicrobial, anticancer, or antihypertensive drugs [18]. PAMAM dendrimers have been studied as carrier transdermal systems for the model NSAIDs: ketoprofen and diflunisal [19]. It is well known that the molecular transport through intact skin is related to the molecular weight of the drug-carrier molecule. Dendrimers failed to show enhancement in drug transport through intact skin, because of its high molecular weights. More research efforts are required in this area to understand the relationship of dendrimers to skin transport mechanism.

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Targeted gene delivery

Dendrimers can function as vectors, or carriers, in gene therapy. Through the cell membrane and into the nucleus, vectors deliver genes. Currently, genetically modified viruses and liposomes are mostly employed for this. PAMAM dendrimers have also been examined for their potential as genetic carriers. By creating compounds with negatively charged genetic materials through electrostatic contact, cationic dendrimers (such as the Polypropylenimine (PPI) dendrimer) carry genetic materials into cells. Because they can bind tightly to DNA, cationic dendrimers are excellent non-viral vectors for delivering genes. Dendrimers coated with sialic acid might be used in another scenario to aid the attachment of the influenza virus to cell surfaces. In addition, dendrimers are non-immunogenic and are thus uniquely suited as carrier structures for drugs or bioactive molecules without degradation in immune system [20].

CNS delivery

Dendrimers, are regularly branched polymer molecules with branches growing from one or several centers. They can be formulated noncovalently with biological agents, such as DNA or conjugated with pro-drug or imaging agents and thus can be used as delivery vehicles for drug therapy or molecular imaging [21-26]. To the best of our knowledge dendrimers have not been evaluated so far for CNS delivery except for few studies on intratumoral delivery of dendrimer conjugates with anti-cancer agents to treat glioma [27, 28]. Notably, the generation and surface properties of dendrimers were found to be very important.

Dendrimer and carbon nanotube

Since Choi and his team proposed the idea of using PAMAM dendrimers for the synthesis of catalytic nanoparticles for single-walled carbon nanotube (SWNT), there has been a growing interest in the use of dendrimers as "Nanotemplates" for the controlled formation of carbon nanotubes. As a result, chemical vapour deposition (CVD) nanotubes with a narrow diameter distribution between 1 and 2 nm were produced employing this dendritic platform [36].]. Later, in another study by Amama et al, the use of fourth-generation PAMAM dendrimers as a platform for synthesizing multi-walled carbon nanotubes (MWCNTs) with systematically varied diameter distributions and defect densities by microwave plasma-enhanced chemical vapor deposition was demonstrated [37] .

Dendritic micelles

Dendrimers, the highly branched monodisperse macromolecules, have a large number of tunable surface groups and an interior that provides space as well as microenvironment suitable for host-guest chemistry. [38, 39] Dendritic micelles are generally unimolecular and do not suffer from even the low CMC that the linear polymer-based micelles have. Also, these have been shown to be rapidly internalized into cells through endocytosis due to their nanometerscale dimensions. By virtue of these unique features, dendrimers are being recently studied for applications in gene therapy and as drug carriers and as contrast agents in imaging [40, 41]. It is evident from the above discussion that dendritic micelles with anionic or PEG groups on the periphery are promising carriers for drug delivery. Further, functionalized biocompatible dendrimers will be attractive for multiple dendrimer-drug conjugates. It will be interesting not only to have highly functionalized dendrimers but also to direct the functionalities towards the concave interior of the dendrimer for better encapsulation of the drug.

- **Cellular Drug Delivery**

The kinetics of cellular entrance of a variety of PAMAM dendrimers (G4-NH2, G3-NH2, G4-OH, PEGlayted G3 [G3-PEG] and a highly branched polymer (polyol) into A549 human lung epithelial carcinoma cells were investigated by Kennan et al. G3-NH2, polyol, and G3-PEG all entered cells more slowly than G4-NH2 and G4-OH. It was proposed that the cationic character of the amine surface groups, which may interact electrostatically with negatively charged epithelial cells and enter via fluid phase pinocytosis, may be the cause of the G4-NH2's quick entrance. Fewer surface charges on the G3-NH2 dendrimer may be the cause of G3-NH2's slower rate of cellular entrance when compared to G4-NH2. Because polyol and G3-PEG do not have cationic surface groups, their cellular entry may result from non-specific adsorption to the cell membrane and subsequent endocytosis. Dendrimer–ibuprofen complexes entered the cells rapidly compared with pure drug (1 hr versus>3 hr), suggesting that dendrimers can efficiently carry the complexes drug inside cells. PAMAM dendrimers were surface engineered with lauryl chains to reduce toxicity and enhance cellular uptake.

- **Dendrimer-based nanoparticles for lung delivery**

Kukowska-Latallo et al investigated the ability of PAMAM dendrimers to augment plasmid DNA gene transfer in-vivo and evaluates the targeting of the lung by alternative routes of administration [42]. They suggested that vascular administration seemed to achieve expression in the lung parenchyma, mainly within the alveoli, while endobronchial administration primarily targeted bronchial epithelium, indicating that each delivery route requires different vectors to achieve optimal trans-gene expression that each approach appears to target different cells within the lung. Rudolph et al compared the properties of branched polyethylenimine (PEI) 25 kDa and fractured PAMAM dendrimers for topical gene transfer to the airways in-vivo [43]. Bai et al produced low molecular weight heparin (LMWH)–dendrimer complex through electrostatic interactions using various PAMAM dendrimers then evaluated both the safety and the efficacy of the drug–dendrimer formulations in preventing deep vein thrombosis in-vivo and in-situ [44] . They concluded that cationic dendrimers can be used as pulmonary delivery carriers for a relatively large molecular weight anionic drug. These carriers bind anionic drug molecules most likely via electrostatic interactions and increase drug absorption through charge neutralization.

- **Dendritic catalysts / enzymes**

The combination of high surface area and high solubility makes dendrimers useful as nanoscale catalysts. Dendrimers have a multifunctional surface and all catalytic sites are always exposed towards the reaction mixture. They can be recovered from the reaction mixture by easy ultra filtration methods [45]. Dendritic shells can be used to create a microenvironment favorable for catalysis or provide shielding for functional groups at the dendritic core. Because of their ‘pseudo’-spherical nature and their resultant conformations the metal sites in these welldefined polymeric catalysts should be easily accessible for substrate molecules and reagents, and therefore exhibit characteristicsfast kinetics, specificity and solubility [46] . Metallodendritic catalysts, catalysis with phosphine-based dendrimers, catalysis with (metallo)

dendrimers containing chiral ligands, non-metal containing dendrimers are some of the examples of dendritic catalysts and enzymes.

- **Future prospect**

More people are beginning to see dendrimer drug delivery systems as a beneficial alternative for bioactives like medicines and genes. They offer a surface on which medications or genes can be attached and released through a variety of ways. Dendrimers have been investigated by scientists for use in oral, transdermal, ophthalmic, and gene delivery, among other uses. Although effective dendrimer drug delivery has to pay attention to certain manufacturing and biological issues. The growth of dendrimer technology's commercial applications will support the technology's utility in the upcoming years.

- **Conclusion:**

Dendrimer also improves the drug's stability. Drugs are integrated into dendrimers using electrostatic, covalent, and simple encapsulation methods. With the addition of polyethylene glycol (PEG), dendrimer has decreased cytotoxicity. Drug distribution is improved by dendrimer characteristics such monodispersity, molecular weight, and architecture. Dendrimers have several applications outside of only drug delivery, including gene transfection and diagnostics. Dendrimers are suitable carriers in biomedical applications such as drug administration, gene transfection, and imaging due to the great degree of control over their architecture, size, shape, branching length and density, and surface activity. Dendrimers were discovered twenty years ago, but the multi-step synthesis still takes a lot of work. Only a small number of applications, for which the distinct dendrimer structure is essential, will pass the cost-benefit analysis unless there is a considerable advancement in this sector.

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